The Role of Psychedelics in Modern Psychiatry
A Review of the Evidence Base

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D. Payton Sterba, M.D., PGY-3 Psychiatry Resident, OHSU
Jovo Vijanderan, M.D., M.S., PGY-2 Psychiatry Resident, OHSU

About the Speakers

- Dr. Melissa Buboltz is an Associate Professor of Psychiatry at Oregon Health and Science University and an inpatient psychiatrist at the Portland VA. She obtained a degree in psychology from the University of Minnesota and attended Mayo Medical school prior to residency at OHSU. Her interests include evidence-based psychopharmacology and medical education.

- Dr. Payton Sterba is a third year adult psychiatry resident at the Oregon Health and Science University Department of Psychiatry. He obtained his M.D. at the Medical College of WI and his bachelor’s degree at Marquette University. His interests include substance use, emergency psychiatry, and psychoanalytic theory.

- Dr. Aryan Sarparast is a third year adult psychiatry resident at the Oregon Health and Science University Department of Psychiatry. He obtained his M.D. at the University of Central Florida College of Medicine, and his B.Sci. in psychology at the University of Oregon. His academic interests include harm-reduction and community education regarding psychedelics, narrative medicine, and psychotherapy.

- Dr. Jovo Vijanderan is a second year adult psychiatry resident at Oregon Health and Science University Department of Psychiatry. He obtained his M.S. in Physiology and his M.D. from the University of Cincinnati. His undergraduate studies were at UCLA in Microbiology, Immunology & Molecular Genetics. His interests include Psychotic Disorders, Psychotherapy, and Medical Student Education.
Disclosures

The presenters have no financial disclosures

Learning Objectives

At the end of the presentation, participants should be able to:

• Describe the historical, cultural, and political context for the therapeutic use of psychedelic substances in psychiatry

• Summarize how MDMA, psilocybin, and LSD have been used and studied to treat psychiatric disorders

• Participate in an educated discussion about the available evidence-base, potential risks vs benefits, and practical considerations regarding use of psychedelics in modern psychiatry
Drug Scheduling

**Schedule I**
no currently accepted medical use and a high potential for abuse.

**Schedule II**
high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous

**Schedule III**
moderate to low potential for physical and psychological dependence

**Schedule IV**
low potential for abuse and low risk of dependence

**Schedule V**
lower potential for abuse than Schedule IV

www.dea.gov/drug-scheduling

http://aidsinfo.nih.gov
**Psychedelic Psychotherapy**

https://heffter.org/cancer-distress/
MDMA
3,4-methylenedioxymethamphetamine

live video from an experimental dosing session
Overview

Brief review of history in the United States
Basics of MDMA
Tolerability

**MDMA assisted psychotherapy for PTSD treatment:**
- 2011: the first pilot study on the topic
- 2013: a follow-up on safety and dependence
- 2018: phase 2 dose-response clinical trial
- 2019: pooled phase 2 analysis from 6 trials

Phase 3?
A Brief “Trip” Through Time

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1912</td>
<td>Anton Köllisch attempts to synthesize Hydrastinin, ends up with MDMA instead</td>
</tr>
</tbody>
</table>
| 1970s | First report of effects of MDMA on humans (Shulgin and Nichols)  
First MDMA-assisted psychotherapy sessions; Leo Zeff |
| 1980s | Recreational use becomes popularized |
| 1985 | MDMA becomes schedule 1 after studies suggesting neurotoxicity |
| 1996 | Grob et al. produces the first FDA approved study on MDMA |
| 2011 | Mithoefer et al. produces the first RCT on MDMA assisted psychotherapy and PTSD |
| 2018 | Mithoefer et al. completes the largest study to date on MDMA assisted psychotherapy |

Basics - Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical dose</td>
<td>75 - 120mg; ~2 mg/kg</td>
</tr>
<tr>
<td>Onset</td>
<td>30 - 60 min after PO ingestion</td>
</tr>
<tr>
<td>Peak</td>
<td>75 - 120 min after PO ingestion</td>
</tr>
<tr>
<td>Duration of psychoactive effect</td>
<td>3 - 6 hrs</td>
</tr>
<tr>
<td>Half-life</td>
<td>8 - 9 hrs</td>
</tr>
<tr>
<td>Human metabolism</td>
<td>CYP2D6</td>
</tr>
</tbody>
</table>
Basics - Effects

- **Neurochemical:**
  - 5HT2A, 5HT2C >> NE > DA
  - SSRIs block effects of MDMA in vitro and in vivo
  - Primarily affects 5-HT transporter; also affects degeneration, activation, and concentration

- **Psychosocial:**
  - anxiolytic
  - prosocial (oxytocin, dec reactivity to perceived threats)
  - euphoria
  - increased sense of interpersonal trust

- **Neurohormonal:**
  - dose dependent acute inc in cortisol, prolactin, ACTH, vasopressin

- **Neurotoxic:**
  - a point of debate, highly exaggerated and rife with scandal

MDMA Assisted Psychotherapy for PTSD: the first pilot study

*Psycho-pharmacology*

2011

*The safety and efficacy of 3,4-methylenedioxymethamphetamine (MDMA) assisted psychotherapy in subjects with chronic, treatment-resistant post-traumatic stress disorder: the first randomized controlled pilot study*

Mithoefer MC, Wagner M, Jerome I, Mithoefer AT, Doblin R

Funding: MAPS
Participants
- predominantly female, white, in their 40s
- predominantly victims of sexual assault or childhood sexual abuse
- baseline CAPS 79.4
- N = 20
  - 12 received MDMA
  - 8 received placebo

Design
- Double-blind, placebo-controlled, with open label phase (subjects who had placebo re-entered experimental cycle with MDMA)
- Primary outcome measure = CAPS IV
- Intro therapy sessions: 90 min therapy sessions intended to create rapport with male-female co-therapy team (1 psychiatrist, 1 nurse practitioner)
- 8 hr Experimental session w/ supervised overnight stay: **125 mg MDMA vs inactive placebo**
  (Most subjects opted for 62.5 mg supplemental dose after 2 hrs)
- 2 experimental “cycles” with 3-5 wk interim with 90 min psychotherapy integration sessions every week

Trended PTSD severity scores are promising
Do the results stand the test of time? Following-up on the 2011 study

**2013**

*Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine (MDMA) assisted psychotherapy: a prospective long-term follow-up study*

Mithoefer MC, Wagner M, Mithoefer AT, Jerome I, Martin SF, Yazar-Klosinski B, Michel Y, Brewerton TD, Doblin R

Funding: MAPS

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**MDMA Assisted Psychotherapy for PTSD:**
Results are durable but the small follow-up cohort translated to having no statistical significance

<table>
<thead>
<tr>
<th>Subjects</th>
<th>● n = 16 had fully completed follow-up data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of Follow Up</td>
<td>● 17-74 months; <strong>mean of 45.4 months after last experimental session</strong></td>
</tr>
<tr>
<td>Substance Use</td>
<td>● <strong>Unchanged from data from original study:</strong> 8 have used cannabis, 1 had used psilocybin, 1 used ‘Ecstasy’ to re-create therapeutic setting</td>
</tr>
</tbody>
</table>
| Durability | ● 2 months after last dose in original study: mean **CAPS 24.6**  
● At time of this study: mean **CAPS 23.7; scores remained low**  
● p = 0.91; no significant change |
Let’s address efficacy, durability, and blinding

Mithoefer goes for Round 2

THE LANCET Psychiatry

2018

3,4-methylenedioxymethamphetamine (MDMA) assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomized, double-blind, dose-response, phase 2 clinical trial


Funding: MAPS

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**Participants**

- Predominantly male, white, in their 30s-40s
- Predominantly veterans with several firefighters and a police officer
- Nearly all had tried first line therapies like CBT (92%), antidepressants (96%)
- 23% had used MDMA/Ecstasy in the past
- Baseline CAPS 87.1
- **N = 26**
  - 7 received active control (30mg MDMA)
  - 7 received 75mg MDMA
  - 12 received 125mg MDMA

**Design**

- Double-blind, randomized, active control (30mg MDMA), with open label phase (subjects who had active control re-entered experimental cycle with full dose MDMA)
- Primary outcome measure = CAPS IV
- Identical to 2011 pilot study in methods with major difference being dosing
  - Most participants received supplemental dose (1/2 of initial dose given after 2hrs)
### Design

- Subjects in 30mg and 75mg dose groups re-entered the experiment to receive 100 - 125mg to gain pilot data for phase 3 study
- Similar to blinded stage of the study
- Subjects in 30mg, 75mg, AND 125mg get at least one open-label session

### Endpoint Data

- Similar to blinded stage of the study, except for when data is gathered
- Secondary endpoint (1 month after 2nd open-label session)
- End of stage II (2 months after 3rd open-label session)

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**Graph**

The graph illustrates the mean CAPS-IV total scores over time for different dose groups and the combined group. The x-axis represents different time points: Baseline, Primary endpoint, End of stage 1, Secondary endpoint, End of stage 2, and 12-month follow-up. The y-axis shows the mean CAPS-IV total scores ranging from 0 to 120. The graph uses different markers and colors to distinguish between the 30mg, 75mg, 125mg, and combined groups, indicating trends and differences in scores across these time points.
Are the results replicable?
MAPS prep for the final phase of studies

2019

MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials


Funding: MAPS

Participants
- predominantly **white**, in their **40s**, **genders well balanced**
- 29% had used ecstasy in the past
- baseline CAPS 84.5, baseline BDI-II 29.1
- **low drop out rate** 7.6% (8 subjects)
- **N = 103**
  - 31 received active control or placebo (0mg, 25mg, 30mg, or 40mg MDMA)
  - 72 received active experimental dose (75mg, 100mg, 125mg MDMA)
  - 51 proceeded to open label 3rd experimental dose (100mg - 125mg MDMA)

Design
- **Pooled data from 6 study sites**: USA (3), Canada, Switzerland, and Israel. 18 total therapy teams, all trained by MAPS Therapy Training Program
  - all sites used the same psychotherapy manual designed by Mithoefer
  - highly similar but some variability in study design between sites
- Collected from April 2004 - March 2017
- Data was pooled together as either active control/placebo vs active dose and then compared post-dosing session CAP-IV to baseline
Breakthrough for Trauma Treatment: Safety and Efficacy of MDMA-Assisted Psychotherapy Compared to Paroxetine and Sertraline

Feduccia AA, Jerome L, Mithoefer MC, Yazar-Klosinski B, Emerson A, Doblin R

### Table

<table>
<thead>
<tr>
<th></th>
<th>Sertraline</th>
<th>Paroxetine</th>
<th>MDMA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAPS-2 (sertraline-placebo)</td>
<td>Dropout %</td>
<td>CAPS-2 (paroxetine-placebo)</td>
</tr>
<tr>
<td>Study 1</td>
<td>$-6.8$ (effect size $0.31$)</td>
<td>29.3%</td>
<td>$-14$ (effect size $0.56$)</td>
</tr>
<tr>
<td>Study 2</td>
<td>$-9.8$ (effect size $0.37$)</td>
<td>28.4%</td>
<td>$-11$ (effect size $0.45$)</td>
</tr>
<tr>
<td>Study 3</td>
<td>--</td>
<td>--</td>
<td>$-6$ (effect size $0.09$)</td>
</tr>
</tbody>
</table>

1. Effect sizes were not reported in FDA statistical package for paroxetine. Placebo subtracted effect. Size were determined from CAPS scores by calculating the change from baseline divided by the standard deviation.
2. Primary endpoint was 1–2 months after 2–3 blinded experimental sessions.
Tolerability

Mean % of commonly reported reactions during MDMA vs placebo treatment from 12 phase 1 studies

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Mean % for placebo (n=57)</th>
<th>Mean % for MDMA (n=174)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of appetite</td>
<td>2%</td>
<td>68%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>N/A</td>
<td>64%</td>
</tr>
<tr>
<td>Jaw clenching</td>
<td>0%</td>
<td>60%</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>16%</td>
<td>53%</td>
</tr>
<tr>
<td>Thirst</td>
<td>4%</td>
<td>48%</td>
</tr>
<tr>
<td>Restlessness</td>
<td>0%</td>
<td>46%</td>
</tr>
<tr>
<td>Restless legs</td>
<td>0%</td>
<td>45%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>43%</td>
</tr>
<tr>
<td>Feeling cold</td>
<td>4%</td>
<td>43%</td>
</tr>
<tr>
<td>Perspiration</td>
<td>0%</td>
<td>40%</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0%</td>
<td>37%</td>
</tr>
</tbody>
</table>

When is MDMA **BAD 4 U**?

**Un**reliable doses
**Un**controlled settings
**Un**derlying co-morbidities
**Un**known quality

<table>
<thead>
<tr>
<th>Psychoactive compounds</th>
<th>Frequency of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No other drugs</td>
<td>17</td>
</tr>
<tr>
<td>Heroin</td>
<td>27</td>
</tr>
<tr>
<td>Other opiates</td>
<td>21</td>
</tr>
<tr>
<td>Alcohol</td>
<td>19</td>
</tr>
<tr>
<td>Cocaine</td>
<td>13</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>12</td>
</tr>
<tr>
<td>Benzo diazepines</td>
<td>9</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>4</td>
</tr>
<tr>
<td>GHB</td>
<td>2</td>
</tr>
</tbody>
</table>
# Phase 3

<table>
<thead>
<tr>
<th><strong>Expected size</strong></th>
<th>200-300 subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>PTSD</td>
</tr>
<tr>
<td><strong>Research status</strong></td>
<td>Recruiting</td>
</tr>
<tr>
<td><strong>Expected completion</strong></td>
<td>January of 2020</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td><strong>15 research sites:</strong> LA, SF, Boulder, Fort Collins, New Orleans, NYC, Charleston, Madison, Boston, Montreal, Vancouver, Israel</td>
</tr>
<tr>
<td><strong>FDA status</strong></td>
<td>New Drug Application to FDA submission in 2021. Expected approval in 2022. Breakthrough Therapy on 8/16/17. Accepted special protocol assessment in 7/28/17.</td>
</tr>
</tbody>
</table>

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**LSD**
Overview

Basics: Psychopharmacology
Brief review of history in United States

Anxiety Associated with Life-Threatening Diseases

The Patient Experience

Alcoholism

Current & Future Studies

Basics

- LSD (Lysergic acid diethylamide) is a semi-synthetic compound synthesized from lysergic acid, which is found in the parasitic rye fungus, *Claviceps purpurea*

- LSD interacts with the serotonergic (5-HT), dopaminergic (DA), and glutaminergic pathways.

- The psychedelic effects of LSD are due to agonist action at 5-HT2A receptors

*Prog Brain Res.* 2018;242:69-96
History

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1938</td>
<td>First synthesized by Swiss chemist Albert Hofmann</td>
</tr>
<tr>
<td>1943</td>
<td>“Bicycle Day”</td>
</tr>
<tr>
<td>1947</td>
<td>Delysid released by Sandoz</td>
</tr>
<tr>
<td>1953</td>
<td>Sandison- Opened first LSD Clinic in England to treat ‘obsessional neuroses and generalized anxiety’</td>
</tr>
<tr>
<td>1953</td>
<td>Project MK Ultra- “Truth Drug” for Soviet Spies during Cold War</td>
</tr>
<tr>
<td>1964</td>
<td>Kast and Collins- LSD with counseling reduced anxiety, depression and pain in patients with advanced cancer</td>
</tr>
<tr>
<td>1970</td>
<td>LSD is made Schedule 1</td>
</tr>
</tbody>
</table>

Pharmacology

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical active dose</td>
<td>200μg</td>
</tr>
<tr>
<td>Onset</td>
<td>20-30 min after PO ingestion</td>
</tr>
<tr>
<td>Peak</td>
<td>3-4 hours after PO ingestion</td>
</tr>
<tr>
<td>Psychoactive duration</td>
<td>8-12 hrs</td>
</tr>
<tr>
<td>Half life</td>
<td>5 hrs</td>
</tr>
<tr>
<td>Human metabolism</td>
<td>CYP2D6 &amp; CYP3A4</td>
</tr>
</tbody>
</table>
Anxiety Associated with Life-Threatening Diseases

Safety and Efficacy of Lysergic Acid Diethylamide-Assisted Psychotherapy for Anxiety Associated With Life-threatening Diseases


Participants
- 12 adults with Life Threatening Diseases- six diagnosed with generalized anxiety disorder, seven with major depressive disorder

Design
- Randomization
  - 8 patients allocated to two sessions of psychotherapy with 200μg LSD and six non-drug psychotherapy sessions
  - 4 patients allocated to two sessions of psychotherapy with 20μg LSD and six non-drug psychotherapy sessions
    - Open label arm: Crossover allocation to two sessions of psychotherapy with 200μg LSD and six non-drug psychotherapy sessions, after 2 month follow-up
- Follow-up
  - 2 month follow up (see above for open label arm crossover)
  - 12 month follow up

Anxiety Associated with Life-Threatening Diseases

Life-Threatening Illness

- Metastatic breast carcinoma
- Metastatic gastric carcinoma
- Plasmocytoma
- Non-Hodgkin’s lymphoma
- Celiac disease
- Parkinson's disease
- Bechterew’s disease (Ankylosing spondylitis)

Psychometric Measures:

- SCID-5- independent rater for screening diagnoses
- STAI Form X (Primary Outcome Measure)

Secondary Outcome Measures

- European Cancer Quality of Life Questionnaire 30 item (EORTC-QLQ-30)
- Symptom Checklist 90 Revised (SCL-90-R)
- Hospital Anxiety and Depression Scale (HADS)
Anxiety Associated with Life-Threatening Diseases

Mean STAI State Anxiety  Mean STAI Trait Anxiety

“Tense; I am worried; I feel calm; I feel secure”

“I worry too much over something that really doesn’t matter”
“I am content; I am a steady person”

LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: A qualitative study of acute and sustained subjective effects

Gasser P, Kirchner K, Passie T

Journal of Psychopharmacology
Editors: David J Nutt and Pierre Blier

2015

J Psychopharmacol. 2015 Jan;29(1):57-68
Anxiety Associated with Life-Threatening Diseases

Goal
- Follow up study at an additional twelve months in 9 of the 12 original participants

Limitations:
- Small sample size
- No control group in comparison to the initial study

Figure 2. LTFU results of STAI state and trait scores.

J Psychopharmacol. 2015 Jan;29(1):57-68
Anxiety Associated with Life-Threatening Diseases

“The following quotes were chosen to illustrate the core elements of the subjective experiences and some of the sustained changes reported...subheadings based on the implications of the statements.”

- Facilitated Access to Emotions and Catharsis
- Deschematizing and viewing experiences in another perspective
- Changes of basic emotions during the LSD experience
- Long-term after-effects: changes in perspectives attitudes, values
- Increases in quality of life
- Comparing LSD in psychotherapy with usual psychotherapy
- Possible negative aspects of the treatment

“...it was sublime. Really. Love, expansion, holding, I knew that this sometimes happens, that participants talk about spiritual experiences. I thought they just meant this dissolution of the self- everything is okay, everything is great. That was a very important experience for me”

““It felt like when you take a glass of water and stir it with a hand full of mud. As if everything is still mixed with the water and only later on it sinks to the ground, like a sediment.”

“I believe that the amygdala is out of order. This switch, which right away judges- good or bad experience. That is simply cut out.”

“What was very important to me was that I got access to my emotions, I went relatively deep inside. I went through heaviness and sadness, but I felt all emotions very intensely”
### Paradigms of Therapy

<table>
<thead>
<tr>
<th>Psycholytic Therapy</th>
<th>Psychedelic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-Dose serial sessions in a psychoanalytic framework</td>
<td>One or two High-Dose sessions directed to mystical peak experiences to initiate a personality change</td>
</tr>
<tr>
<td>Places more emphasis on the role of the therapist, with the substance as a catalyst</td>
<td>Focused on transformational power of ‘strong experiences’</td>
</tr>
</tbody>
</table>


#### LSD for alcoholism*

<table>
<thead>
<tr>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>LSD for alcoholism: meta-analysis of randomized controlled trials</em></td>
</tr>
<tr>
<td>Krebs T, Johansen P</td>
</tr>
</tbody>
</table>

*DSM-I “well established addiction to alcohol without recognizable underlying disorder”

\[\text{J Psychopharmacol. 2012 Jul; 26(1) 994-1002}\]
LSD for alcoholism: Meta-Analysis

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Location</th>
<th>LSD (n)</th>
<th>Control (n)</th>
<th>Blinding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smart et al.</td>
<td>1966</td>
<td>Toronto, Canada</td>
<td>800 mcg (10)</td>
<td>60 mg ephedrine sulfate (10) or no drug (10)</td>
<td>Double-blind, independent assessors</td>
</tr>
<tr>
<td>Hollister et al.</td>
<td>1969</td>
<td>Palo Alto, CA</td>
<td>600 mcg (36)</td>
<td>60 mg d-amphetamine (36)</td>
<td>Double-blind, independent assessors</td>
</tr>
<tr>
<td>Ludwig et al.</td>
<td>1969</td>
<td>Madison, WI</td>
<td>3 mcg/kg (132)</td>
<td>No drug, sit alone and write for 3 hours (44)</td>
<td>Double-blind until LSD session, independent assessors</td>
</tr>
<tr>
<td>Bowen et al.</td>
<td>1970</td>
<td>Topeka, KS</td>
<td>500 mcg (22)</td>
<td>25 mcg LSD (22)</td>
<td>Double-blind, not stated if assessors independent</td>
</tr>
<tr>
<td>Pahnke et al.</td>
<td>1970</td>
<td>Baltimore, MD</td>
<td>450 mcg (73)</td>
<td>50 mcg LSD (44)</td>
<td>Double-blind, independent assessors</td>
</tr>
<tr>
<td>Tomsovic and Edwards</td>
<td>1970</td>
<td>Sheridan, WY</td>
<td>500 mcg (52)</td>
<td>Treatment as usual (45)</td>
<td>Double-blind until LSD session, self-report assessment</td>
</tr>
</tbody>
</table>

Summary of Meta-Analysis

- From these six RCTs, a single dose of LSD had a **statistically significant** beneficial effect on alcohol misuse at the first reported follow up assessment (1-12 months after discharge)
  - Treatment effect also seen at 2-3 months, and at 6 months
  - Tx effect was **not statistically significant** at 12 months post treatment
- Three RCTs reported total abstinence from alcohol use
  - Tx effect seen at first reported follow up assessment (1-3 months after discharge)
Important Considerations

- These trials typically lacked detailed descriptions of the populations studied
- Not enough trials to examine effect of LSD dose or other treatment variables
- Meta-analysis may not have been all-encompassing
- Three trials concealed that LSD was used, and others gave little information about its effects
- Low-dose LSD was used as a placebo in two trials
- Variable outcome measures

Alcoholism

Table 3. Data from recent meta-analyses of randomized controlled clinical trials on the effectiveness of LSD, naltrexone, acamprosate and disulfiram for alcoholism or alcohol dependence.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LSD, single dose</th>
<th>Naltrexone, daily</th>
<th>Acamprosate, daily</th>
<th>Disulfiram, daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benefit difference (95% CI)</td>
<td>NNT</td>
<td>Benefit difference (95% CI)</td>
<td>NNT</td>
</tr>
<tr>
<td>Improvement on alcohol misuse, or return to heavy drinking</td>
<td>16% (8%, 25%)</td>
<td>6</td>
<td>11% (7%, 15%)</td>
<td>9</td>
</tr>
<tr>
<td>Maintained abstinence, or return to any drinking</td>
<td>15% (4%, 25%)</td>
<td>7</td>
<td>3% (1%, 6%)</td>
<td>33</td>
</tr>
</tbody>
</table>

LSD outcomes are at first follow-up after single dose and are compared to no drug or active placebo. Naltrexone and acamprosate outcomes are during daily drug treatment and are compared to placebo. Disulfiram outcomes are during daily unsupervised drug treatment and are compared to other or no treatment. Data on naltrexone, acamprosate and disulfiram extracted from published meta-analyses (Rössner et al., 2010a, 2010b; Krause and Ehrenreich, 2010). Pooled benefit differences calculated using a random-effects, inverse variance method. Benefit difference = % patients with beneficial outcome in experimental – % patients with beneficial outcome in control. Number needed to treat (NNT) = 1/(benefit difference).
Studies in Progress

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Psychiatric Disorder</th>
<th>Institution</th>
<th>Sponsors</th>
<th>Phase</th>
<th>Est Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects of Hallucinogens and Other Drugs on Mood and Performance</td>
<td></td>
<td>Johns Hopkins</td>
<td>N/A</td>
<td>Phase 1</td>
<td>January 2020</td>
</tr>
<tr>
<td>Mood Effects of Serotonin Agonists</td>
<td></td>
<td>University of Chicago</td>
<td>N/A</td>
<td>Phase 1</td>
<td>May 2020</td>
</tr>
<tr>
<td>LSD Treatment in Persons Suffering From Anxiety Symptoms in Severe Somatic Diseases or in Psychiatric Anxiety Disorders</td>
<td>Anxiety Disorders</td>
<td>University Hospital, Basel, Switzerland</td>
<td>N/A</td>
<td>Phase 2</td>
<td>May 2021</td>
</tr>
</tbody>
</table>

Psilocybin
Psilocybin Service Initiative of Oregon

https://psi-2020.org/the-measure/

Balot Title

Allows manufacture, delivery, administration of psilocybin at supervised, licensed facilities; imposes two-year development period.

Result of “Yes” Vote: Allows manufacture, delivery, administration of psilocybin (psychoactive mushroom) at supervised, licensed facilities; imposes two-year development period. Creates enforcement/taxation system, advisory board, administration fund.

Result of “No” Vote: “No” vote retains current law, which prohibits manufacture, delivery, and possession of psilocybin and imposes misdemeanor or felony criminal penalties.

https://psi-2020.org/the-measure/

12 Reasons to Support the 2020 Psilocybin Service Initiative of Oregon

- Psilocybin Services are safe
- The psilocybin service modality is well-established
- Psilocybin is wrongly scheduled
- Psilocybin services can address Oregon’s mental health crisis
- The mechanism is mystical
- Psilocybin treats anxiety and depression
- Psilocybin breaks the nicotine addiction
- Psilocybin kidstarts recovery from alcoholism
- This is not Big Pharma
- PSI reduces penalties for common possession
- PSI supports personal growth
- Psilocybin engenders eco-mindedness

https://psi-2020.org/the-measure/
**Basics**

Psilocybin (3-[2-(dimethylamino)ethyl]-1H-indol-4-yl)dihydrogen phosphate) is a natural product produced by numerous species of *Psilocybe mushrooms*.

The phosphate group is enzymatically cleaved in the body to produce psilocin, an agonist at a variety of 5-HT receptors, the most important of which is the 5-HT$_{2A}$ receptor (also 5-HT$_{1A}$ and 5-HT$_{2C}$).

---

**Basics - Pharmacokinetics**

<table>
<thead>
<tr>
<th>Typical dose</th>
<th>Min to achieve effect: 4-10 mg (0.05-0.3 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recreational use: 10-50 mg</td>
</tr>
<tr>
<td></td>
<td>10-50 g of fresh mushrooms</td>
</tr>
<tr>
<td></td>
<td>1-5 g of dried mushrooms</td>
</tr>
<tr>
<td>Onset</td>
<td>10 - 40 min after PO ingestion</td>
</tr>
<tr>
<td>Peak</td>
<td>75 - 120 min after PO ingestion</td>
</tr>
<tr>
<td>Duration of psychoactive effect</td>
<td>2 - 6 hrs</td>
</tr>
<tr>
<td>Half-life</td>
<td>163 ± 64 minutes (~3 hours) oral</td>
</tr>
<tr>
<td>Human metabolism</td>
<td>Hepatic, undergoes a first-pass effect, converts to psilocin</td>
</tr>
<tr>
<td></td>
<td>Psilocin is broken down by MAO</td>
</tr>
<tr>
<td></td>
<td>Glucuronidated by UGT1A9, UGT1A10</td>
</tr>
<tr>
<td></td>
<td>Excretion: 65% in urine, 20% feces</td>
</tr>
</tbody>
</table>
History

<table>
<thead>
<tr>
<th>From the beginning of civilization</th>
<th>Used in several cultures worldwide ceremonially</th>
</tr>
</thead>
<tbody>
<tr>
<td>1957</td>
<td>Wasson describes psychedelic visions in “Seeking the Magic Mushroom,” an article published in <em>Life</em> magazine</td>
</tr>
<tr>
<td>1959</td>
<td>Albert Hoffman isolates and synthesizes psilocybin</td>
</tr>
<tr>
<td>1961</td>
<td>Sandoz launches psilocybin</td>
</tr>
<tr>
<td>1965</td>
<td>A bill outlaws the possession of “hallucinogenic drugs”</td>
</tr>
<tr>
<td>1968</td>
<td>Psilocybin is officially regulated under US federal law</td>
</tr>
<tr>
<td>1970</td>
<td>Psilocybin is made Schedule 1</td>
</tr>
</tbody>
</table>

http://beckleyfoundation.org/psychedelic-research-timeline-2/
Overview

- Obsessive-Compulsive Disorder
  - 1 pilot study
- Tobacco Use Disorder
  - 1 study + long-term follow up study
- Alcohol Use Disorder
  - 1 moderate sized study, 1 small study (n=3), same author
- Treatment-Resistant Depression
  - 2 studies, moderate sized, same authors
- Cancer-related Anxiety & Depression
  - 1 pilot study, 2 moderate sized studies from different institutions

Obsessive-Compulsive Disorder

2006

Safety, tolerability and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder

Moreno FA, Wiegand CB, Taitano EK, Delgado PL

Funding:
MAPS, Heffter Research Institute, Nathan Cummings Foundation
### Participants
- 9 adults with OCD (2 women)
- No other psychiatric illness

### Design
- **Proof-of-concept, phase I study, modified blind**
- Subjects received up to 4 different doses, at least 1 week apart
  - **Placebo:** 0.025 mg/kg of psilocybin (very low dose)
  - **Treatment:** 0.1 mg/kg, 0.2 mg/kg, and 0.3 mg/kg of psilocybin

### Assessment Measures
- **Primary outcomes:**
  - Yale-Brown Obsessive Compulsive Scale (YBOCS)
  - Visual analog scale (VAS)
- **Secondary outcomes:** The Hallucinogen Rating Scale (HRS)

### Assessment Frequency
- Immediately before ingestion (baseline)
- 4, 8, and 24 hours post-ingestion

---

![Graph showing the change in mean YBOCS scores over time](image1)

---

![Graph showing the change in mean YBOCS scores for all subjects](image2)
Take Away Points

- Small sample size (9 patients)
- Open-label design, lack of control condition
- **Limited conclusions** can be drawn about treatment efficacy
- Modest, transient improvements in YBOCS over 24 hours, no long-term data
- Minimal side effects, treatment well tolerated in this **controlled setting**
- Safety and efficacy outcomes continue to support the case for **further research**

Tobacco Use Disorder

<table>
<thead>
<tr>
<th>Year</th>
<th>Journal</th>
<th>Title</th>
<th>N</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td><em>The American Journal of Drug and Alcohol Abuse</em></td>
<td>Long-term Follow-up of Psilocybin-facilitated Smoking Cessation</td>
<td>15</td>
<td>Johns Hopkins University</td>
</tr>
</tbody>
</table>
Tobacco Use Disorder

Pilot study of the 5-HT₂A agonist psilocybin in the treatment of tobacco addiction

Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR

2014

Participants
- 15 participants (5 women, 93% white, 7% Asian) who smoke at least 10 cigarettes a day

Design
- Open-label pilot study
- 15-week course with psilocybin administration occurring in weeks 5, 7, and 13
- 4 weekly preparation meetings, participants received smoking cessation CBT based on Quit for Life
- Two oral doses of psilocybin 7 weeks apart in a supportive setting
  - Moderate dose (20 mg/70 kg) on week 5
  - High dose (30 mg/70 kg) on week 7 and 13 (week 13 optional, could elect to take moderate dose)

Assessment Measures
- Primary outcomes:
  - Timeline follow-back, Fagerstrom Test for Cigarette Dependence, Breath CO, Urine cotinine, Questionnaire on Smoking Urges, Smoking Abstinence Self-efficacy Scale, WI Smoking Withdrawal Scale
- Secondary outcomes:
  - Visual Effects Questionnaire, Post-session Headache Interview, Mysticism Scale, States of Consciousness Questionnaire, Persisting Effects Questionnaire

Assessment Frequency
- Intake, weeks 2-15, 6-month follow-up

Funding:
Beckley Foundation, Heffter Research Institute, NIH grant T32DA07209

6-month follow-up:
12 of 15 (80%) participants were smoking abstinent

12-month follow-up:
10 of 15 (67%) participants were smoking abstinent

Long-term* follow-up:
9 of 15 (60%) participants were smoking abstinent

*(mean 30 months post-TQD; range = 16–57 months)

Take Away Points

- Small sample size (15 patients), homogenous population
- Open-label design, lack of control condition
- **Limited conclusions** can be drawn about treatment efficacy
- Minimal side effects, treatment well tolerated in this **controlled setting**
- Safety and efficacy outcomes continue to support the case for **further research**

Alcohol Use Disorder

**2015**

*Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study*

Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PCR, Strassman RJ

Funding: Hefftter Research Institute, NIH Grant 1UL1RR031977

---

**2018**

*Clinical Interpretations of Patient Experience in a Trial of Psilocybin-Assisted Psychotherapy for Alcohol Use Disorder*

---

<table>
<thead>
<tr>
<th>Year</th>
<th>Journal</th>
<th>Title</th>
<th>N</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>Journal of Psychopharmacology</td>
<td>Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study</td>
<td>10</td>
<td>UNM</td>
</tr>
<tr>
<td>2018</td>
<td>frontiers in Pharmacology</td>
<td>Clinical Interpretations of Patient Experience in a Trial of Psilocybin-Assisted Psychotherapy for Alcohol Use Disorder</td>
<td>3</td>
<td>NYU</td>
</tr>
</tbody>
</table>
## Participants
- Ten volunteers with DSM-IV severe alcohol dependence
- Four women, six men; two Native, one AA, four Hispanic, three white

## Design
- Single-group proof-of-concept study
- Open-label design, lack of control condition or blinding
- 1 or 2 psilocybin sessions
- Motivational Enhancement Therapy

## Assessment Measures
- Vital signs
- **Primary outcomes:**
  - Time-Line Follow-Back, BAC at each visit

## Assessment Frequency
- Weekly up to 36 weeks

---

**Percent heavy drinking days and percent drinking days:**
Significantly lower than baseline at all follow-up points. Significantly decreased relative to weeks 1–4 except heavy drinking days during weeks 9–12 (p = 0.059).
Take Away Points

- Small sample size (10 patients)
- Open-label design, lack of control condition or blinding
- Lack of biological verification of alcohol use
- Promising data but not possible to separate unequivocally the effects of attention, psychosocial treatment, and time
- Minimal side effects, treatment well tolerated in this controlled setting
- Safety and efficacy outcomes continue to support the case for further research

Bogenschutz MP et al. J Psychopharmacol Jan 2015 29:3 1-11

---

Treatment Resistant Depression

<table>
<thead>
<tr>
<th>Year</th>
<th>Journal</th>
<th>Title</th>
<th>N</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>THE LANCET Psychiatry</td>
<td>Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study</td>
<td>12</td>
<td>Imperial College London</td>
</tr>
<tr>
<td>2018</td>
<td>Psychopharmacology</td>
<td>Psilocybin with psychological support for treatment-resistant depression: six-month follow-up</td>
<td>20</td>
<td>Imperial College London</td>
</tr>
</tbody>
</table>
Psilocybin with psychological support for treatment-resistant depression: six-month follow-up


Funding:
UK Medical Research Council Grant MR/J00460X/1, Alex Mosley Charitable Trust

Participants
- 20 patients (6 women, 15 white, 3 black, 1 Asian, 1 Hispanic)
- Dx: moderate-to-severe, unipolar, treatment-resistant major depression

Design
- Open-label feasibility trial, no control group
- Two oral doses of psilocybin 7 days apart in a supportive setting
  - 10 mg (safety dose)
  - 25 mg (treatment dose) 7 days later

Assessment Measures
- Vital signs
- Post treatment fMRI
- Primary outcomes:
  - Quick Inventory of Depressive Symptoms (QIDS), Beck Depression Inventory (BDI), Montgomery-Åsberg Depression Rating Scale (MADRS), HAM-D
- Secondary outcomes:
  - Global Assessment of Functioning (GAF), State-Trait Anxiety Inventory (STAI-T), Snaith-Hamilton Pleasure Scale (SHAPS)

Assessment Frequency
- Immediately after study enrollment (baseline)
- 1 week, 2 week, 3 week, 5 week, 3 months, 6 months
At 5 weeks:
9 patients met criteria for **response**; 5 patients met criteria for **remission**

**Take Away Points**

- Small sample size (20 patients), homogenous population
- Open-label design, lack of control condition
- **Limited conclusions** can be drawn about treatment efficacy
- Treating MDD with psilocybin plus psychological support is feasible
- Treatment was generally well tolerated in this **controlled setting**
- Safety and efficacy outcomes continue to support the case for **further research**
Cancer Related Anxiety & Depression

<table>
<thead>
<tr>
<th>Year</th>
<th>Journal</th>
<th>Title</th>
<th>N</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>JAMA Psychiatry</td>
<td>Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer</td>
<td>12</td>
<td>Harbor-UCLA Medical Center</td>
</tr>
</tbody>
</table>

Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, Cosimano MP, Klinedinst MA

Funding:
Heffter Research Institute, RiverStyx Foundation, Betsy Gordon Foundation, McCormick Family, Fetzer Institute, NIH Grant RO1DA03889
### Participants
- 51 adults with advanced-stage cancer and anxiety (49% female, 94% white, 4% AA, 2% Asian)
- Breast (13), upper aerodigestive (7), GI (4), GU (18), hematologic (8), other (1)

### Design
- Double-blind, placebo-controlled, cross-over (subjects served as own control)
- 2 experimental treatment sessions weeks apart
  - Psilocybin: 0.31 mg /kg (initially .43 mg/kg)
  - Placebo: 0.014 mg/kg of psilocybin (initially 0.042 mg/kg)

### Assessment Measures
- Vital signs
- **Primary outcomes:**
  - Depression: GRID-HAM-D-17
  - Anxiety: HAM-A
- **Secondary outcomes:** BDI, HADS, STAI, POMS, BSI, MQOL, LAP-R

### Assessment Frequency
- Immediately after study enrollment (baseline)
- On both session days (at the end of the session)
- Approximately 5 weeks after each session and 6 months after session 2

---

Collapsing across the two dose sequence groups:

- the overall rate of clinical response at 6 months **78%** for depression
- the overall rate of symptom remission at 6 months **65%** for depression

---

![Graph showing clinical significant response and remission to normal range](image)
Take Away Points

- Relatively small sample (n = 51), highly educated and predominately white
- Randomized, controlled with low dose psilocybin, double blinded
- Significant decreases in measures of depression, anxiety, & increases in quality of life, life meaning, death acceptance, and optimism sustained at 6 months
- Treatment was generally well tolerated in this controlled setting
- Safety and efficacy outcomes continue to support the case for further research

Side Effects & Tolerability

- Adverse effects associated with psilocybin reported in these studies:
  - Modest acute increases in blood pressure and heart rate
  - Dysphoric subjective effects (e.g. anxiety, fear; typically <7 hours)
  - Headaches (typically <24 hours)
  - Transient paranoia or referential ideas
  - Transient nausea
## On the Horizon

### Studies in Progress

<table>
<thead>
<tr>
<th>Study Title</th>
<th>Psychiatric Disorder</th>
<th>Institution</th>
<th>Sponsors</th>
<th>Phase</th>
<th>Est Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psilocybin Cancer Anxiety Study</td>
<td>Cancer-induced anxiety disorder</td>
<td>New York University School of Medicine</td>
<td>N/A</td>
<td>Phase 2</td>
<td>June 2019</td>
</tr>
<tr>
<td>Psilocybin-facilitated Treatment for Cocaine Use</td>
<td>Cocaine use disorder</td>
<td>University of Alabama at Birmingham</td>
<td>N/A</td>
<td>Phase 2</td>
<td>December 2019</td>
</tr>
<tr>
<td>Psilocybin-assisted Group Therapy for Demoralization in Long-term AIDS Survivors</td>
<td>Depression, grief</td>
<td>University of California, San Francisco</td>
<td>Heffter Research Institute, River Styx Foundation, Usona Institute, Stupski Foundation</td>
<td>Phase 1</td>
<td>December 2019</td>
</tr>
<tr>
<td>Effects of Psilocybin in Major Depressive Disorder</td>
<td>Major depressive disorder</td>
<td>Johns Hopkins Bayview Medical Center</td>
<td>N/A</td>
<td>Phase 1</td>
<td>December 2020</td>
</tr>
<tr>
<td>Psilocybin for Treatment of Obsessive Compulsive Disorder</td>
<td>Obsessive-compulsive disorder</td>
<td>University of Arizona</td>
<td>Beckley Foundation, Heffter Research Institute</td>
<td>Phase 2</td>
<td>July 2021</td>
</tr>
<tr>
<td>Psilocybin-facilitated Smoking Cessation Treatment: A Pilot Study</td>
<td>Tobacco use disorder</td>
<td>Johns Hopkins University</td>
<td>Heffter Research Institute</td>
<td>Phase 1</td>
<td>December 2021</td>
</tr>
<tr>
<td>Efficacy of Psilocybin in OCD: a Double-Blind, Placebo-Controlled Study</td>
<td>Obsessive-compulsive disorder</td>
<td>Yale University</td>
<td>Heffter Research Institute</td>
<td>Phase 2</td>
<td>July 2022</td>
</tr>
<tr>
<td>Psilocybin - Induced Neuroplasticity in the Treatment of Major Depressive Disorder</td>
<td>Major depressive disorder</td>
<td>VA Connecticut Healthcare System (Yale University)</td>
<td>Heffter Research Institute</td>
<td>Phase 1</td>
<td>April 2023</td>
</tr>
</tbody>
</table>
In Development

**U.S. FOOD & DRUG ADMINISTRATION**

COMPASS Pathways Receives FDA Breakthrough Therapy Designation for Psilocybin Therapy for Treatment-resistant Depression

October 23, 2018

**MECHANISM OF PSYCHEDELIC ADDICTION TREATMENT** | $750,000
Identification of the mechanisms that make psilocybin effective in treating addiction.

**LSD & ALCOHOL DEPENDENCY** | $850,000
Research on the impact that LSD can have on improving addiction treatments.

**MOMA VS PSilocybin THERAPEUTICS** | $350,000
Study evaluating the similarities and differences between NMMA and psilocybin therapies.

**EMOTION, CREATIVITY & COGNITION** | $400,000
Research on psilocybin enhancing creativity and cognition.

**PSilocybin GROUP THERAPY PROCESS** | $350,000
Examination of psilocybin group therapy process and outcomes.

**Psychotherapist Education WITH Psilocybin** | $50,000
Educational training workshop on the psilocybin experience for psychotherapists.

**SPIRITUAL VS NON-SPRITUAL** | $200,000
Study of psilocybin effects in “spiritually-oriented” vs “non-spiritually-oriented” volunteers.

**Psilocybin VS Mushrooms** | $350,000
Comparison of chemically synthesized psilocybin with psilocybin naturally occurring in mushrooms.

**SSRI-Psilocybin INTERACTION** | $500,000
Study on how psilocybin interacts with an SSRI antidepressant.

**LSD MICRODOSEING** | $500,000
Study measuring and characterizing the cognitive and psychological impact of microdosing.
Limitations & Considerations

- **Study design:**
  - Open-label, feasibility, proof-of-concept, phase 1 trials
  - Small sample sizes
  - Inherent difficulties with blinding, choosing placebo with psychedelics

- **Access to treatment / equity / ethics:**
  - Cost of psychedelic psychotherapy
  - Demographics of research subjects in current body of evidence
  - Equitable access to psychedelic psychotherapy

- **In your practice:**
  - Patients requesting referrals, underground practice
  - Patients using these substances recreationally, unsupervised
References - MDMA


Carhart-Harris RL, et al. (2015). The effects of acutely administered 3,4-methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers measured with arterial spin labeling and blood oxygen level-dependent functional magnetic resonance imaging. Biol Psychiatry. 2150-2158


References - Psilocybin


Clinicaltrials.gov

References - LSD


Discussion