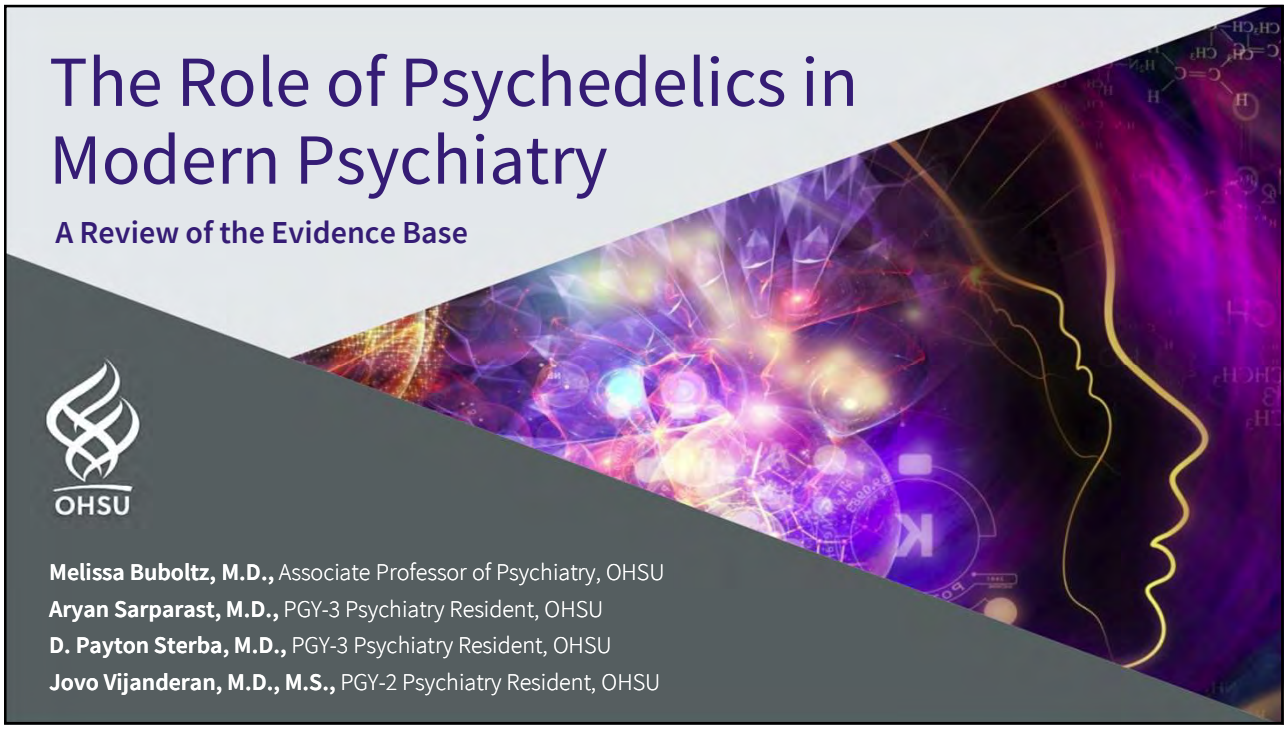
The Role of Psychedelics in Modern Psychiatry

A Review of the Evidence Base



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D. Payton Sterba, M.D., PGY-3 Psychiatry Resident, OHSU
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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.

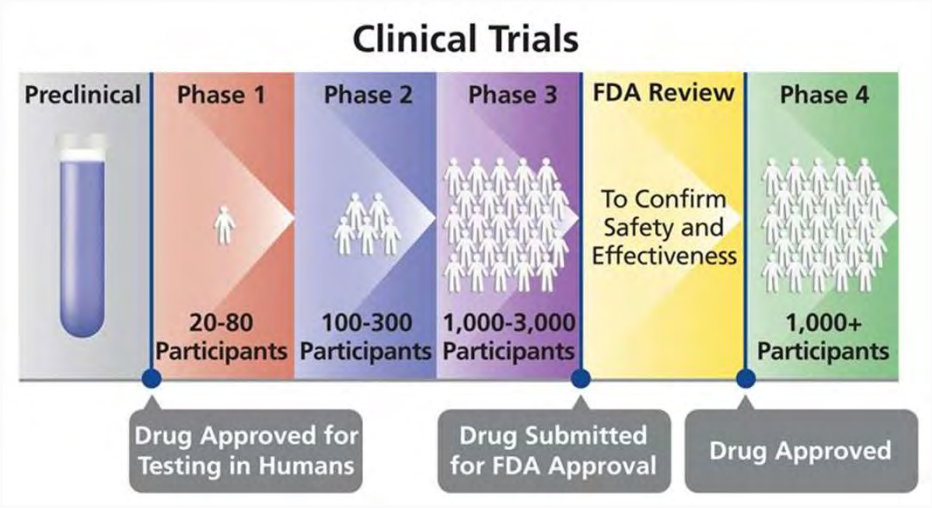
Schedule II
high potential for abuse, with use potentially leading to severe psychological or physical dependence. These drugs are also considered dangerous

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

https://www.fda.gov/ForPatients/Approvals/Fast/default.htm

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

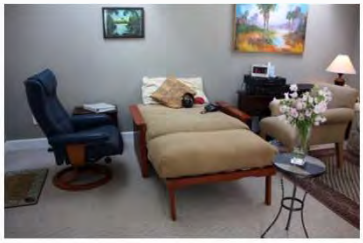
Basics of MDMA

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?



Overview

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Phase 3?

A Brief "Trip" Through Time

1912	Anton Köllisch attempts to synthesize Hydrastinin, ends up with MDMA instead
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

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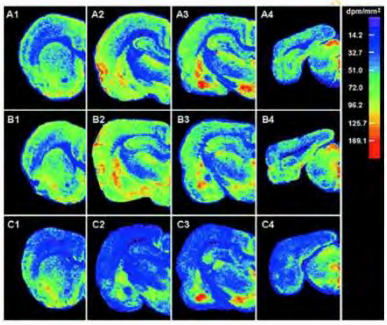
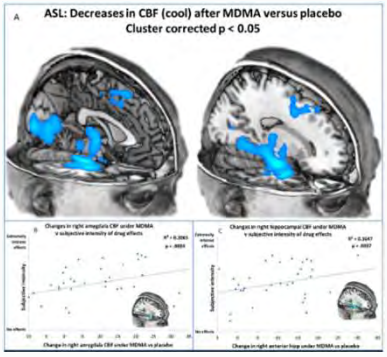
Typical dose	• 75 - 120mg; ~2 mg/kg
Onset	• 30 - 60 min after PO ingestion
Peak	• 75 - 120 min after PO ingestion
Duration of psychoactive effect	• 3 - 6 hrs
Half-life	• 8 - 9 hrs
Human metabolism	• CYP2D6

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

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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

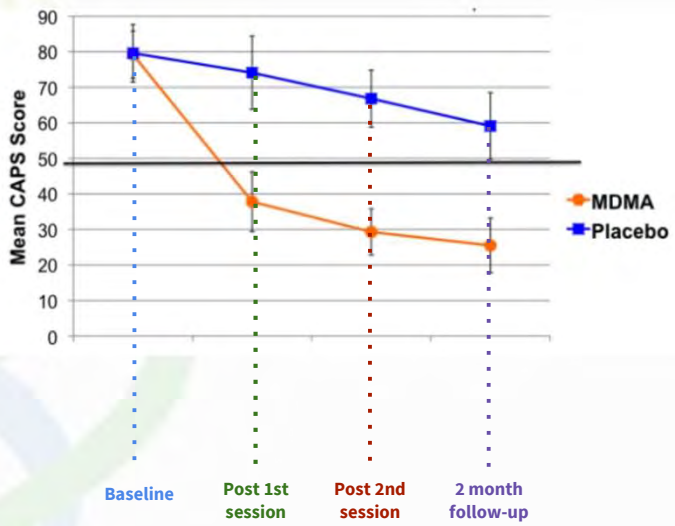
Funding:
MAPS

stage 1 double blind → Initial baseline data collection → Intro therapy sessions (2) → experimental session → repeat data collection → Integration sessions (weekly) → repeat cycle for 2nd experimental session

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

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

Subjects	• **n = 16** had fully completed follow-up data collection
Duration of Follow Up	• 17-74 months; **mean of 45.4 months after last experimental session**
Substance Use	• **Unchanged from data from original study**; 8 have used cannabis, 1 had used psilocybin, 1 used 'Ecstasy' to re-create therapeutic setting
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

Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome I, Wagner M, Wymer J, Holland J, Hamilton S, Yazar-Klosinski B, Emerson A, Doblin R

Funding:
MAPS

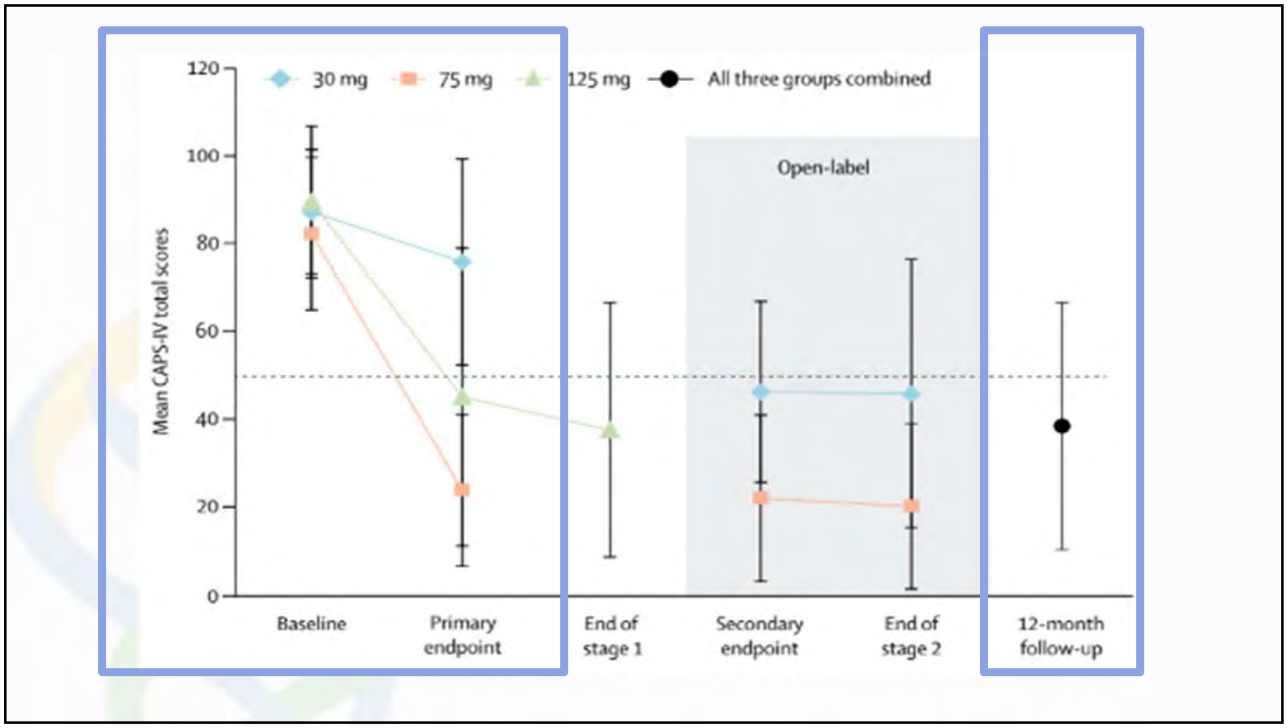
stage 1 double blind → Initial baseline data collection → Intro therapy sessions (3) → experimental session → repeat data collection → Integration sessions (weekly) → repeat cycle for 2nd experimental session

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)

stage 2: open label | blind broken | Intro therapy session | experimental session | Integration sessions (weekly) | repeat cycle for 2nd open-label session | secondary endpoint | 3rd open-label session

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)



Are the results replicable?
MAPS preps 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

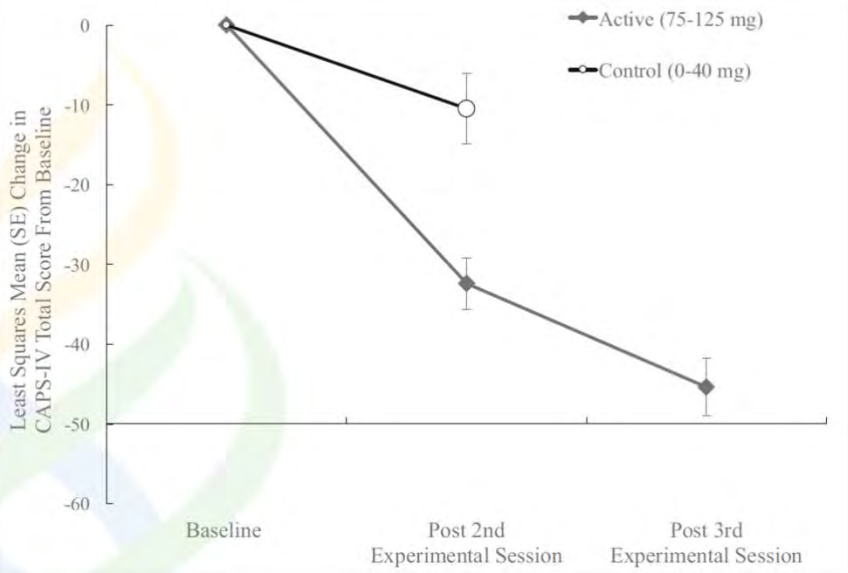
Mithoefer MC, Feduccia AA, Jerome I, Mithoefer AT, Wagner M, Walsh Z, Hamilton S, Yazar-Klosinski B, Emerson A, Doblin R

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

Psychopharmacology (2019) 236:2735–2745



frontiers in Psychiatry

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Breakthrough for Trauma Treatment: Safety and Efficacy of MDMA-Assisted Psychotherapy Compared to Paroxetine and Sertraline

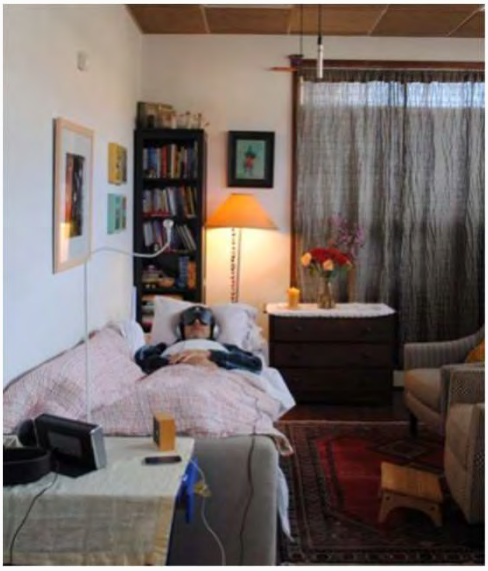
Feduccia AA, Jerome L, Mithoefer MC, Yazar-Klosinski B, Emerson A, Doblin R

	Sertraline		Paroxetine		MDMA	
	CAPS-2 (sertraline–placebo)[a]	Dropout %	CAPS-2 (paroxetine–placebo)[a]	Dropout %	CAPS-IV (MDMA–control)[b]	Dropout %
Study 1	–6.8 (effect size 0.31)	29.3%	–14 (effect size 0.56)	35.5%	–26.2 (effect size 0.9)	7.6%
Study 2	–9.8 (effect size 0.37)	28.4%	–11 (effect size 0.45)	39.0%	—	
Study 3	—		–6 (effect size 0.09)	33.0%	—	

[a]*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.*
[b]*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		
Reaction	**Mean % for placebo (n=57)**	**Mean % for MDMA (n=174)**
Lack of appetite	2%	68%
Dry mouth	N/A	64%
Jaw clenching	0%	60%
Difficulty concentrating	16%	53%
Thirst	4%	48%
Restlessness	0%	46%
Restless legs	0%	45%
Dizziness	2%	43%
Feeling cold	4%	43%
Perspiration	0%	40%
Palpitations	0%	37%



When is MDMA **BAD 4 U** ?

Unreliable doses
Uncontrolled settings
Underlying co-morbidities
Unknown quality

Table 2. Ecstasy-related fatalities in England and Wales (August 1996–April 2002): psychoactive substances implicated in death together with ecstasy[a]

Psychoactive compounds	Frequency of cases (%)
No other drugs	17
Heroin	27
Other opiates	21
Alcohol	19
Cocaine	13
Amphetamines	12
Benzodiazepines	9
Cannabinoids	4
GHB	2

Phase 3

Expected size	200-300 subjects
Population	PTSD
Research status	Recruiting
Expected completion	January of 2020
Location	**15 research sites:** LA, SF, Boulder, Fort Collins, New Orleans, NYC, Charleston, Madison, Boston, Montreal, Vancouver, Israel
FDA status	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
How to enroll in research	**clinicaltrials.gov**, search "A Multi-Site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD", identifier number **NCT03537014** https://clinicaltrials.gov/ct2/show/NCT03537014

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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

$C_{20}H_{25}N_3O$

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**

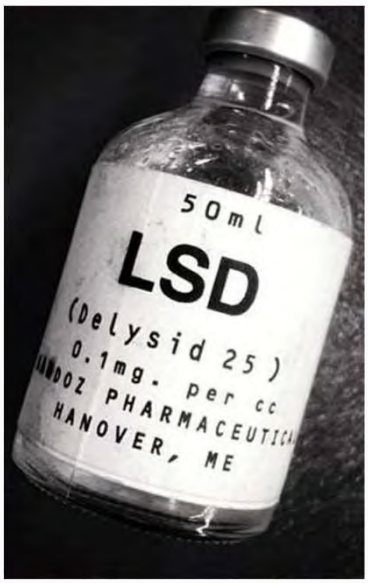
Prog Brain Res. 2018;242:69-96
CNS Neurosci Ther. 2008 Winter;14(4):295-314

History

1938	First synthesized by Swiss chemist Albert Hofmann
1943	"Bicycle Day" 
1947	*Delysid* released by Sandoz
1953	*Sandison*- Opened first LSD Clinic in England to treat 'obsessional neuroses and generalized anxiety'
1953	Project MK Ultra- "Truth Drug" for Soviet Spies during Cold War
1964	*Kast and Collins*- LSD with counseling reduced anxiety, depression and pain in patients with advanced cancer
1970	LSD is made Schedule 1

Pharmacology

Typical active dose	200µg
Onset	20-30 min after PO ingestion
Peak	3-4 hours after PO ingestion
Psychoactive duration	8-12 hrs
Half life	5 hrs
Human metabolism	CYP2D6 & CYP3A4



Anxiety Associated with Life-Threatening Diseases

The Journal of NERVOUS AND MENTAL DISEASE

2014

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

Gasser P, Holstein D, Michel Y, Doblin R, Yazar-Klosinski B, Passie T, Brenneisen R

J Nerv Ment Dis. 2014 Jul;202(7):513-20

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

J Nerv Ment Dis. 2014 Jul;202(7):513-20

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)

J Nerv Ment Dis. 2014 Jul;202(7):513-20

Anxiety Associated with Life-Threatening Diseases

Psychometric Measures:

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

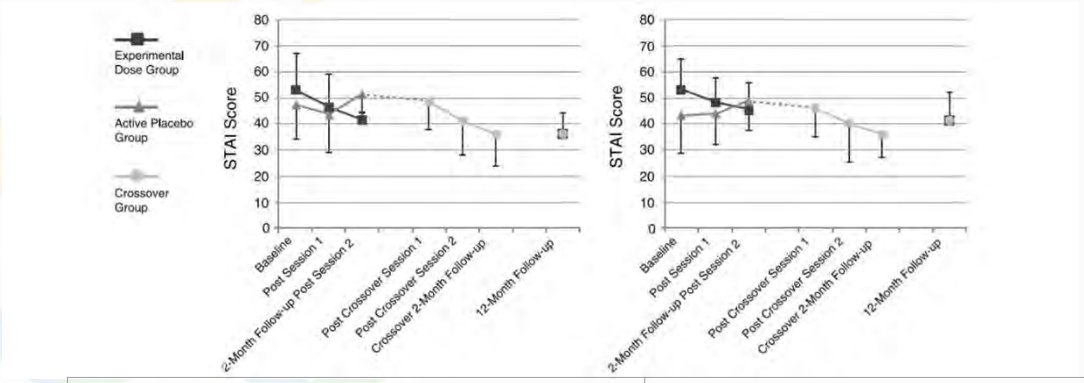
Secondary Outcome Measures

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

J Nerv Ment Dis. 2014 Jul;202(7):513-20

Anxiety Associated with Life-Threatening Diseases

Mean STAI State Anxiety **Mean STAI Trait Anxiety**



"I am 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"

J Nerv Ment Dis. 2014 Jul;202(7):513-20

Anxiety Associated with Life-Threatening Diseases

Journal of Psychopharmacology
Editors: David J Nutt and Pierre Blier

2015

*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

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

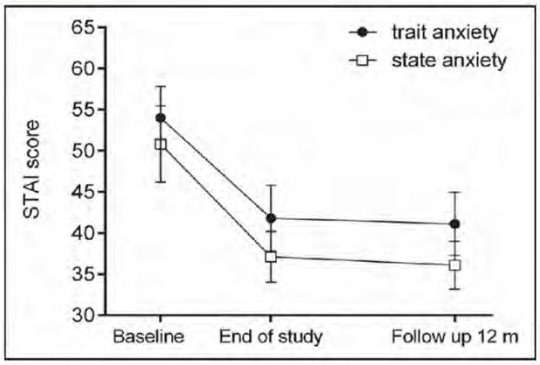


Figure 2. LTFU results of STAI state and trait scores.

Limitations:

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

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

J Psychopharmacol. 2015 Jan;29(1):57-68

"The things you normally consider as reality **are just not as they seem to be**"

"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."

"In usual psychotherapy, it is mainly about talking, about words. in lsd-assisted psychotherapy it is mainly about inner processes, inner change, inner experience- **it gets enriched by it**"

"...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"**

"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

Psycholytic Therapy	Psychedelic Therapy
Low-Dose serial sessions in a psychoanalytic framework	One or two High-Dose sessions directed to mystical peak experiences to initiate a personality change
Places more emphasis on the role of the therapist, with the substance as a catalyst	Focused on transformational power of 'strong experiences'

Grof, Stanislav (1976). *Realms of the Unconscious: Observations from LSD Research*. New York: Viking Press.

LSD for alcoholism*

Journal of Psychopharmacology
Editors: David J Nutt and Pierre Blier

2012

LSD for alcoholism: meta-analysis of randomized controlled trials

Krebs T, Johansen P

J Psychopharmacol. 2012 Jul; 26(1) 994-1002

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

LSD for alcoholism: Meta-Analysis

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

J Psychopharmacol. 2012 Jul; 26(1) 994-1002

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)

J Psychopharmacol. 2012 Jul; 26(1) 994-1002

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

J Psychopharmacol. 2012 Jul; 26(1) 994-1002

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.

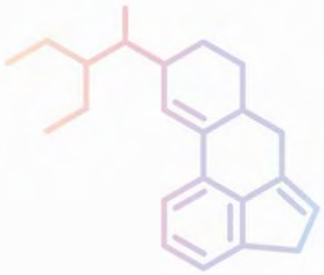
Outcome	LSD, single dose		Naltrexone, daily		Acamprosate, daily		Disulfiram, daily	
	Benefit difference (95% CI)	NNT	Benefit difference (95% CI)	NNT	Benefit difference (95% CI)	NNT	Benefit difference (95% CI)	NNT
Improvement on alcohol misuse, or return to heavy drinking	16% (8%, 25%)	6	11% (7%, 15%)	9	1% (-2%, 5%)	100	Not reported	
Maintained abstinence, or return to any drinking	15% (4%, 25%)	7	3% (1%, 6%)	33	11% (7%, 15%)	9	11% (-1%, 22%)	9

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 (Rösner et al., 2010a, 2010b; Krampe 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).

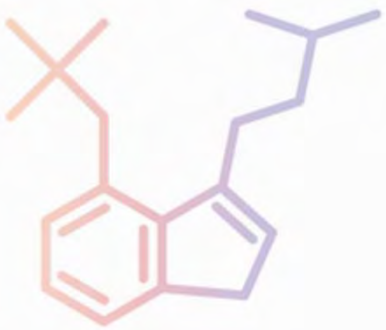
J Psychopharmacol. 2012 Jul; 26(1) 994-1002

Studies in Progress

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



Psilocybin



Psi

Certified by Attorney General on September 5, 2019.
/s/ Shannon T. Reel
Assistant Attorney General

BALLOT 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.

SECRETARY OF STATE

OHSU

2020

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

12 REASONS TO SUPPORT THE 2020 PSILOCYBIN SERVICE INITIATIVE OF OREGON

click any reason to toggle more information

- 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 kickstarts recovery from alcoholism
- This is not Big Pharma
- PSI reduces penalties for common possession
- PSI supports personal growth
- Psilocybin engenders eco-mindedness

OHSU

PSI 2020

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

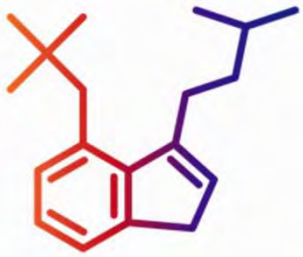
Basics

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$_{2C}$)

Psilocybe semilanceata

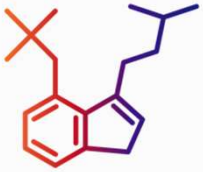
Psilocybe cyanescens



Basics - Pharmacokinetics

Typical dose	• *Min to achieve effect:* **4-10 mg**, (0.05-0.3 mg/kg)
	• *Recreational use:* **10-50 mg**
	  ○ 10-50 g of fresh mushrooms
	  ○ 1-5 g of dried mushrooms

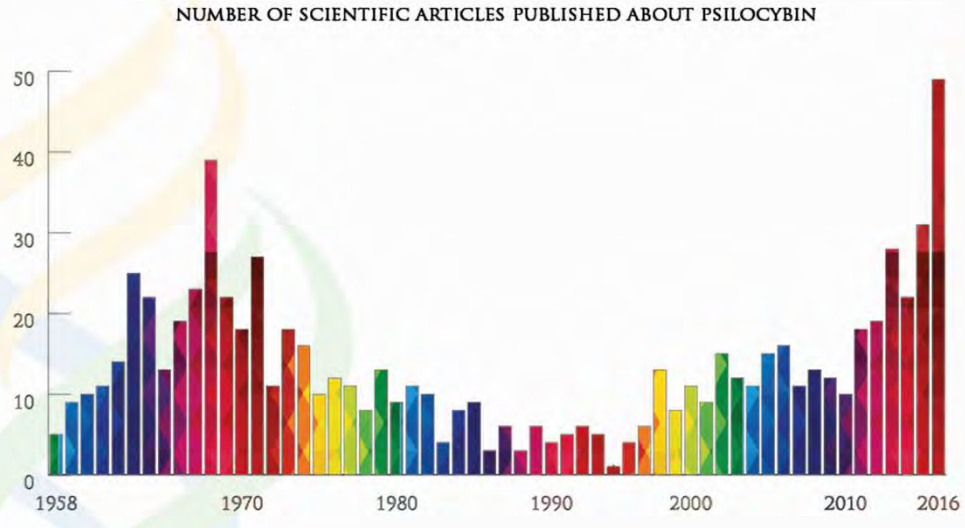
Onset	• 10 - 40 min after PO ingestion
Peak	• 75 - 120 min after PO ingestion
Duration of psychoactive effect	• 2 - 6 hrs
Half-life	• 163 ∓ 64 minutes (~3 hours) oral
Human metabolism	• Hepatic, undergoes a first-pass effect, converts to **psilocin** • Psilocin is broken down by **MAO** • Glucuronidated by UGT1A9, UGT1A10 • Excretion: 65% in urine, 20% feces



History

From the beginning of civilization	Used in several cultures worldwide ceremonially
1957	Wasson describes psychedelic visions in "Seeking the Magic Mushroom," an article published in *Life* magazine
1959	Albert Hoffman isolates and synthesizes psilocybin
1961	Sandoz launches psilocybin
1965	A bill outlaws the possession of "hallucinogenic drugs"
1968	Psilocybin is officially regulated under US federal law
1970	Psilocybin is made Schedule 1

History



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

Imperial College London
The University of Arizona
Johns Hopkins University
NYU
UNM
Harbor-UCLA Medical Center

Obsessive-Compulsive Disorder

OHSU

The Journal of Clinical Psychiatry

2006

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

Moreno FA, Wiegand CB, Taitano EK, Delgado PL

The University of Arizona

Funding:
MAPS, Heffter Research Institute, Nathan Cummings Foundation

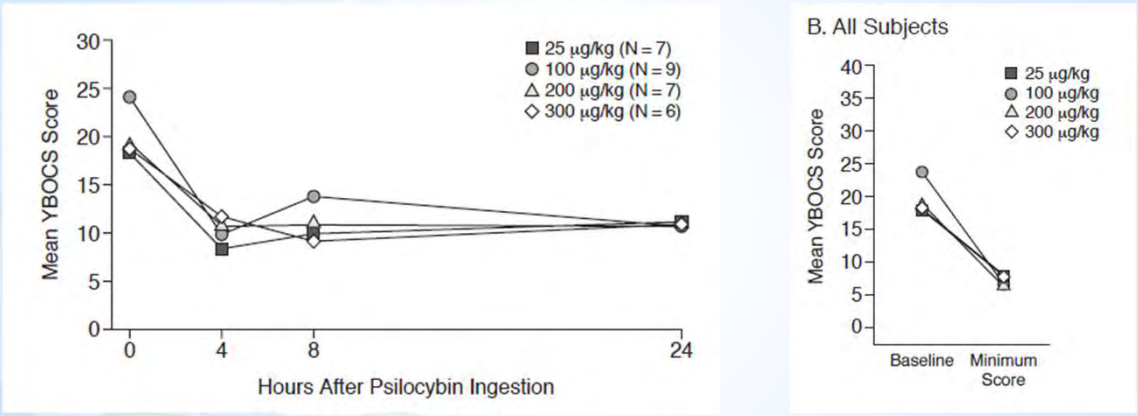
Participants	• **9 adults** with OCD (2 women) • No other psychiatric illness

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

Moreno FA et al. *J Clin Psychi* 2006 67: 1735-1740



Moreno FA et al. *J Clin Psychi* 2006 67: 1735-1740

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**

Moreno FA et al. *J Clin Psychi* 2006 67: 1735-1740

Tobacco Use Disorder

Year	Journal	Title	N	Institution
2014	Journal of Psychopharmacology Editors: David J Nutt and Pierre Blier	Pilot study of the 5-HT_{2A}R agonist psilocybin in the treatment of tobacco addiction	15	Johns Hopkins University
2017	The American Journal of Drug and Alcohol Abuse	Long-term Follow-up of Psilocybin-facilitated Smoking Cessation	15	Johns Hopkins University

Tobacco Use Disorder

Journal of Psychopharmacology
Editors: David J Nutt and Pierre Blier

2014

Pilot study of the 5-HT$_{2A}$R agonist psilocybin in the treatment of tobacco addiction

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

JOHNS HOPKINS UNIVERSITY

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

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

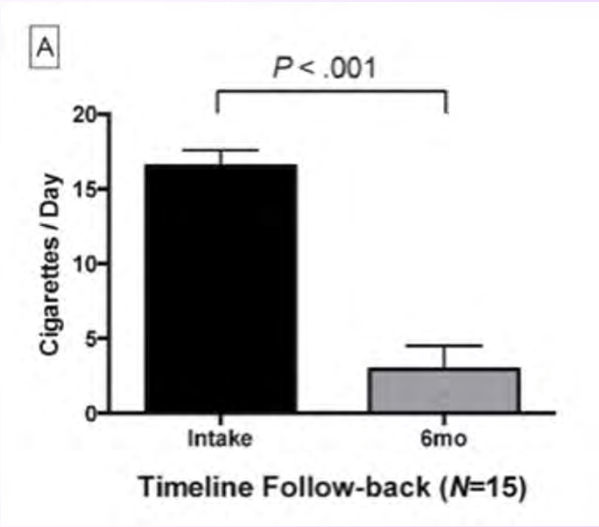
Johnson MW et al. *J Psychopharmacol* Sep 2014 28:11 983– 992

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)*



Johnson MW et al.

J Psychopharmacol Sep 2014 28:11 983– 992. *Am J Drug Alcohol Abuse* Jan 2017 43(1): 55–60.

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**

J Psychopharmacol Sep 2014 28:11 983– 992. *Am J Drug Alcohol Abuse* Jan 2017 43(1): 55–60.

Johnson MW et al.

Alcohol Use Disorder

Year	Journal	Title	N	Institution
2015	Journal of Psychopharmacology Editors: David J Nutt and Pierre Blier	Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study	10	UNM
2018	frontiers in Pharmacology	Clinical Interpretations of Patient Experience in a Trial of Psilocybin-Assisted Psychotherapy for Alcohol Use Disorder	3	NYU

Alcohol Use Disorder

Journal of Psychopharmacology
Editors: David J Nutt and Pierre Blier

2015

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

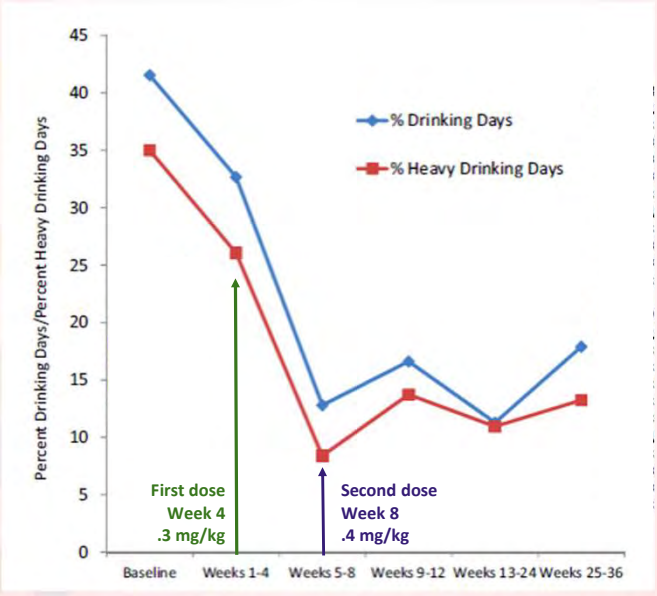
Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PCR, Strassman RJ

Funding:
Heffter Research Institute, NIH Grant 1UL1RRo31977

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

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

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).**



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

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

Year	Journal	Title	N	Institution
2016	THE LANCET Psychiatry	Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study	12	Imperial College London
2018	Psycho-pharmacology	Psilocybin with psychological support for treatment-resistant depression: six-month follow-up	20	Imperial College London

Treatment Resistant Depression

2018

Psilocybin with psychological support for treatment-resistant depression: six-month follow-up

Carhart-Harris RL, Bolstridge M, Day CMJ, Rucker J, Watts R, Erritzoe DE, Kaelen M, Giribaldi B, Bloomfield M, Pilling S, Rickard JA, Forbes B, Feilding A, Taylor D, Curran HV, Nutt DJ

Imperial College London

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

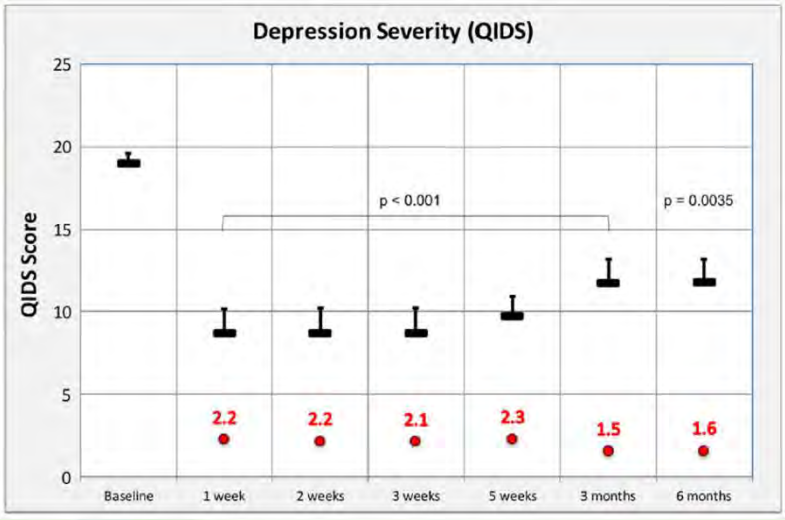
Design	• **Open-label feasibility trial,** no control group
	• Two oral doses of psilocybin 7 days apart in a supportive setting
	  ○ **10 mg (safety dose)**
	  ○ **25 mg (treatment dose) 7 days later**

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

Carhart-Harris RL et al. *Psychopharmacology (Berl).* 2018 Feb;235(2):399-408

At 5 weeks:
9 patients met criteria for **response**; 5 patients met criteria for **remission**



Carhart-Harris RL et al. *Psychopharmacology (Berl).* 2018 Feb;235(2):399-408

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**

Carhart-Harris RL et al. *Psychopharmacology (Berl).* 2018 Feb;235(2):399-408

Cancer Related Anxiety & Depression

Year	Journal	Title	N	Institution
2011	JAMA Psychiatry	Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer	12	Harbor-UCLA Medical Center
2016	Journal of Psychopharmacology Editors: David J Nutt and Pierre Blier	Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: Randomized double-blind trial	51	Johns Hopkins University
2016	Journal of Psychopharmacology Editors: David J Nutt and Pierre Blier	Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a RCT	29	NYU

Cancer Related Anxiety & Depression

Journal of Psychopharmacology
Editors: David J Nutt and Pierre Blier

2016

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

Johns Hopkins University

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)

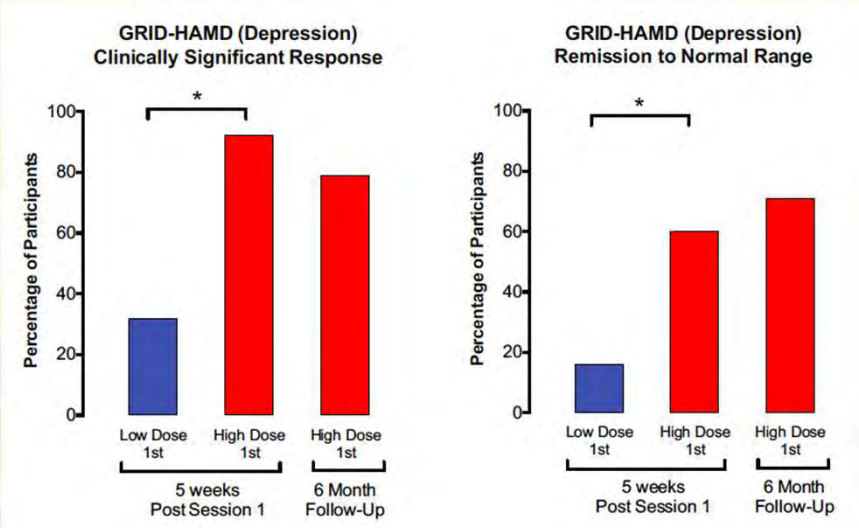
Design	• **Double-blind, placebo-controlled, cross-over** (subjects served as own control)
	• 2 experimental treatment sessions weeks apart
	  ○ **Psilocybin:** 0.31 mg /kg (initially .43 mg/kg)
	  ○ **Placebo:** 0.014 mg/kg of psilocybin (initially 0.042 mg/kg)

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

Griffiths RR et al. *J Psychopharmacol* Dec 2016 30: 1181-1197

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



Griffiths RR et al. *J Psychopharmacol* Dec 2016 30: 1181-1197

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**

Griffiths RR et al. *J Psychopharmacol* Dec 2016 30: 1181-1197

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

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

In Development

OHSU

FDA U.S. FOOD & DRUG ADMINISTRATION

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

October 23, 2018

COMPASSION

HEFFTER RESEARCH INSTITUTE

TOP PRIORITY

ANOREXIA NERVOSA | $300,000
Feasibility pilot study with 12 patients will pave the way for a definitive study of the impact psilocybin has on eating disorders, which have the highest mortality rate of any mental illness.

OPIOID DEPENDENCE | $350,000
Pilot study building on other psilocybin addiction research will seek to discover how psiloycbin-assisted treatment could mitigate the opioid epidemic.

ALZHEIMER'S | $800,000
Two studies: one will explore treating emotional distress resulting from early-onset Alzheimer's diagnoses; the other will investigate psilocybin-assisted treatment for caregivers and family members of Alzheimer's patients.

DEPRESSION & ANXIETY | $380,000
Research to measure the clinical effect psilocybin has for stress-induced depression and anxiety.

PTSD | $380,000
Study on the clinical effects of psilocybin facilitating the recovery from the fearful memories and other symptoms for patients with PTSD.

COCAINE DEPENDENCE | $500,000
Study evaluating psilocybin as a treatment for cocaine dependence.

By contributing financial support to this research, you can make a difference in understanding human consciousness and alleviating suffering. To make a tax-deductible donation online visit **heffter.org/donate** or write to us directly at **donate@heffter.org**.

OTHER AREAS OF INTEREST

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.

MDMA VS PSILOCYBIN THERAPEUTICS | $350,000
Study evaluating the similarities and differences between MDMA 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-SPIRITUAL | $300,000
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 MICRODOSING | $500,000
Study measuring and characterizing the cognitive and psychological impact of microdosing.

OHSU

Limitations & Considerations

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

photo courtesy of Psymposia

Organizations

References - MDMA

Reneman L, Booij J, Schmand B, van den Brink W, Gunning B. Memory disturbances in "Ecstasy" users are correlated with an altered brain serotonin neurotransmission. Psychopharmacology. 2000;148:322–424.

Mcgregor, I. S., Clemens, K. J., Plasse, G. V., Li, K. M., Hunt, G. E., Chen, F., & Lawrence, A. J. (2003). Increased Anxiety 3 Months after Brief Exposure to MDMA ('Ecstasy') in Rats: Association with Altered 5-HT Transporter and Receptor Density. *Neuropsychopharmacology,28*(8), 1472-1484. doi:10.1038/sj.npp.1300185

Freye, E. (2010). *Pharmacology and Abuse of Cocaine, Amphetamines, Ecstasy and Related Designer Drugs a comprehensive review on their mode of action, treatment of abuse and intoxication.* Dordrecht: Springer Netherlands.

Multidisciplinary Association for Psychedelic Studies Public Benefit Corporation. (2016, December 27). Annual Report 3,4-methylenedioxymethamphetamine (MDMA). Retrieved February 24, 2019, from https://s3-us-west-1.amazonaws.com/mapscontent/pdfs/MDMA-Annual-Report_FINAL_30DEC2016.pdf

Multidisciplinary Association for Psychedelic Studies. (2018, July 10). Investigator's Brochure 10th Edition. Retrieved February 24, 2019, from https://s3-us-west-1.amazonaws.com/mapscontent/research archive/mdma/MAPS_2018_MDMA_Investigators_Brochure_Edition10_10JUL2018.pdf

Multidisciplinary Association for Psychedelic Studies. MDMA Scientific Literature, Government Hearings, and Archive. Retrieved February 24, 2019, from https://maps.org/mdma-science/364-mdma_scientific_literature_government_hearings_and_archive

Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., & Doblin, R. (2011). The safety and efficacy of ±3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: The first randomized controlled pilot study. *Journal of Psychopharmacology,25*(4), 439-452. doi:10.1177/0269881110378371

Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., Martin, S. F., Yazar-Klosinski, B., Michel, Y., Brewerton, T. D., Doblin, R. (2013). Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4 methylenedioxymethamphetamine-assisted psychotherapy: A prospective long-term follow-up study. *Journal of Psychopharmacology,27*(1), 28-39. doi:10.1177/0269881112456611

Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., Holland, J., Hamilton, S., Yazar-Klosinski, B., Emerson, A., Doblin, R. (2018). 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: A randomised, double-blind, dose-response, phase 2 clinical trial. *The Lancet Psychiatry,5*(6), 486-497. doi:10.1016/s2215-0366(18)30135-4

Mithoefer, MC, Feduccia, AA, Jerome, L et al. (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. *Psychopharmacology* (2019) 236: 2735

National Programme on Substance Abuse Deaths, International Centre for Drug Policy, St George's University, & University of London. (2012). Drug related deaths in the UK – Annual Report 2012. Retrieved February 24, 2019, from https://www.sgul.ac.uk/images/docs/idcp_pdfs/National programme on substance abuse deaths/np-SAD_13th_annual_report_2012FinalVersionJuno3MasterCopy.pdf

Bradley R, Greene J, Russ E, Dutra L, Westen D. A multi-dimensional meta-analysis of psychotherapy for PTSD. *Am J Psychiatry.* 2005;162(2):214,227

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 resting state functional connectivity. *Biol Psychiatry* 78(8):554–562

Feduccia AA, Jerome L, Yazar-Klosinski B, Emerson A, Mithoefer MC, Doblin R. (2019), Breakthrough for Trauma Treatment: Safety and Efficacy of MDMA-Assisted Psychotherapy Compared to Paroxetine and Sertraline. *Frontiers in Psychiatry*.

References - Psilocybin

Bogenschutz, M.P., Forcehimes, A.A., Pommy, J.A., Wilcox, C.E., Barbosa, P.C.R., & Strassman, R.J. (2015). Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. *Journal of Clinical Psychopharmacology, 29:3,* 1-11.

Carhart-Harris, R.L., Bolstridge, M., Day, C.M.J., Rucker, J., Watts, R., Erritzoe, D.E., . . . Nutt, D.J. (2018). Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology (Berl), 235(2),* 399-408.

Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, Cosimano MP, & Klinedinst MA. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology, 30,* 1181-1197.

Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, & Greer GR. (2011). Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer. *Arch Gen Psychiatry, 68(1),* 71-78.

Johnson, M.W., Garcia-Romeu, A., Cosimano, M.P., & Griffiths, R.R. (2014). Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *Journal of Clinical Psychopharmacology, 28:11,* 983– 992.

Johnson, M.W., Garcia-Romeu, A., & Griffiths, R.R. (2017). Long-term follow-up of psilocybin-facilitated smoking cessation. *American Journal of Drug and Alcohol Abuse, 43(1),* 55-60.

Moreno, F.A., Wiegand, C.B., Taitano, E.K., & Delgado, P.L. (2006). Safety, tolerability and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *The Journal of Clinical Psychiatry, 67.* 1735-1740.

Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., . . . Schmidt, B. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *Journal of Psychopharmacology, 30,* 1165-1180.

Clinicaltrials.gov

References - LSD

Krebs, T. & Johansen, P. (2012). LSD for alcoholism: meta-analysis of randomized controlled trials. *Journal of Psychopharmacology, 26(1),* 994-1002.

Gasser P, Holstein D, Michel Y, Doblin R, Yazar-Klosinski B, Passie T, & Brenneisen R. (2014). Safety and Efficacy of Lysergic Acid Diethylamide-Assisted Psychotherapy for Anxiety Associated With Life-threatening Diseases. *Journal of Nervous and Mental Disorders, 202(7),* 513-20.

Gasser P, Kirchner K, & Passie T. (2015). LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: A qualitative study of acute and sustained subjective effects. *Journal of Psychopharmacology, 29(1),* 57-68.

Grof, Stanislav (1976). Realms of the Unconscious: Observations from LSD Research. New York: Viking Press.

Discussion