

Therapeutic Applications of Psychedelics

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Disclosures

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- R01 from National Institute of Mental Health
 - *“Bioinformatics for posttraumatic stress”*

Local Funding

- University of Minnesota Foundation
 - *“Psychedelic Assisted Therapy (PATH) Fund”*

Founder and former Associate Director, Psychedelic Society of Minnesota;
Co-Founder, Decriminalize Minneapolis; Founder, Psychonauts of
Minnesota

DISCLAIMER: *The information presented here is not intended or implied to be a substitute for professional medical advice, diagnosis or treatment recommendations. All content, including text, graphics, images and information, contained on or available through this talk is for educational purposes only. A full database of current clinical trials with psychedelics in the US and abroad, can be found at:*
<https://clinicaltrials.gov/ct2/home>

I am a neuroscientist, not a clinician or medical doctor.

Learning Objectives



Know the history of psychedelics



Understand objective and subjective effects of psychedelics



Identify common psychedelics



Know the therapeutic and healing uses of common psychedelics



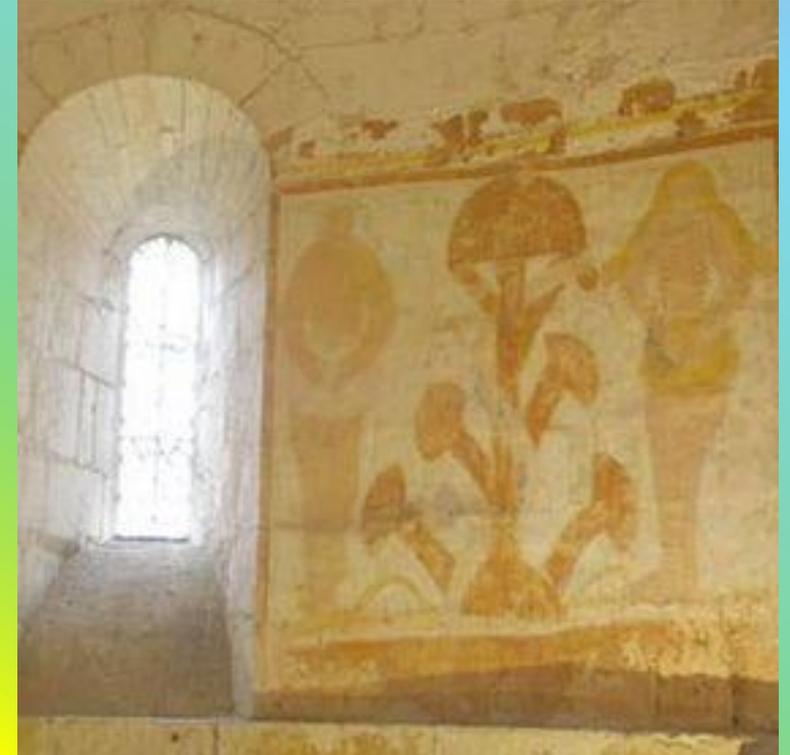
Be aware of current research with psychedelics

Overview

- What are psychedelics and entheogens?
- History of clinical research on natural and synthetic psychedelics and the War on Drugs
- Current renaissance of clinical trials with psychedelics
- The future of psychedelic-assisted therapy and research

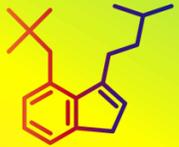
What Are Entheogens?

“Entheogens are psychoactive substances that induce alterations in perception, mood, consciousness, cognition, or behavior for the purposes of engendering spiritual development or otherwise in sacred contexts.”



<https://en.wikipedia.org/wiki/Entheogen>

Common Entheogens



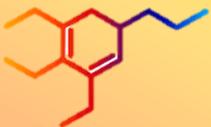
Psilocybin-containing mushrooms



Ayahuasca



Ibogaine



Mescaline-containing cacti

History of Entheogens

- Entheogenic plants and fungi are central to ritualistic and traditional medical practices in indigenous cultures worldwide
- Civilizations have used entheogens for thousands of years



MODERN HISTORY

- Earliest scientific research: 1896 isolation of Mescaline from peyote cactus by Arthur Heffter.
- 1938 => LSD synthesized at the Sandoz research labs in Switzerland by Dr. Albert Hofmann.
- LSD marketed as *Delysid* => Tool to aid the release of repressed material during therapy. Psychiatrists able to “experience the world of psychotic patients”.
- The first experimental use of LSD was as a *psychotomimetic* - a drug mimicking psychosis.
- CIA project MK-Ultra => “Truth drug” for interrogations.
- 1959 => Albert Hoffman isolated the active principle psilocybin from the mushroom *Psilocybe mexicana*. “*Indocybin*”

Psychedelics ≠ Psychotomimetic

Schizophrenia Bulletin vol. 46 no. 6 pp. 1396–1408, 2020

doi:10.1093/schbul/sbaa117

Advance Access publication 18 September 2020

Hallucinations Under Psychedelics and in the Schizophrenia Spectrum: An Interdisciplinary and Multiscale Comparison

Pantelis Leptourgos^{*,1,#,10}, Martin Fortier-Davy^{2,#}, Robin Carhart-Harris³, Philip R. Corlett¹, David Dupuis⁴, Adam L. Halberstadt^{5,6}, Michael Kometer⁷, Eva Kozakova^{8,9,10}, Frank Larøi^{10–12}, Tehseen N. Noorani^{4,10}, Katrin H. Preller⁷, Flavie Waters¹³, Yuliya Zaytseva^{8,14}, and Renaud Jardri^{15,16,10}

Psychedelics ≠ Psychotomimetic

Table 3. Comparison of the phenomenology of psychotic and serotonergic hallucinations

	Schizophrenia Spectrum	5-HT _{2A} Agonists	Comparison
Sensory modalities	Mainly AH (multimodal in some cases)	Mainly VH (multimodal in some cases)	Different
Content	No geometric hallucinations Complex hallucinations (mostly ordinary entities)	Geometric hallucinations Complex hallucinations (ordinary and extraordinary entities)	Different
Meaning	Strong existential/metaphysical meaning	Strong existential/metaphysical meaning	Similar
Reality monitoring/insight	Poor reality monitoring and insight	Reality monitoring and insight often preserved	Different
Duration	Recurrent psychotic episodes; they can last from several weeks to several months. Hallucinatory episodes during psychotic episodes can last several seconds or minutes; continuously present in some individuals.	Transient states, lasting a few hours. Long-term perceptual effects are rare.	Different

connectivity between visual cortex and amygdala in SCZs (AH and VH)

Psychedelic - What's in a name?

Phanerothyme: From Greek *phanein*, “to reveal,” and *thymos*, “mind, soul”.

Coined by British writer Aldous Huxley (1894–1964) to describe the effect of mind-altering drugs such as LSD. He first used the term in a letter (1956) to his friend Humphry Osmond (1917–2004), who counter-proposed the term **psychedelic**, which has the same etymological sense of “mind-revealing.”

“To make this trivial world
sublime

Take half a gramme of
phanerothyme”.

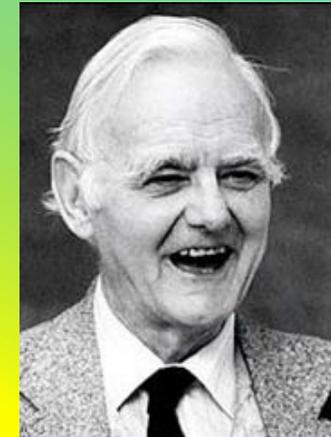
- Aldous Huxley, 1956



“To fathom hell or soar
angelic

Just take a pinch of
psychedelic”.

- Humphry Osmond



Psychedelic: Psychē (**mind**) + dēloun (**to make visible, to reveal**) = “mind-revealing”

Integration of Entheogens into Modern Culture

- Popularized in Western cultures in the 1950s and 60s
- Became Schedule I substances in the 1970s

Recent revival in psychedelic research

- **Breakthrough Therapy Designation** for psilocybin treating depression



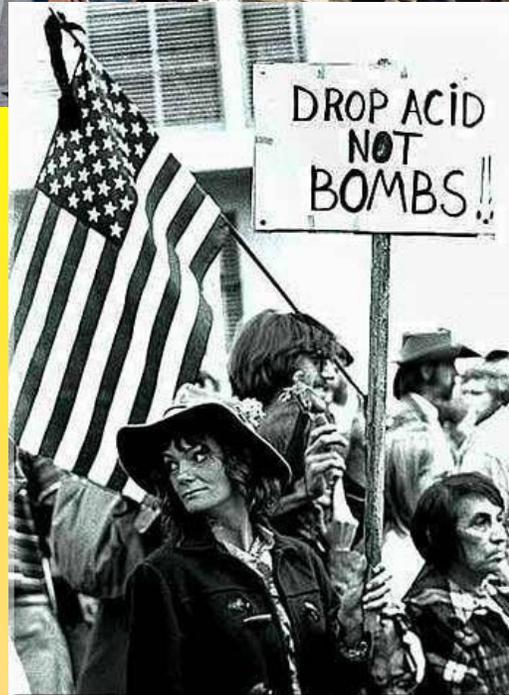
MODERN HISTORY

- Psycholytic therapy: Low doses to aid psychoanalytic process.
- Psychedelic therapy: High doses leading to so-called mystic experiences.
- Abram Hoffer and Humphrey Osmond; Canada 1953.
- Initial intention: produce delirium tremens like experiences with psychedelics.
- Change of approach → pleasant, non-threatening surroundings, talked them through the experience, facilitating transcendental “mystical” experience.
- Bill Wilson (AA) → Took LSD under the guidance of Humphrey Osmond.
- LSD → Profound insight and connection to a higher power.
- AA strongly opposed to his experimenting with a mind-altering substance.

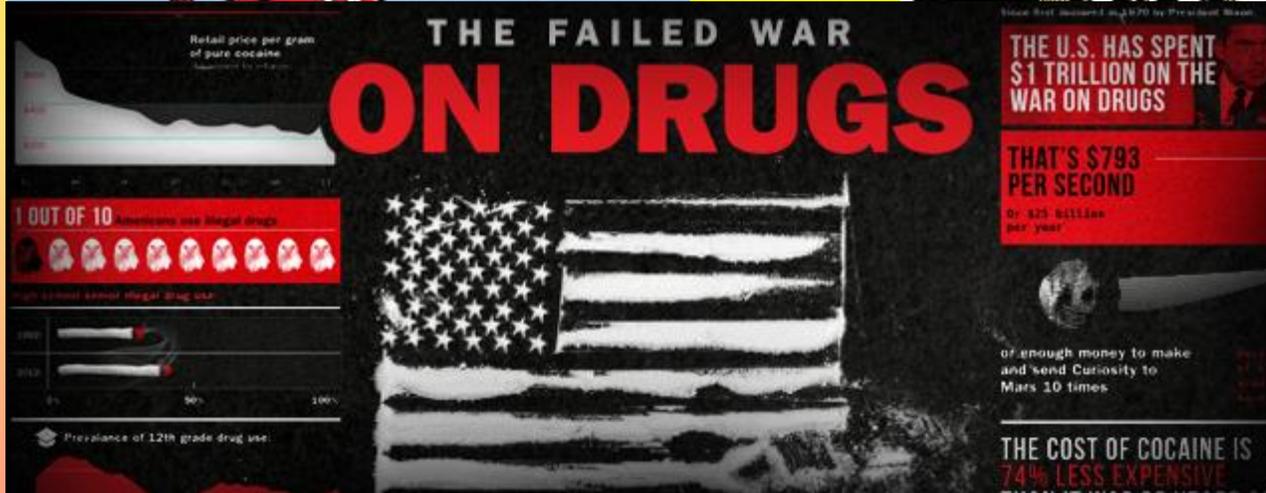
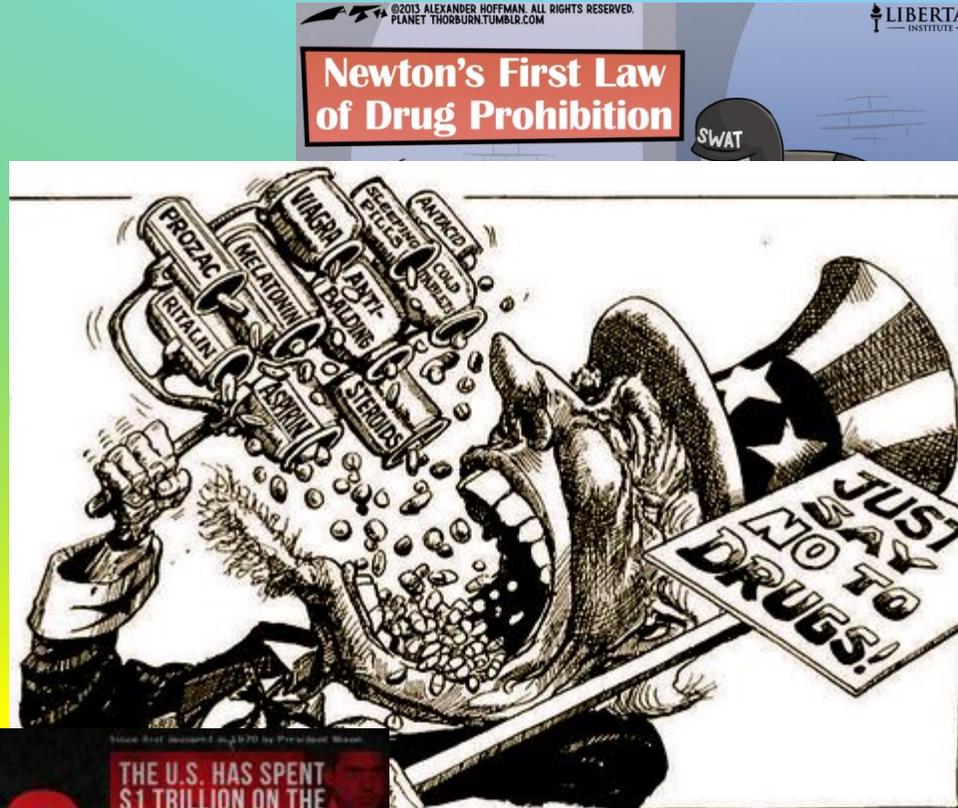
CLASSIFICATION

- Classical psychedelics:
 - **Indoleamines**
 - Ergolines (i.e., LSD)
 - Ibogoids (i.e., Ibogaine)
 - Tryptamines (i.e., DMT, 5-MeO-DMT, psilocybin, psilocin).
 - **Phenylalkylamines**
 - Phenethylamines (i.e., Mescaline)
 - Phenylisopropylamines (i.e., DOI)
- Entactogenic phenylalkylamines (i.e., MDMA)
- Dissociative anesthetics/miscellaneous (i.e., PCP, ketamine, Salvia).

War on Drugs

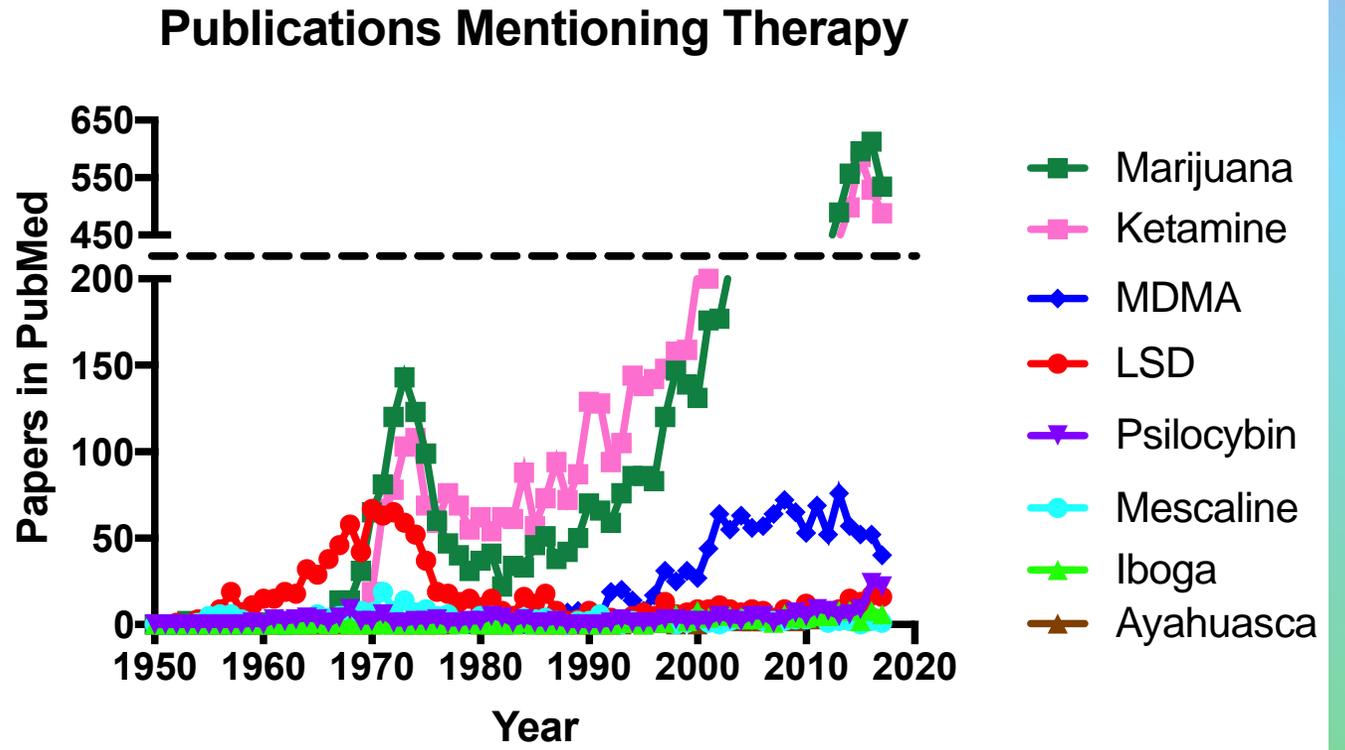
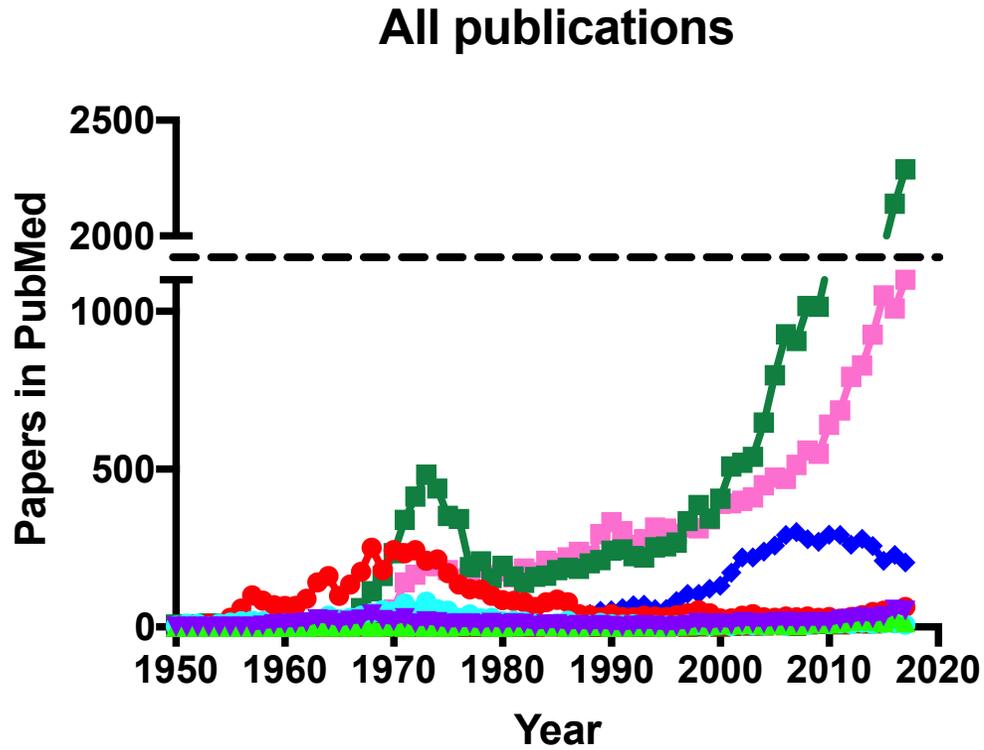


War on Drugs

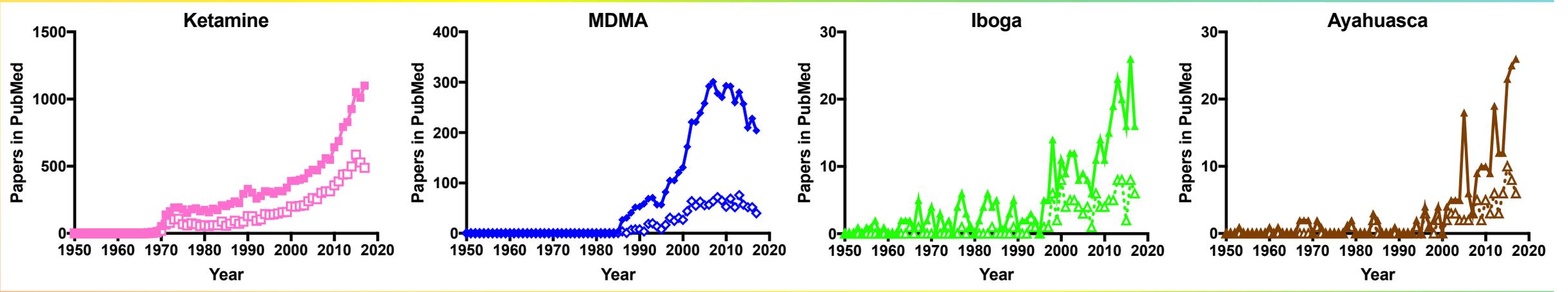
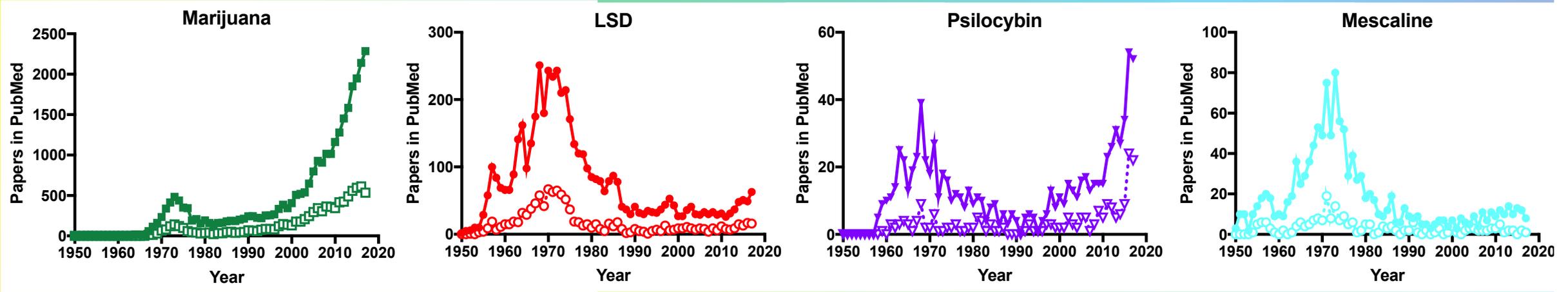


D.A.R.E.
TO RESIST
THE WAR ON DRUGS

Publication Trends: 1950-2017



Publication Trends: 1950-2017



● All Papers

○ Mention therapy

Psychedelics Could Trigger A 'Paradigm Shift'



NEWS CULTURE BOOKS SCIENCE & TECH BUSINESS

THE TRIP TREATMENT

Alcoholics stop drinking, moved

theory, but his experiments upset other



Receives FDA Breakthrough



with disorders, substance

Usona Institute
Receives FDA
Breakthrough
Therapy
Designation
for Psilocybin for
the Treatment of
Major Depressive
Disorder



SHARE

FEATURE

Can ecstasy treat

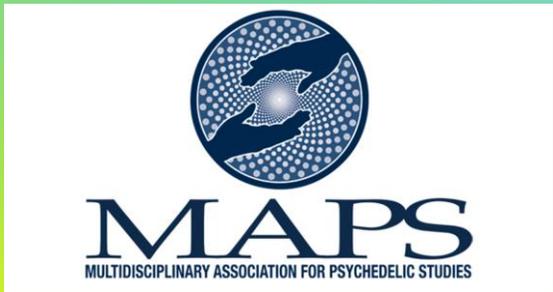
Kai Kupferschmidt

Science 04 Jul 2014:
Vol. 345, Issue 6192, pp. 22-23
DOI: 10.1126/science.345.6192.22



Michael Pollan

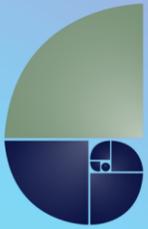
Author of *The Omnivore's Dilemma*



New Hope



The
Psychedelic
Society



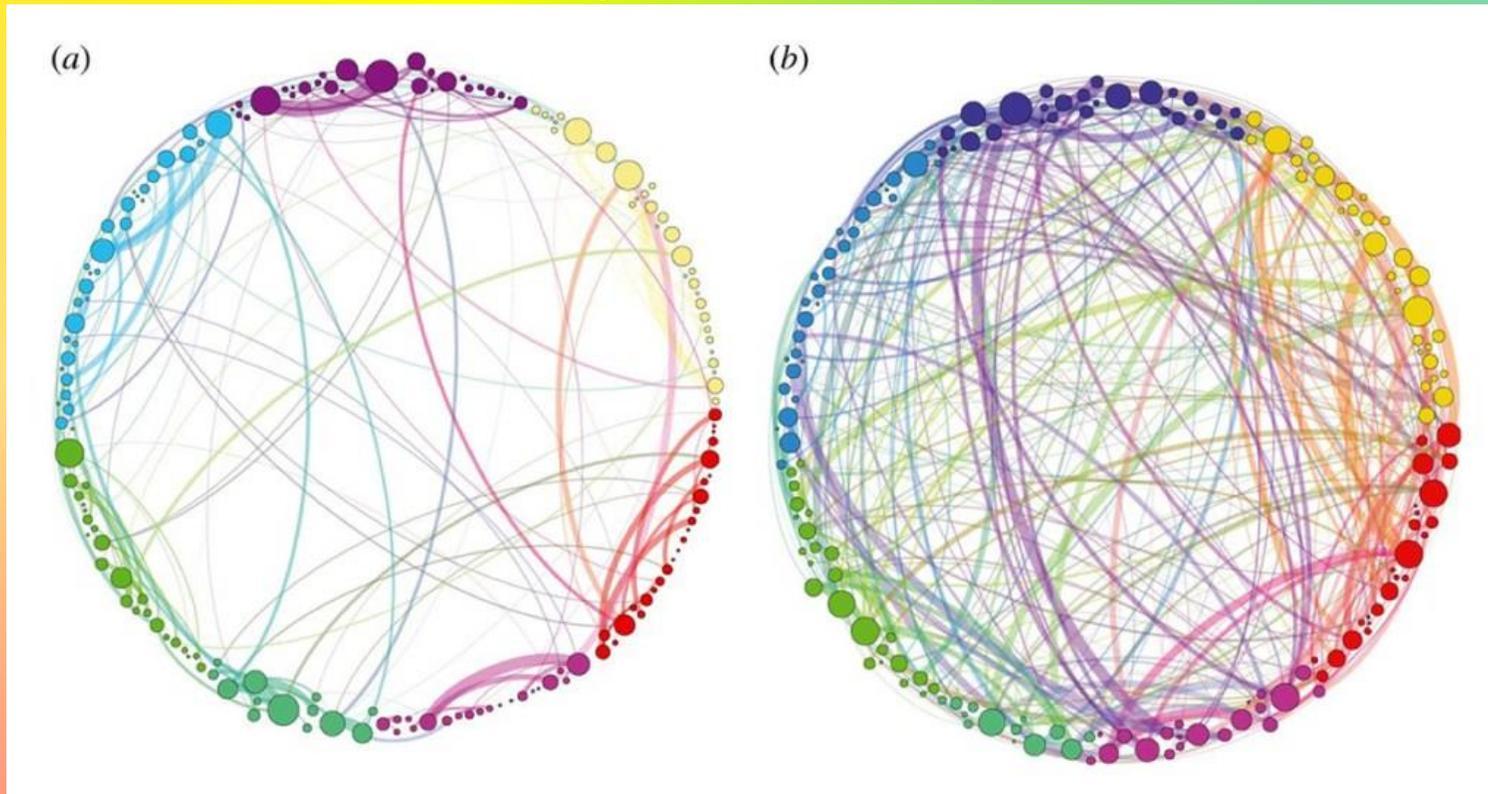
HEFFTER
RESEARCH INSTITUTE



Objective Effects

Default Mode Network

Entheogens reduce “...connectivity within brain networks and boost connectivity *between* brain networks that do not normally interact”.



PLACEBO

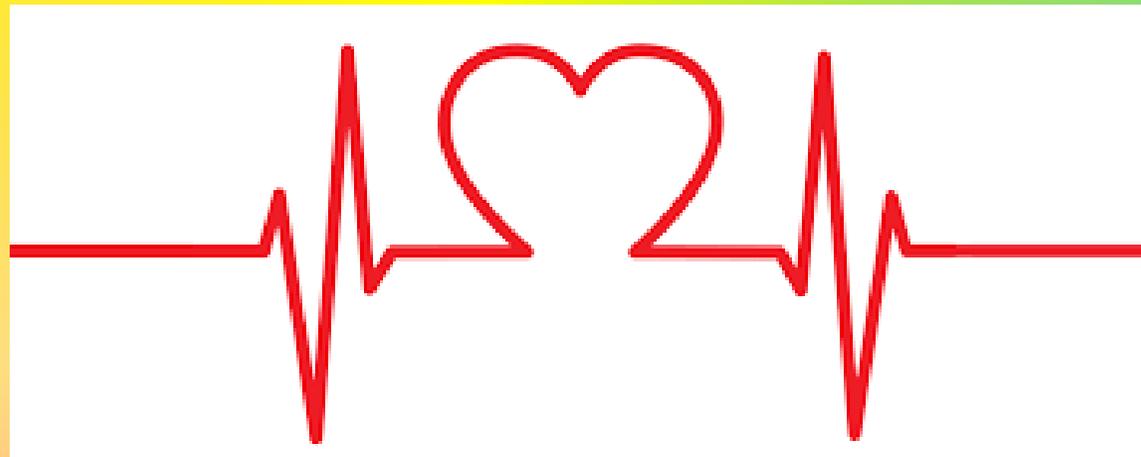
PSILOCYBIN

Petri et al. (2014) J. R. Soc. Interface.
<https://doi.org/10.1098/rsif.2014.0873>

Objective Effects

Physiological

- Increased heart rate and blood pressure
- Increased body temperature



Subjective Effects

Sensory distortions

- Closed-eye imagery
- Open-eyed imagery
- Distortions of body image
- Synesthesia

Dream-like ideation & processing

Hypersensitivity to sensory stimuli

Unusual thought processes

Childlike sense of wonder and imagination



Subjective Effects

Internal unity

External unity

Transcendence of time and space

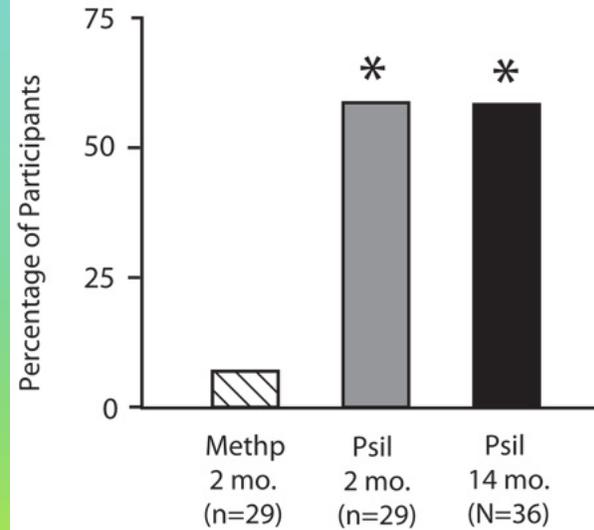
Sense of sacredness

Poetic quality

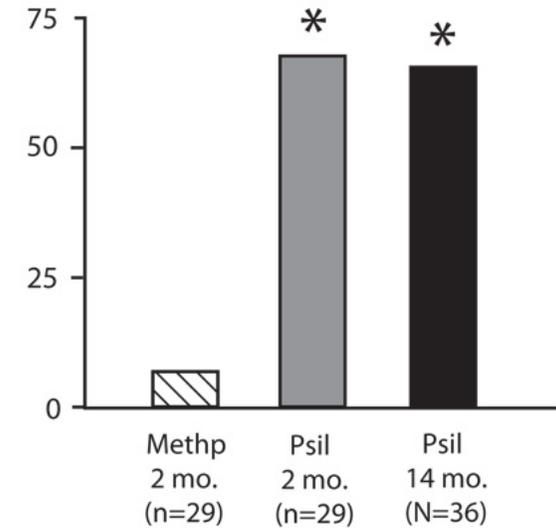
Deeply felt positive mood

Griffiths et al. *Journal of psychopharmacology* (2008)
doi:10.1177/0269881108094300

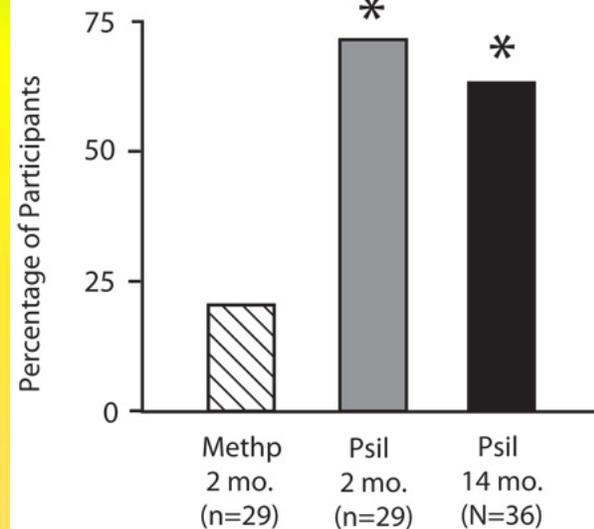
Among the Top 5 Personally Meaningful Experiences of Lifetime



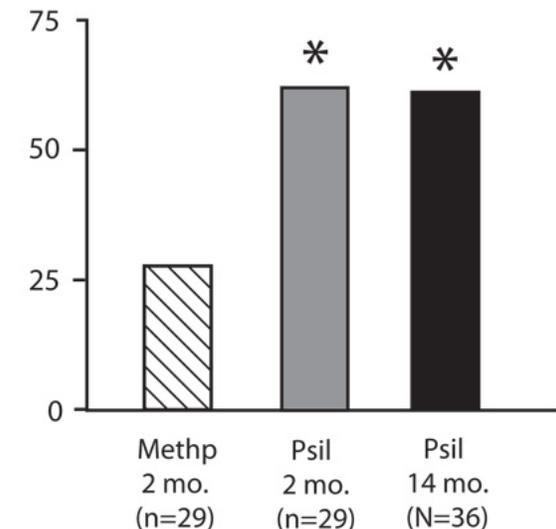
Among the Top 5 Spiritually Significant Experiences of Lifetime



Increased Current Personal Well-Being or Life Satisfaction



Positive Behavior Change



Psychedelic-Assisted Psychotherapy

Assist the therapeutic process

- Inner healer

Integration sessions are important

Therapeutic effect

- Mindset of patient and therapists
- Intentions
- Environment
- Entheogens



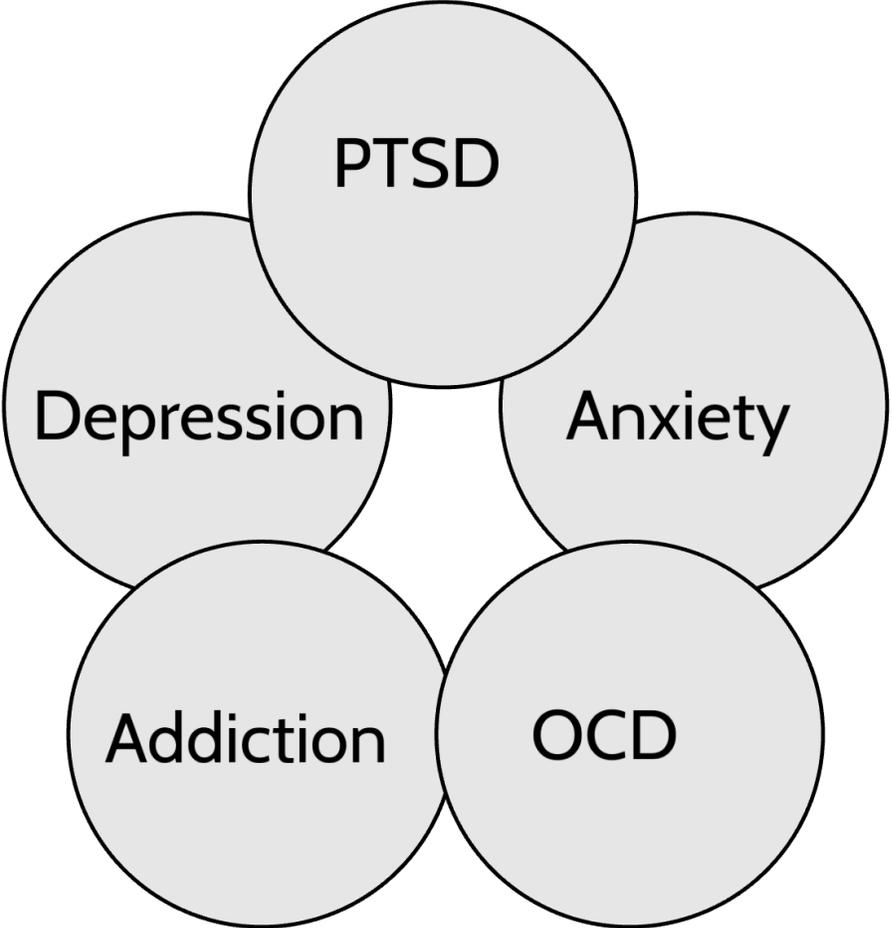
Therapeutic Applications of Psychedelics

An evidence-based conceptual framework for mental health

Ketamine

Ayahuasca

Psilocybin



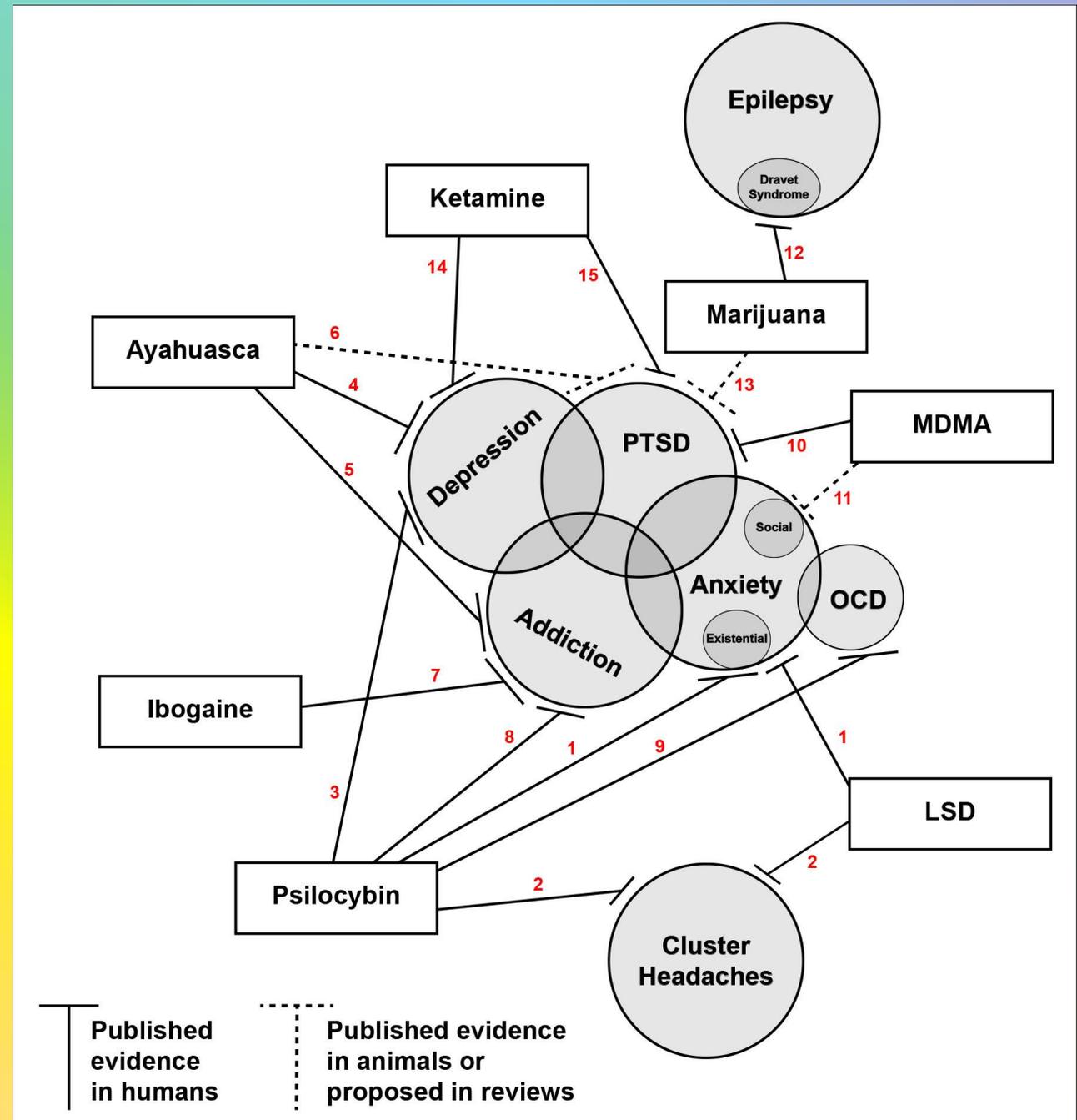
Marijuana

MDMA

Ibogaine

LSD

1. LSD and psilocybin for end of life anxiety
2. LSD and psilocybin for cluster headaches
3. Psilocybin for depression
4. Ayahuasca for depression
5. Ayahuasca for addiction
6. Ayahuasca for PTSD
7. Ibogaine for addiction
8. Psilocybin for addiction
9. Psilocybin for OCD
10. MDMA for PTSD
11. MDMA for social anxiety in autistic adults
12. Cannabidiol for Dravet's syndrome
13. Marijuana for PTSD
14. Ketamine for depression
15. Ketamine for PTSD



Safety and Risks

Who should be cautious about consuming psychedelics?

- Current diagnosis or family history of:
Schizophrenia, Bipolar Disorder and Borderline Personality Disorder
- Cardiovascular problems
- Pre-existing heart conditions

Patient Vulnerability

Sexual assault and exploitation

Three different structural classes of psychedelics

1. Phenylalkylamines: selective for $5HT_{2A}$ + $5HT_{2C}$ Mescaline (Peyote, San Pedro)

2. Tryptamines: non-selective for serotonin receptors

- $5HT_{1A}$ + $5HT_{1B}$ + $5HT_{1D}$
- $5HT_{2A}$ + $5HT_{2C}$
- $5HT_5$ + $5HT_6$ + $5HT_7$

Psilocybin, Ayahuasca (DMT), Ibogaine (low affinity)

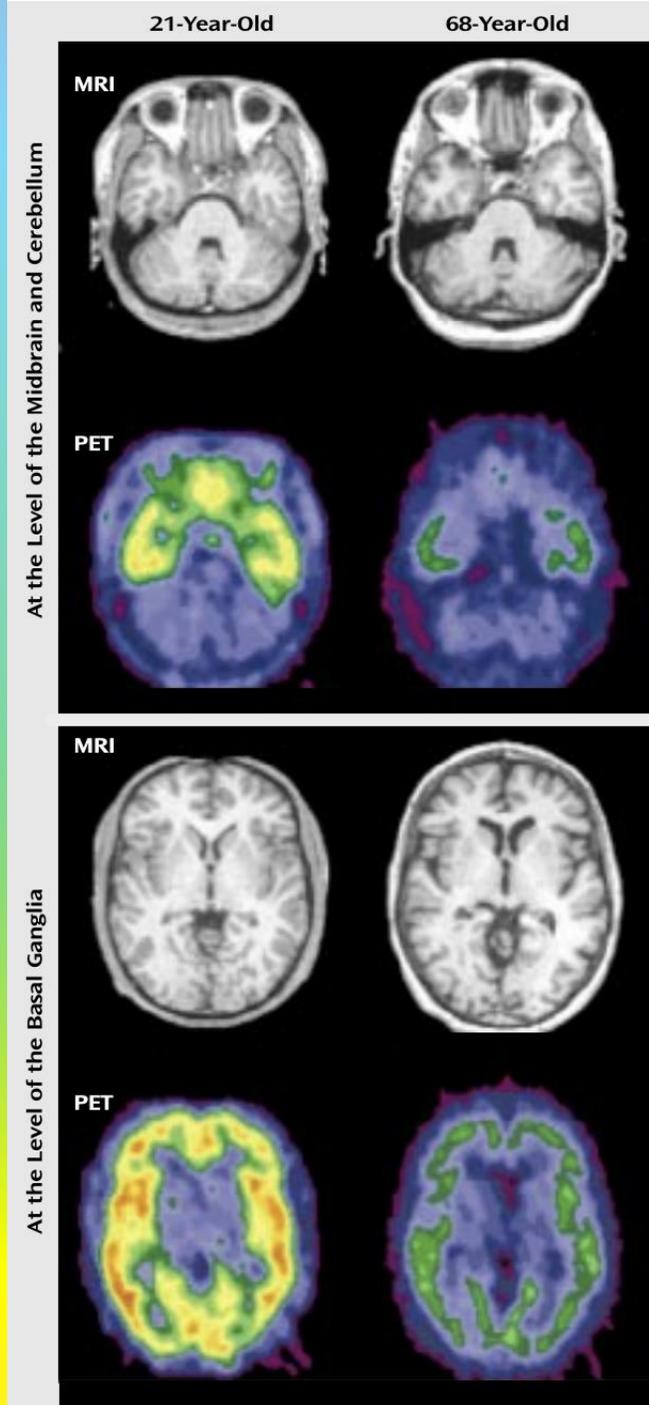
3. Lysergamides: non-selective for serotonin, dopamine and norepinephrine receptors

- $5HT_{1A}$ + $5HT_{1B}$ + $5HT_{1D}$ + $5HT_{2A}$ + $5HT_{2C}$ + $5HT_5$ + $5HT_6$ + $5HT_7$
- D_1 + D_2 + D_3 + D_4
- α_1 + α_2 + β_1 + β_2

LSD

Function of 5-HT_{2A}R Agonism?

- 5-HT - ↑ plasticity ↑ & environmental sensitivity ↑ & key role in brain development
- 5-HT_{2A}R functioning ↑ key development periods
- 5HT_{2A}R agonism → learning/unlearning/cog-flex ↑
- 5-HT_{2A}R agonism → neuroplasticity (cortex) ↑
- 5-HT_{2A}R agonism → system regression



Function of 5-HT2AR Agonism?

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- 5-HT2AR agonism → system regression
- **Range of stressors → 5-HT2AR functioning ↑**



Ascetic

Psychedelic Neurobiology - Mechanisms

Cell Reports

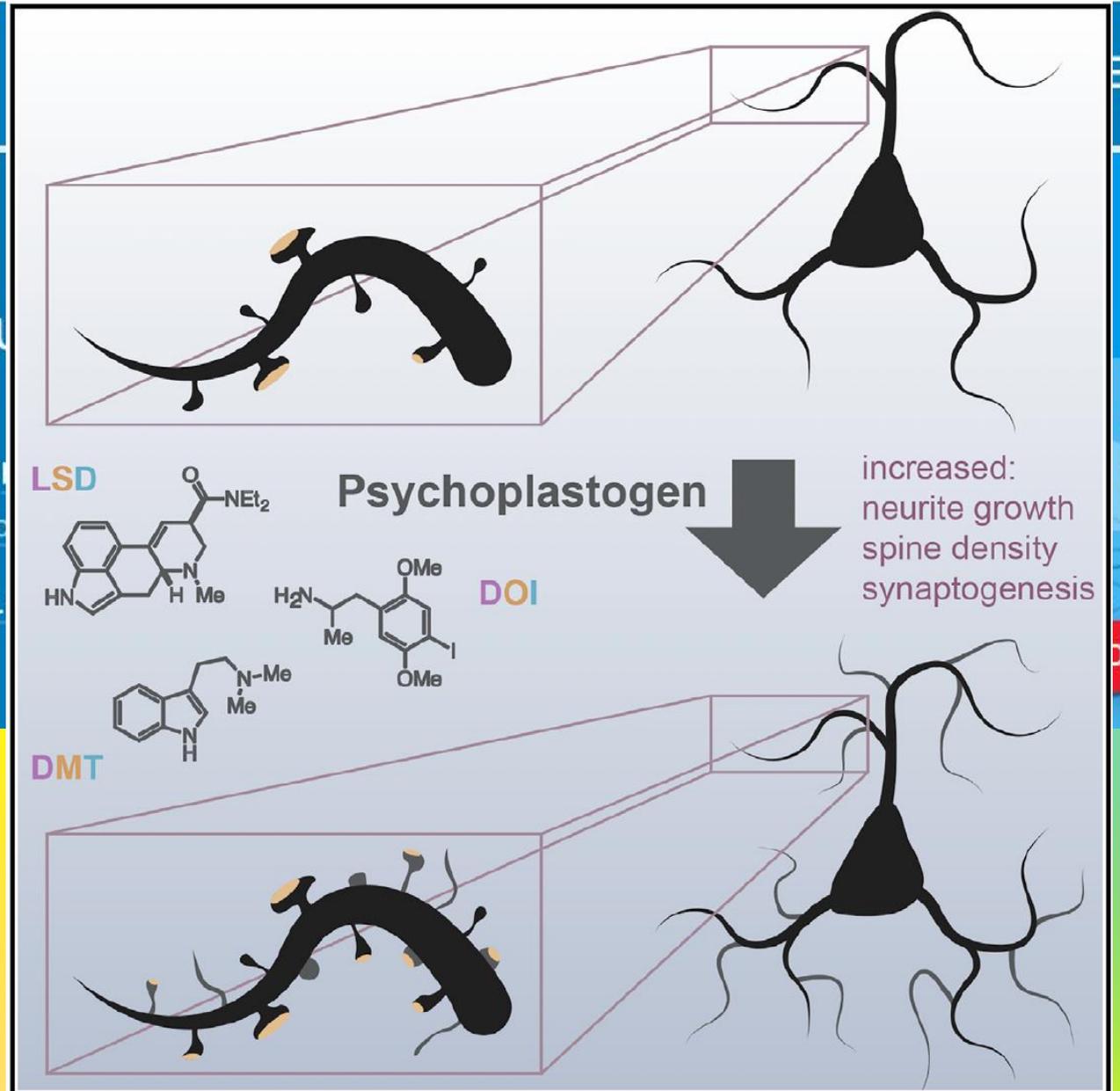
ARTICLE | VOLUME 23, ISSUE 11, P3170-3182, JUNE 12, 2018

Psychedelics Promote Structural Plasticity

Calvin Ly • Alexandra C. Greb • Lindsay P. Cameron • ...

David E. Olson ¹⁰ • Show all authors • Show footnotes

Open Access • DOI: <https://doi.org/10.1016/j.celrep.2018.05.101>



Psychedelic Neurobiology - Mechanisms

Neuron

Report

Psilocybin induces rapid increase of dendritic spines in the prefrontal cortex

Ling-Xiao Shao,¹ Clara Liao,² Ian Gregg,¹ Pasha Ghosh,³ and Alex C. Kwan^{1,2,4,5,*}

¹Department of Psychiatry, Yale University School of Medicine

²Interdepartmental Neuroscience Program, Yale University

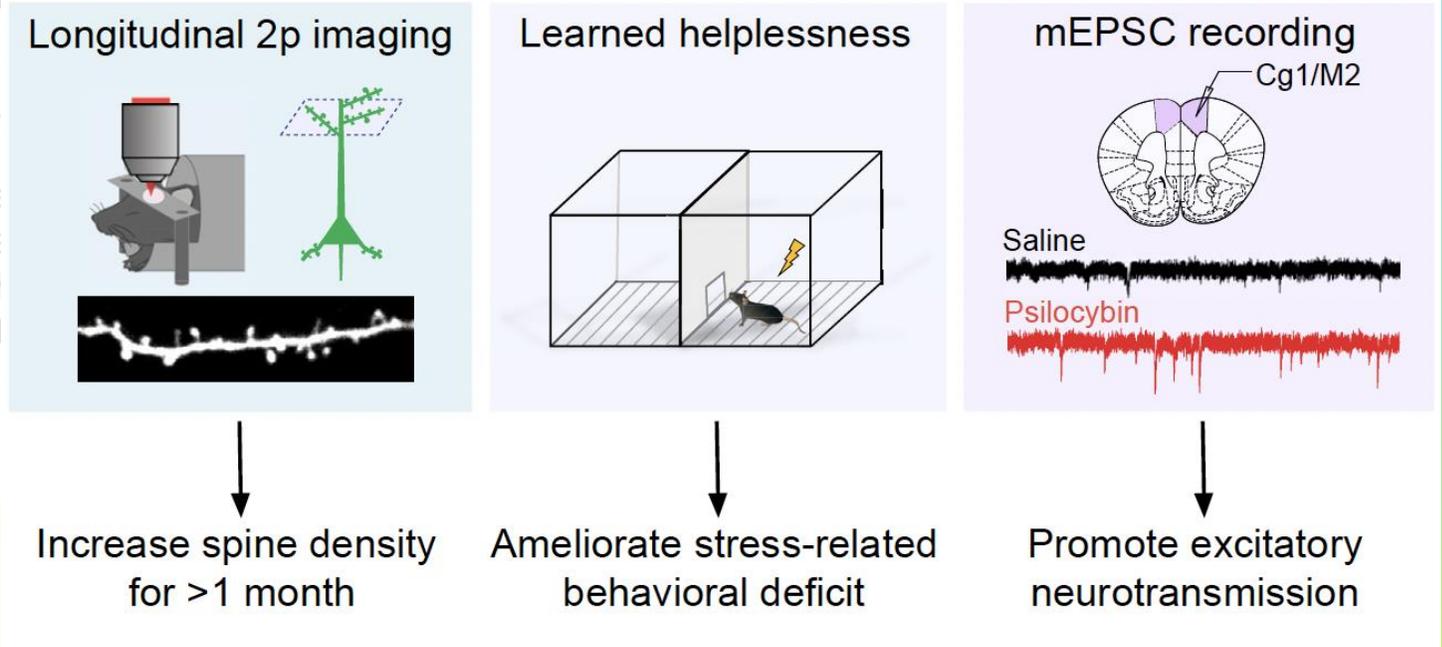
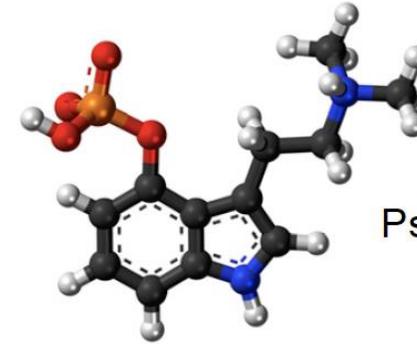
³Medical Scientist Training Program, Yale University School of Medicine

⁴Department of Neuroscience, Yale University School of Medicine

⁵Lead contact

*Correspondence: alex.kwan@yale.edu

<https://doi.org/10.1016/j.neuron.2021.06.008>



Psilocybin Surround Suppression Study



University of Minnesota researchers are seeking healthy adults who have tried “magic mushrooms” for a study exploring how the drug psilocybin changes perception and expectation.

[Sources](#) ▾ [About Site](#) ▾ [PRS Login](#)

[Home](#) > [Search Results](#) > Study Rec

Save this study

Visual Surround Suppression a

⚠ The safety and scientific validity of this study is not guaranteed by the sponsor and investigators. Listing a study does not mean it has been approved by the Federal Government. [Know the risks and potential benefits](#) to your health care provider before participating.

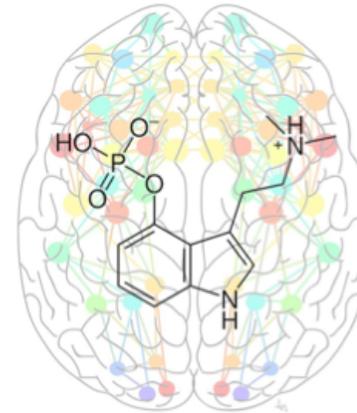
This study may be a good fit if you:

- Are 25 – 65 years of age
- Have good physical and mental health
- Have previous experience with psilocybin

This study will involve a total of 7 visits over a 12-week period and will include:

- Interviews and psychological testing
- EEG, MRI, blood draws
- 2 separate day-long drug/placebo sessions
- Weekly check-in visits with questionnaires
- Baseline, between session, and one-month follow ups.

Participants will be compensated for their time.



For more information, contact: psilo001@umn.edu

Study website:



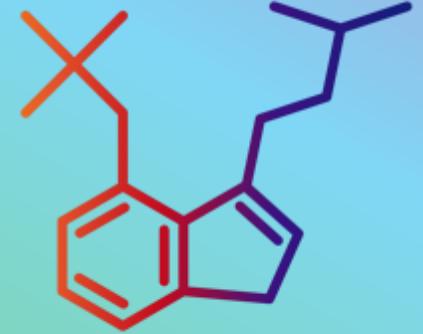
Identifier: NCT04424225

Recruiting
2020
September 1, 2021

[Locations](#)

Mushrooms (Psilocybin)

4-phosphoroyloxy-N,N-dimethyltryptamine



Mushrooms (Psilocybin)



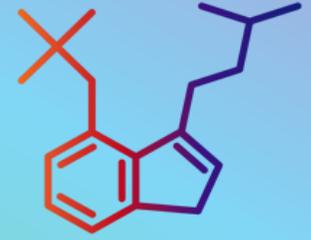
- Humans have used for more than 7,000 years
- Gordon Wasson and Maria Sabina made popular in the West from *Psilocybe Mexicana* mushrooms in 1957
- Isolated and patented by Albert Hoffman in 1963

Pharmacology

- 5-HT_{2A} receptors (serotonin)
- Effects last from 3-6 hours
- Moderate dose is around 2-3.5 grams



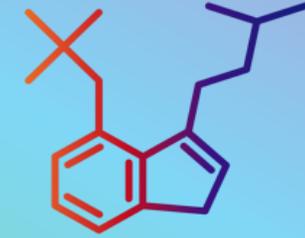
Mushrooms (Psilocybin)



Therapeutic uses

- Addiction (alcohol, nicotine, cocaine)
- Depression
- Cluster Headaches
- Existential Anxiety
- OCD
- Palliative Care

Mushrooms (Psilocybin)

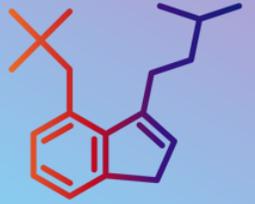


Completed or active trials on ClinicalTrials.gov for treatment of various disorders with psilocybin



NCT Number	Title	Conditions
NCT02061293	A Double-Blind Trial of Psilocybin-Assisted Treatment of Alcohol Dependence	Alcohol Dependence
NCT04141501	Clinical and Mechanistic Effects of Psilocybin in Alcohol Addicted Patients	Alcohol Use Disorder
NCT04052568	Effects of Psilocybin in Anorexia Nervosa	Anorexia Nervosa
NCT00302744	Effects of Psilocybin in Advanced-Stage Cancer Patients With Anxiety	Anxiety
NCT00957359	Psilocybin Cancer Anxiety Study	Cancer
NCT02981173	Psilocybin for the Treatment of Cluster Headache	Cluster Headache
NCT02037126	Psilocybin-facilitated Treatment for Cocaine Use	Cocaine-Related Disorders
NCT03866174	A Study of Psilocybin for Major Depressive Disorder (MDD)	Depressive Disorder, Major
NCT03715127	Clinical, Neurocognitive, and Emotional Effects of Psilocybin in Depressed Patients - Proof of Concept	Depressive Disorder, Major
NCT03429075	Psilocybin vs Escitalopram for Major Depressive Disorder: Comparative Mechanisms	Depressive Disorder, Major
NCT00465595	Psychopharmacology of Psilocybin in Cancer Patients	Depressive Symptoms Anxiety Cancer
NCT04123314	Psilocybin for Depression in People With Mild Cognitive Impairment or Early Alzheimer's Disease	Depressive Symptoms Depression Alzheimer Disease Mild Cognitive Impairment
NCT02950467	Psilocybin-assisted Group Therapy for Demoralization in Long-term AIDS Survivors	Distress Depression Grief
NCT03181529	Effects of Psilocybin in Major Depressive Disorder	Major Depressive Disorder
NCT03554174	Psilocybin - Induced Neuroplasticity in the Treatment of Major Depressive Disorder	Major Depressive Disorder
NCT04218539	Repeat Dosing of Psilocybin in Migraine Headache	Migraine Headache
NCT03341689	Psilocybin for the Treatment of Migraine Headache	Migraine Headache
NCT01943994	Psilocybin-facilitated Smoking Cessation Treatment: A Pilot Study	Nicotine Dependence
NCT03356483	Efficacy of Psilocybin in OCD: a Double-Blind, Placebo-Controlled Study.	Obsessive-Compulsive Disorder
NCT03300947	Psilocybin for Treatment of Obsessive Compulsive Disorder	Obsessive-compulsive Disorder (OCD)
NCT04161066	Adjunctive Effects of Psilocybin and Buprenorphine	Opioid Use Disorder
NCT03806985	Effects of Psilocybin in Post-Traumatic Headache	Post-Traumatic Headache
NCT03380442	Psilocybin and Depression	Severe Depression
NCT03775200	The Safety and Efficacy of Psilocybin in Participants With Treatment Resistant Depression	Treatment Resistant Depression

Mushrooms (Psilocybin)



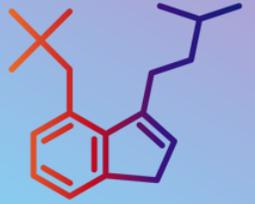
Psilocybin-Assisted Treatment for Alcohol Dependence – 2015 Study

Results

- Percent heavy drinking days decreased during weeks 5-12
- Percent drinking days decreased during weeks 5-12
- Change in drinking correlated with mystical quality of experience



Mushrooms (Psilocybin)



Psilocybin-Assisted Treatment for Tobacco Addiction – 2016 Study

Results

- 80% abstinent 6 months post-treatment
- 67% abstinent at 12 months post-treatment
- 60% abstinent at a long-term follow-up an average of 30 months post-treatment



Mushrooms (Psilocybin)

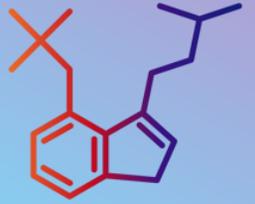


Psilocybin-Assisted Treatment for Tobacco Addiction – 2016 Study

- Strengthened belief in ability to quit (73%)
- Now act in long term holistic benefit (73%)
- Reduction in stress regarding quitting smoking (47%)
- Mystical experience correlated with smoking abstinence
- Positive persisting effects about life, self, mood, and spirituality



Mushrooms (Psilocybin)



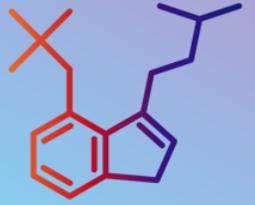
Psilocybin with psychological support for treatment-resistant depression – Open-Label Study 6-month follow-up

Results

- Relative to baseline, Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR16) scores were significantly reduced at all six post-treatment time points
- Of 19 patients who completed, all showed some reduction in depression severity at 1 week and these were sustained in the majority for 3–5 weeks
- No serious adverse events



Mushrooms (Psilocybin)



Psilocybin with psychological support for treatment-resistant depression - Study

“Psilocybin’s low toxicity, favourable side effect profile and putative rapid and enduring antidepressant action could render it at least competitive with currently available treatments for major depression, whose therapeutic actions may be either delayed, e.g. in the cases of SSRIs and psychotherapy, or short-lived, e.g. in the case of ketamine”

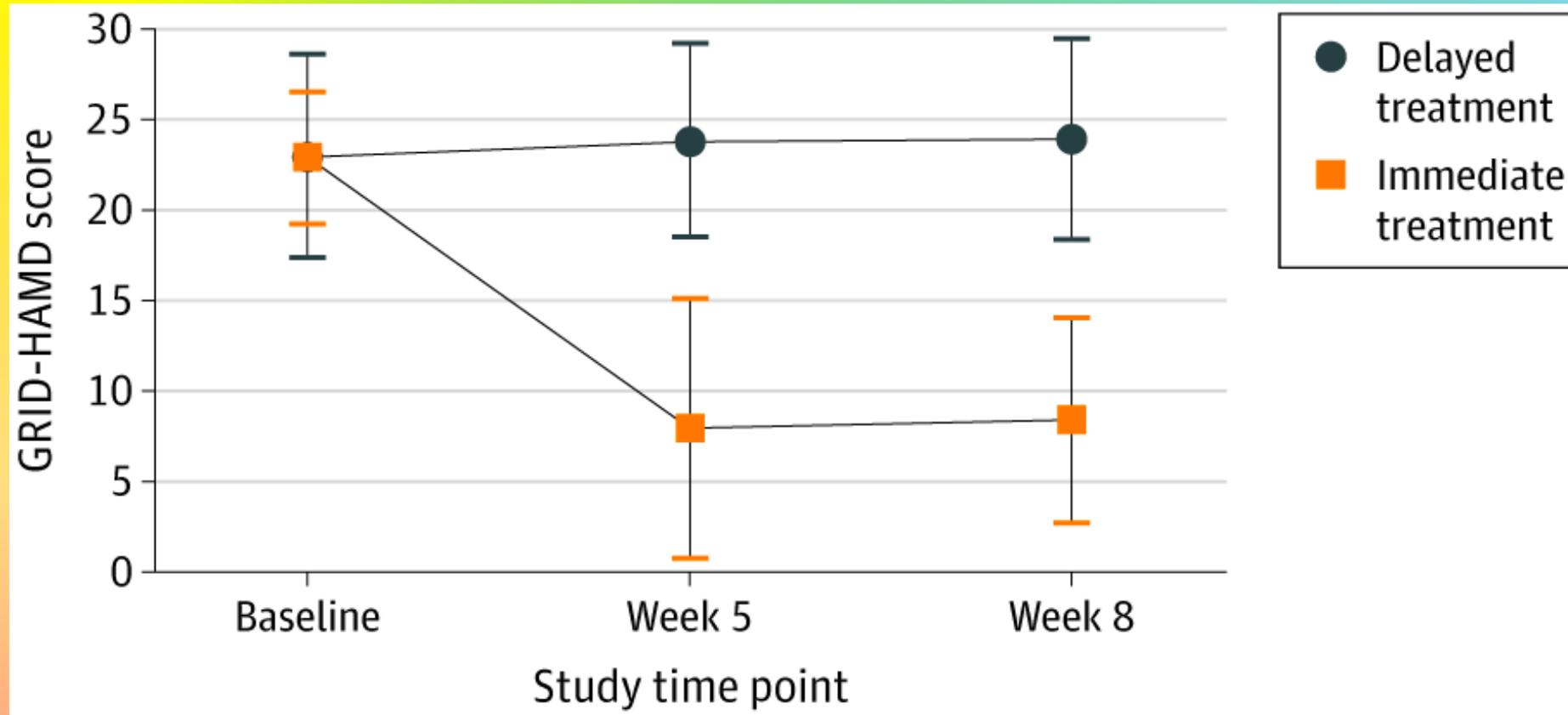
Carhart-Harris et al (2018). *Psychopharmacology (Berl)*.



Mushrooms (Psilocybin)



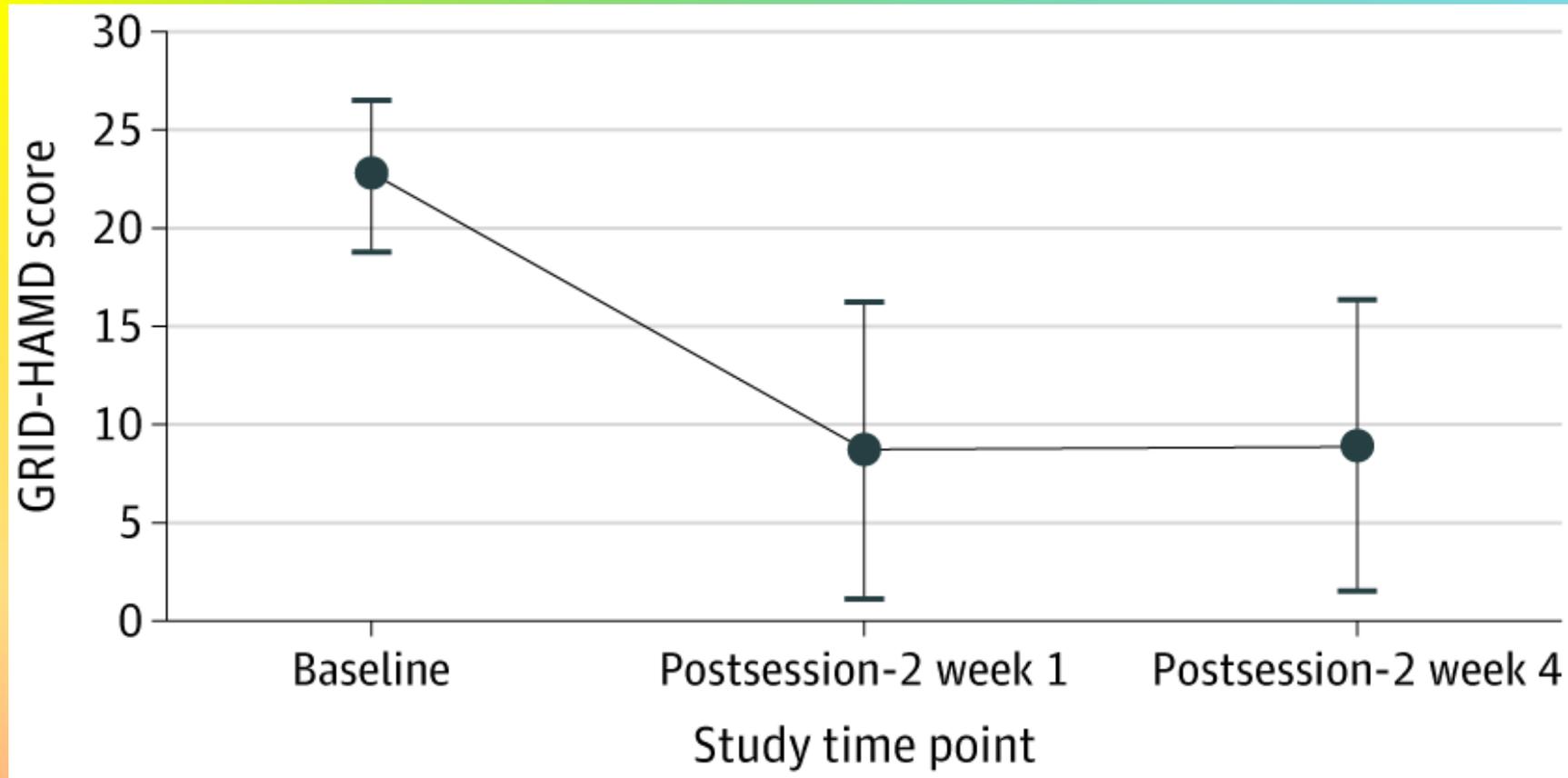
Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder A Randomized Clinical Trial



Mushrooms (Psilocybin)



Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder A Randomized Clinical Trial



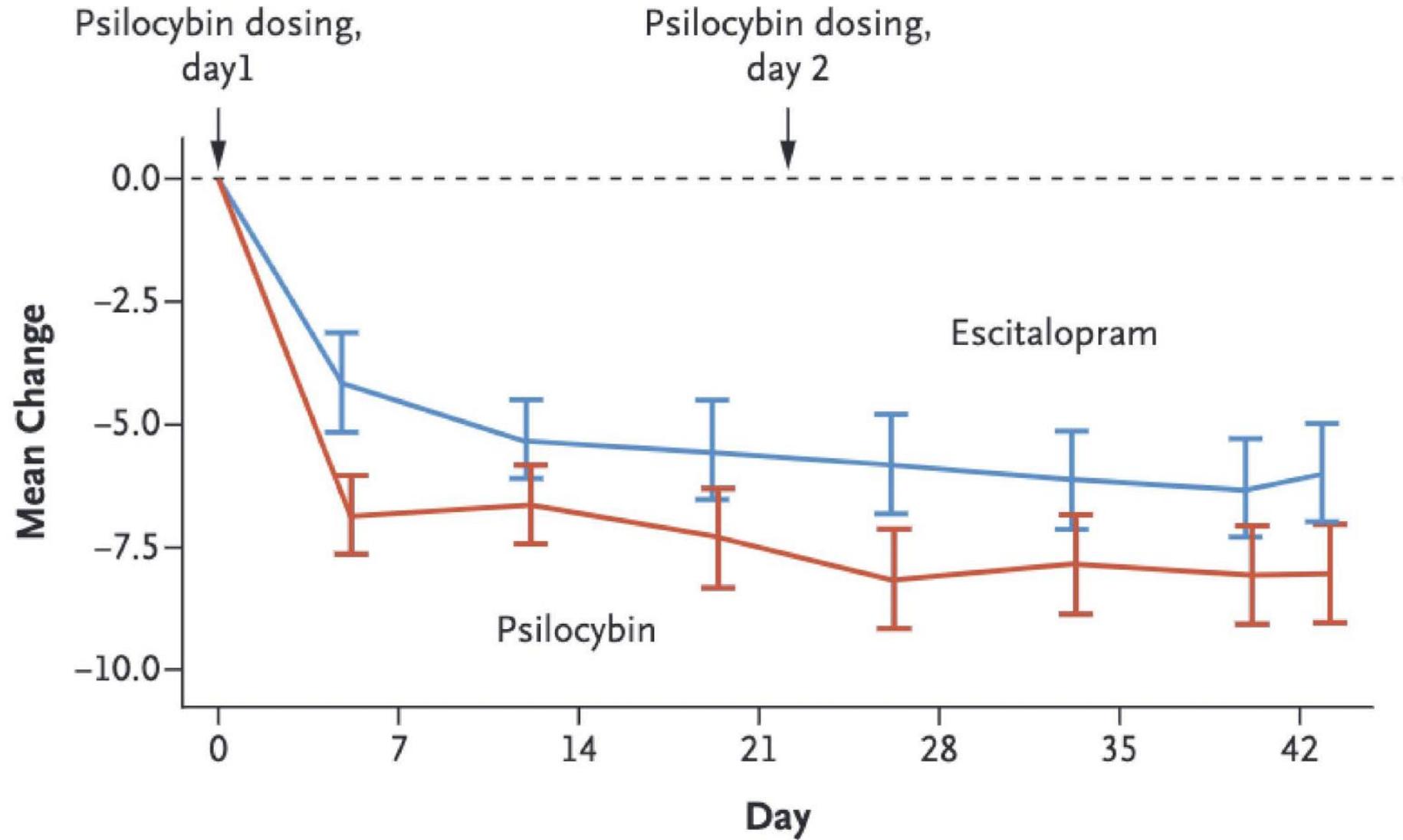
The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

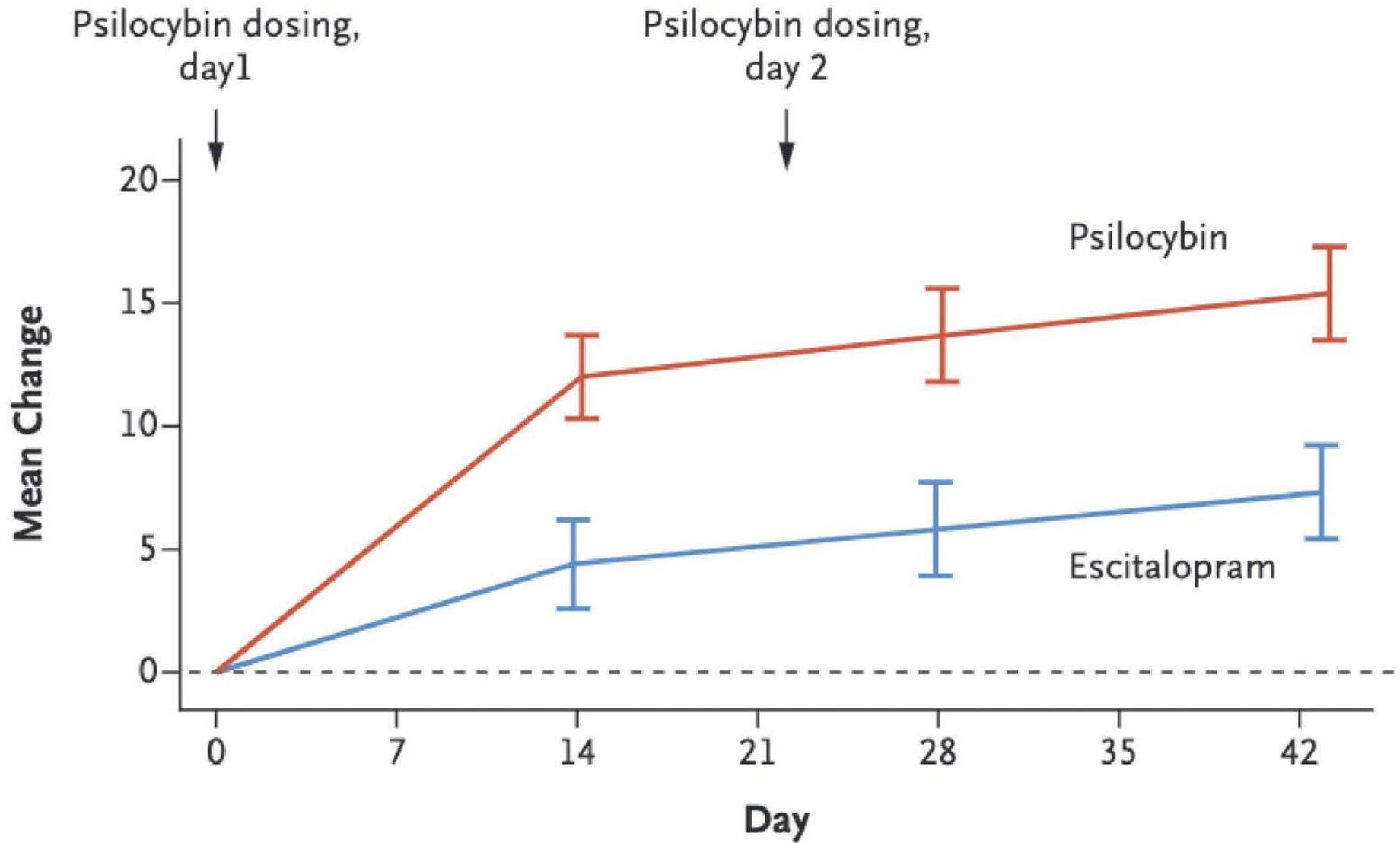
Trial of Psilocybin versus Escitalopram for Depression

Robin Carhart-Harris, Ph.D., Bruna Giribaldi, B.Sc., Rosalind Watts, D.Clin.Psy.,
Michelle Baker-Jones, B.A., Ashleigh Murphy-Beiner, M.Sc.,
Roberta Murphy, M.D., Jonny Martell, M.D., Allan Blemings, M.Sc.,
David Erritzoe, M.D., and David J. Nutt, M.D.

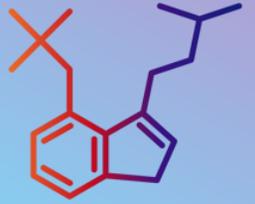
A Change from Baseline in QIDS-SR-16 Score



B Change from Baseline in WEMWBS Score



Mushrooms (Psilocybin)



Palliative Care

Randomized controlled trial - 29 participants: **Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer**

Single moderate-dose psilocybin (in conjunction with psychotherapy)

- Rapid and sustained anxiolytic and anti-depressant effects

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

Roland R Griffiths, Matthew W Johnson, Michael A Carducci, Annie Umbricht, William A Richards, Brian D Richards, Show less ^
Mary P Cosimano, Margaret A Klinedinst

First Published November 30, 2016 | Research Article | [Find in PubMed](#) | [Check for updates](#)

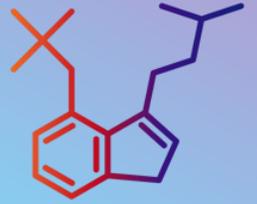
<https://doi.org/10.1177/0269881116675513>

[Article information](#) ▾



- NO serious adverse events occurred

Mushrooms (Psilocybin)

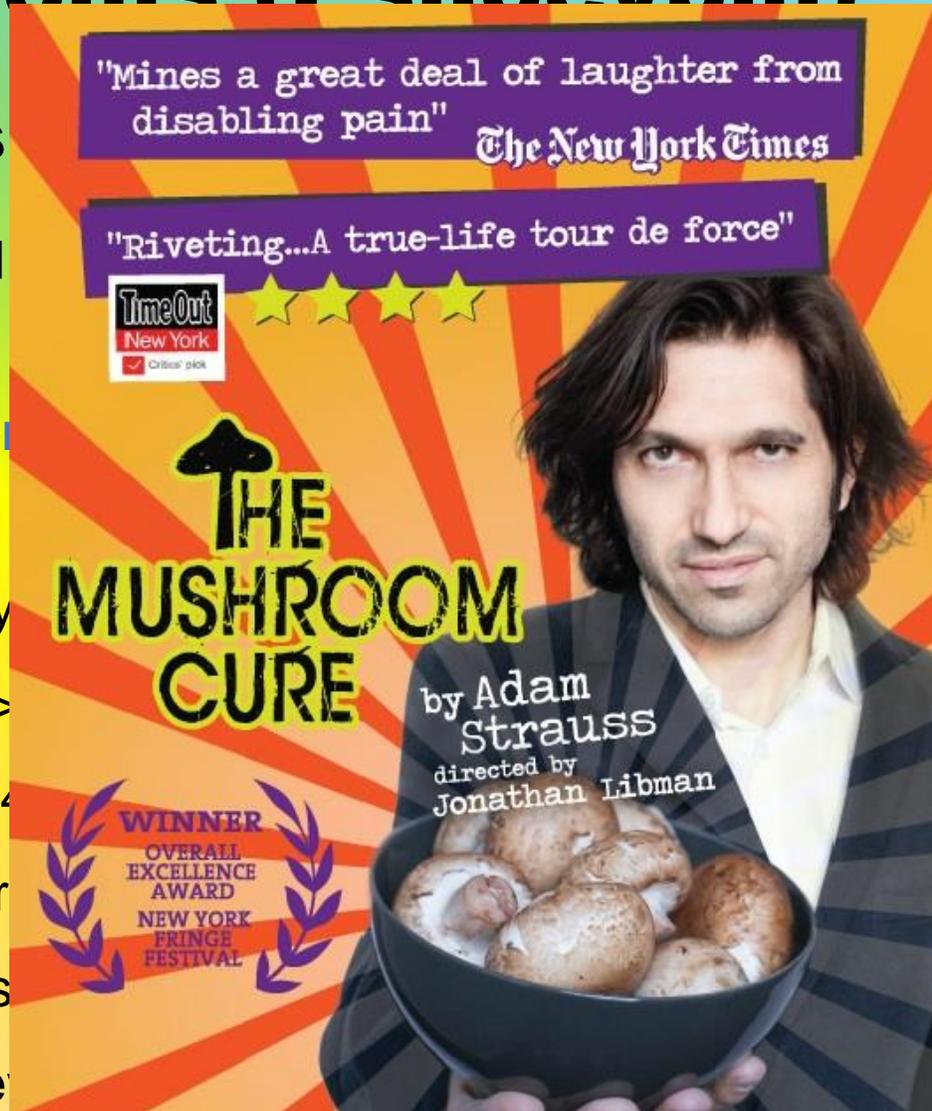


Obsessive

Safety, tolerability, and compulsive disorder

4 sessions with different

- Decreases in OCD symptoms
- 66.7% maintained a > 50% reduction in (YBOCS) scores at 24 weeks
- 2 reported symptom re-emergence
- Psychologically and socially improved
- No serious adverse effects

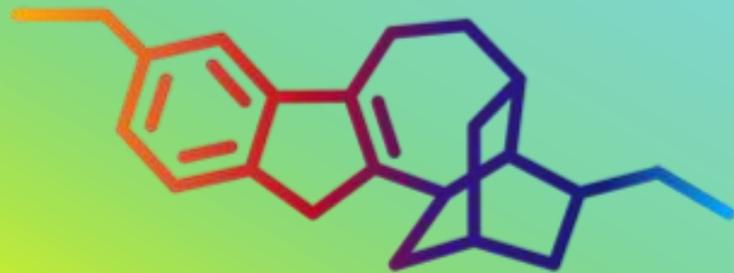


th obsessive-

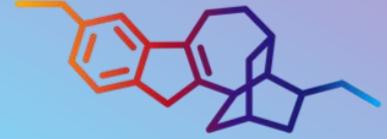
e Compulsive Scale

psilocybin ingestion

Ibogaine



Ibogaine



- Tabernanthe Iboga bush
- Native to West Central Africa
- Used by Bwiti religion in Gabon for healing and spiritual purposes
- Rite of passage into adulthood
- Sustainability is a problem



Ibogaine



Howard Lotsof

- Discovered addiction interruption effects for opioids
- 75-100 ibogaine treatment centers worldwide

Pharmacology

- High affinity for sigma-2 receptor
- Moderate affinity for opioid receptors
- Metabolized into Noribogaine



Ibogaine



Toxicology and safety

- Fatalities from drug-drug interactions and pre-existing heart conditions
- 19 known deaths after ibogaine, no evidence toxic drug effects to blame

Psychological effects

- Phase 1: Awakened dream state
- Phase 2: Evaluative phase
- Phase 3: Residual stimulation phase



Ibogaine



Treatment of opioid use disorder with ibogaine: detoxification and drug use – 2018 Study

Objective: Study outcomes following opioid detoxification with ibogaine in 30 Participants

Treatment

- Test dose= 3mg/kg
- Flood dose= four times the test dose (2-12 hours after test dose)
- Booster dose= 3 to 5 mg/kg



Ibogaine



Treatment of opioid use disorder with ibogaine: detoxification and drug use – 2018 Study

Results

- Subjective Opiate Withdrawal Scale (SOWS) scores decreased from 31.0 to 14.0
- Improvement in Drug Use, Family/Social Status and Legal Status at 12 months
- Ibogaine effects on opioid withdrawal symptoms comparable to methadone
- Treatment effects extending up to 12 months

Ibogaine

Qualitative Perspective



Ibogaine state of consciousness produced insight and meaning

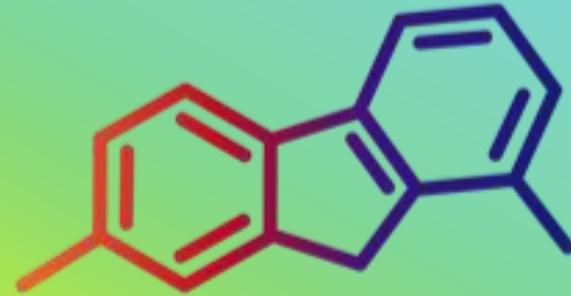
Diminished posttreatment drug craving

“...you could safely say that iboga will give an opiate addict several months to a half a year of freedom from cravings and an expanded awareness. This gives the user a period of time in which to get his/her life together and learn to face things straightforwardly, directly and honestly. Iboga will not do the work for you. However, it will help you do your own work.”

No clinically significant cardiovascular or other medical events occurred



Ayahuasca



Ayahuasca



- Indigenous tribes of Amazonia
- Entheogenic brew or tea
 - Banisteriopsis caapi vine and the Psychotria viridis leaf (containing DMT)



Ayahuasca



Pharmacology

- *B. caapi* contains monoamine oxidase inhibitors (MAOIs)
- Serotonin 5-HT1a and 5-HT2a/2c receptor sites

Effects

- Intensified emotions
- Heightened visual and auditory sensations
- Duration of effects last 4+ hours



Ayahuasca



Therapeutic uses

- Addiction
- Depression
- Anorexia Nervosa*
- PTSD*



* Emerging evidence, still under investigation

Ayahuasca



Ayahuasca-Assisted Therapy for Addiction – 2013 Study

- “Working with Addiction and Stress” retreat
- 12 participants from First Nations Band in Canada



Ayahuasca



Ayahuasca-Assisted Therapy for Addiction – 2013 Study

- No serious adverse health or psychological consequences
- Enhanced mindfulness, personal empowerment, and hopefulness
- Quality of life and increased connection with self, nature, others, and spirit
- Reduced problematic cocaine use
- Tobacco and alcohol use also declined from baseline reports

Ayahuasca



Qualitative Reports

- “With my last experience with the ayahuasca, I really faced myself. Like, my fear, my anger. . . . I wish I was introduced to it [ayahuasca] like twenty years ago. It could have saved me a lot of time and trouble.”
- “[The retreat] affected my life in giving me another chance at life rather than being stuck in my addiction and just living for my addiction . . . [Ayahuasca] really opened my eyes. It was like I was shut down [before drinking ayahuasca]. My mind and my eyes were shut down to everything. After the retreat I felt like a brick was lifted off of my shoulders and I was just feeling free.”

Ayahuasca



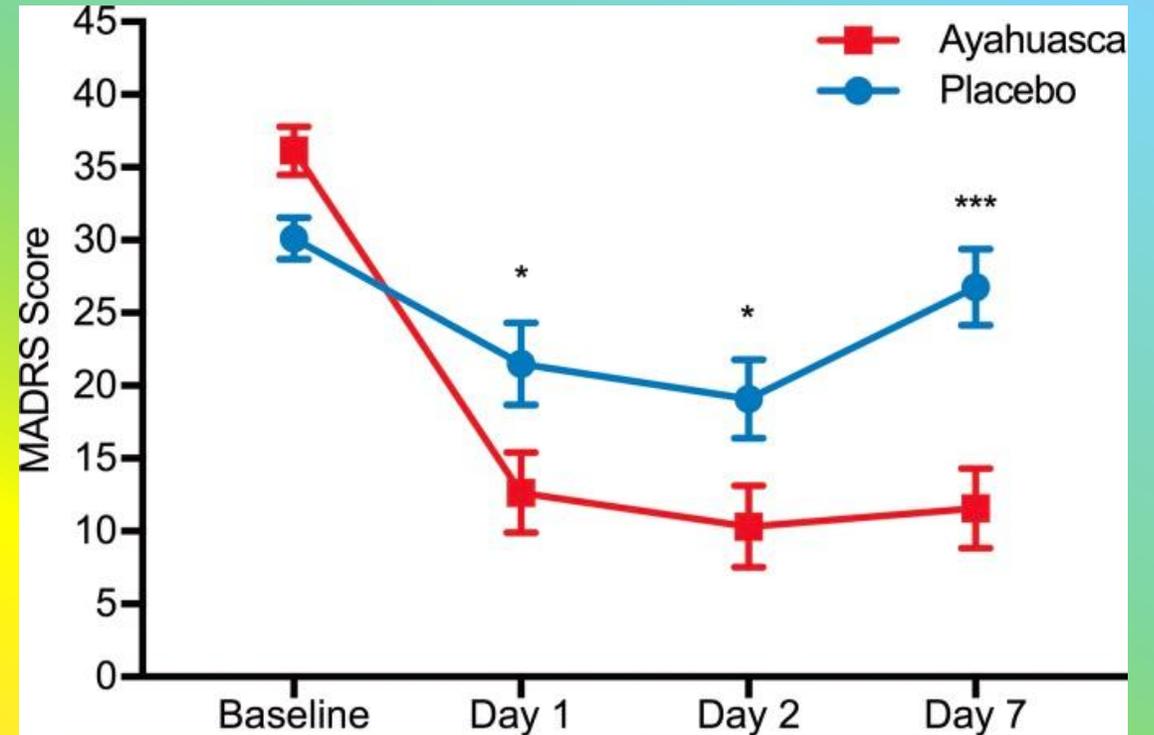
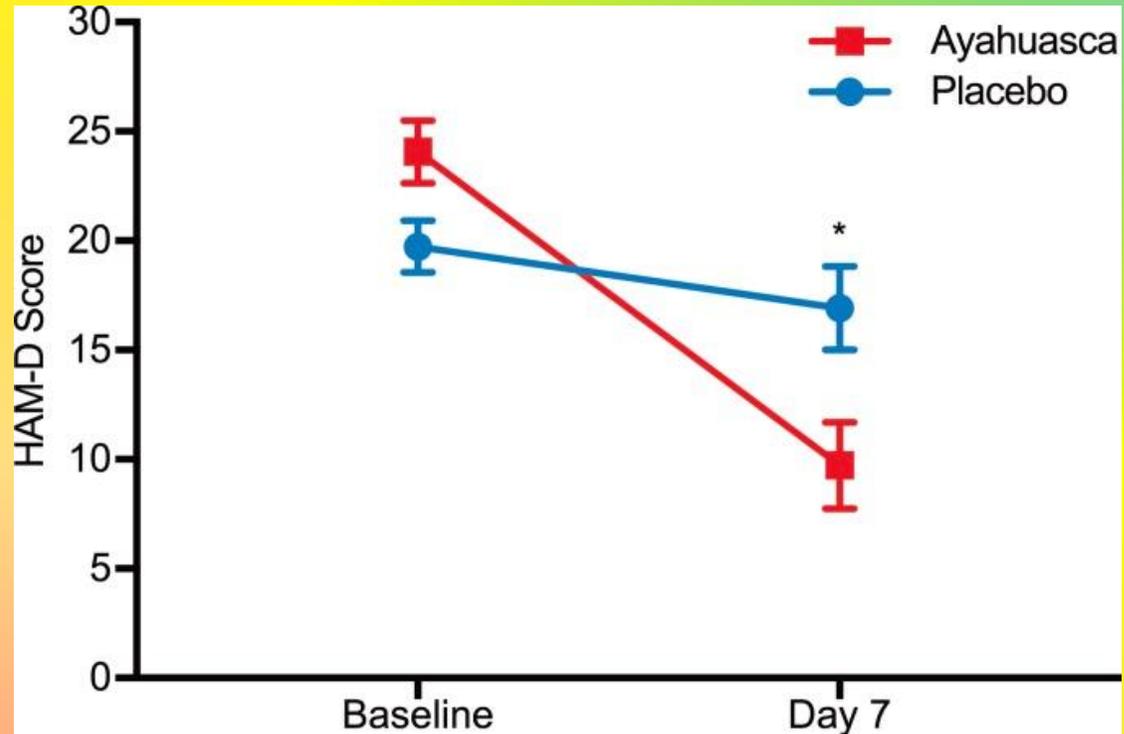
Ayahuasca for Depression – 2019 Study

- Design: parallel-arm, double-blind randomized placebo-controlled trial in 29 patients with treatment-resistant depression.
 - Patients received a single dose of either ayahuasca (n=14) or placebo (n=15).
- Outcomes: Changes in Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating scale at baseline, and at 1 (D1), 2 (D2), and 7 (D7) days after dosing.

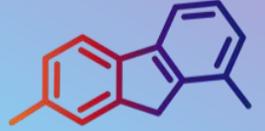
Ayahuasca



Ayahuasca for Depression – 2019 Study



Ayahuasca



Ayahuasca treating PTSD



Ayahuasca in Peru



2012 Annual Report BULLETIN



Winter 2012

Consideration of Ayahuasca for the Treatment of Posttraumatic Stress Disorder

JESSICA L. NIELSON, PH.D.

JULIE D. MEGLER, MSN, NP-BC

THERE IS A GROWING AMOUNT OF RESEARCH on the development of PTSD and its various treatments. The fact that many people who suffer from PTSD struggle with the currently approved therapeutic options that are available to them suggests that we need to start exploring alternative strategies to treat this disorder.¹ With the large number of veterans returning home from war that may have or will develop PTSD, we must have a diverse framework of therapy and integration in place for them.

Alternative options that are currently being explored for the treatment of PTSD include MDMA-assisted psychotherapy² and marijuana.³ Current research indicates that ayahuasca mimics mechanisms of currently accepted treatments to PTSD, and its use as an alternative treatment for other types of disorders are also being considered.⁴ However, in order to understand the implications of ayahuasca in the treatment of PTSD, we need to understand how PTSD develops, which involves memory formation.

★

Memory can be divided into three types: perceptual memory, episodic memory, and semantic memory.⁵ Before it reaches conscious awareness, information from the outside world first passes through the sensory cortices of our brain. This is perceptual memory. Sensory input then travels up to higher processing regions. Within our limbic system lies the hippocampus and amygdala. The cognitive aspect of memory occurs in the hippocampus. There we are able to perceive the sensory information and form “episodic” memories. The amygdala links the episodic memory to the associated emotions.⁵ At this stage, when an event is recalled the original sensations and emotions are replayed with it.

Over time, relevant information from episodic memory is transferred to the neo-cortex to create semantic memory networks. Here the information is integrated into your general knowledge, and becomes available for understanding events in the future. It is in the cortex that we assign meaning to our memories. A feedback loop from the cortex to the hippocampus then tells it to weaken the episodic memory.⁵ The memory can then be recalled without provoking the original sensations and emotions.

In PTSD, the brain fails to appropriately consolidate and integrate episodic memories into the semantic memory system.⁵ The memory and its associated emotions become trapped in the hippocampus, so that whenever the adverse memory is triggered

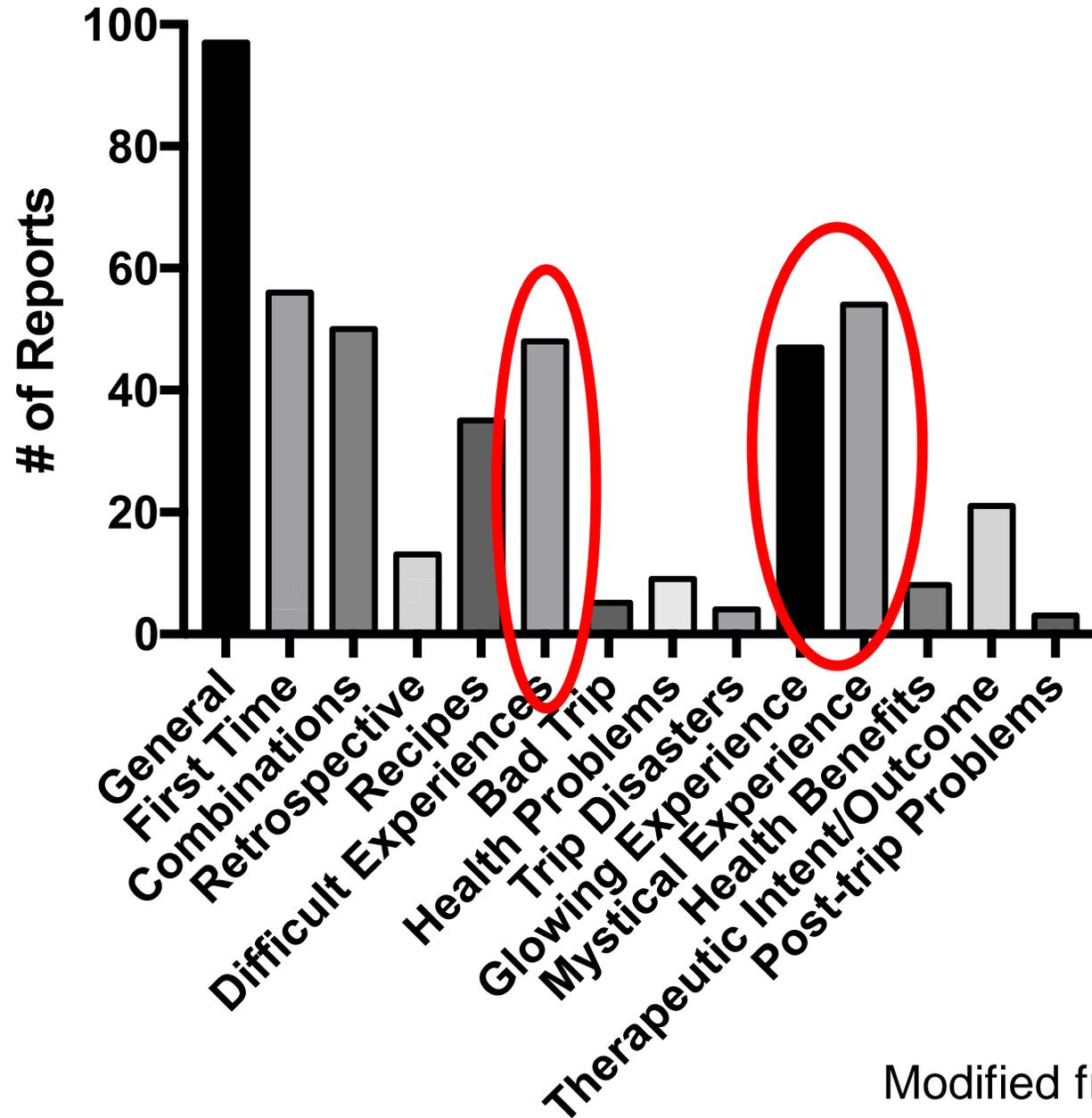


Jessica L. Nielson, Ph.D.



Julie D. Megler, MSN, NP-BC

Erowid Ayahuasca Experience Categories



Ayahuasca in the Media

DRUGS

Ayahuasca: Coming to a Clinic Near You?

Psychedelic drug ayahuasca improves hard-to-treat depression

For me, ayahuasca was as good as therapy. Here's what the science says.

Is Peru's Psychedelic Potion a Cure or a Curse?

Are Psychedelics the New Prozac?

How Tripping on Ayahuasca Could Help People with Eating Disorders

Hallucinogenic plant ayahuasca gains foothold in US

Ayahuasca Can Change Your Life — As Long as You're Willing to Puke Your Guts Out

Ayahuasca in the Media

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Is Peru's Psychedelic Potion a Cure or a Curse?

Foreigners are flocking to try a traditional brew called ayahuasca that some say eases psychological distress—but it has dangers, too

AP / April 23, 2018, 6:04 AM

Canadian man lynched over shaman's death in Peru

FEATURES

The Dark Side of Ayahuasca

By **Kelly Hearn**

Sad Easter in Florida, Death Soul Quest

April 8, 2018 | Shaman Steve Hupp

Our hearts and healing thoughts go out to the Family of the 22 year old young man who died during a ceremony at the embattled Soul Quest in Orlando Florida on easter weekend.

NEWS

2 die in north-Colombia ayahuasca ceremony

written by *Adriaan Alsema* | August 16, 2011

American Found Dead After Taking Ayahuasca

September 14, 2012 10:25 am · 5 comments

The mother and sister of Kyle Nolan, a young American whose body was found Tuesday near Puerto Maldonado, in Madre de Dios, arrived in the jungle river town yesterday to identify the body and to find out how he had died.

Shipibo Medicine Woman Gunned Down in Peruvian Amazon

APRIL 20, 2018 | AMAZON WATCH STATEMENT



Peruvian shaman confesses he buried body of U.S. teen who died from drinking hallucinogenic herbal brew at spiritual retreat

British backpacker dies after taking hallucinogenic brew in Colombia

Gap year teenager from Bristol, Henry Miller, suffered allergic reaction after taking part in tribal ritual

Psychedelic tourism thriving in Peru despite recent killing



...te village in the Peruvian Amazon



Ayahuasca for PTSD Survey

SurveyMonkey Inc. [US] | <https://www.surveymonkey.com/r/AyaPTSD>



Exit



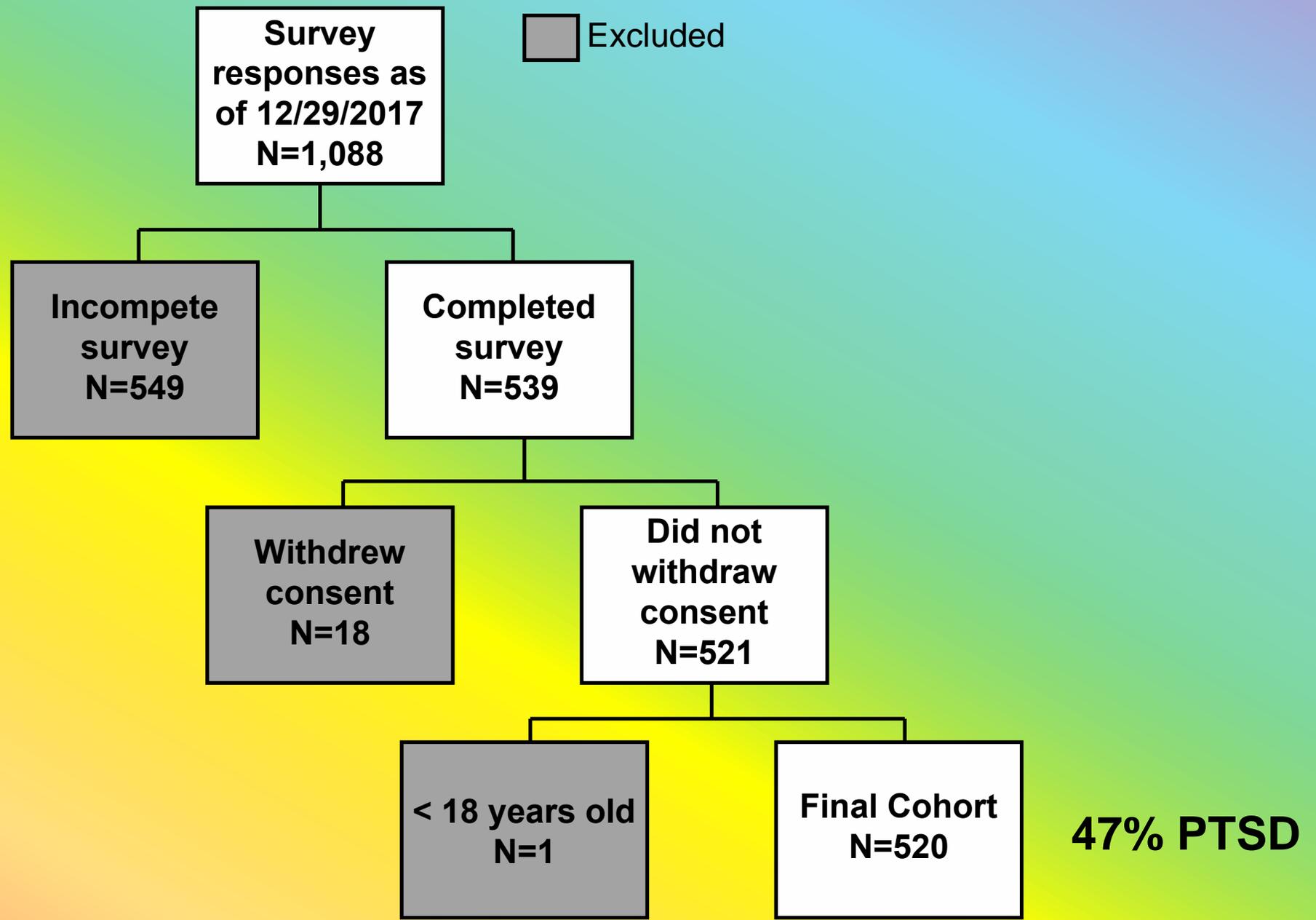
Ayahuasca for PTSD

Study Description

This is an anonymous questionnaire to gather preliminary data about the potential risks and benefits associated with taking Ayahuasca as a therapy for post-traumatic stress disorder (PTSD). The data collection is being sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS). Dr. Jessica Nielson, Ph.D. is the Principal Investigator for this research study (UCSF IRB #16-19906).

Study Limitations

- Anonymous, online survey
- Retrospective, cross-sectional study
- Variability in set and settings of participants
- Limited to English speaking participants



QUALITATIVE OUTCOMES

Dangerous Experience Themes

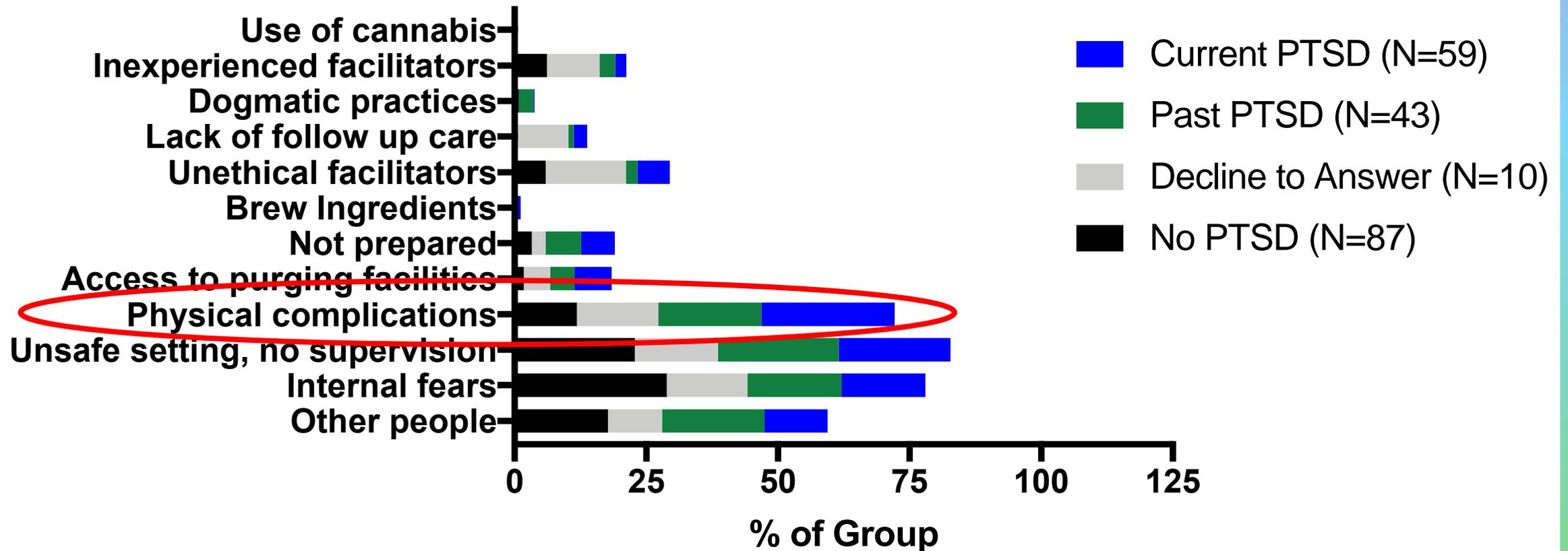


Table 1. Common themes related to dangerous aspects of an ayahuasca experience.

THEMES	DETAILS
Complications with other participants in the ceremony	Overcrowding, lack of screening for unstable people
Psychological complications	Internal fears, panic, intense emotions, feeling out of control, presence of “entities”, psychosis
Unsafe setting, no supervision	No medical supervision, lack of one-on-one support, fires, language barriers, dangers of the jungle, intoxicated facilitators
Physical complications	Increased heart rate and blood pressure, problems breathing, exhaustion, dehydration, unsteady gait
Access to purging facilities	Difficult or no access to toilet/bucket, walking to bathroom without help/falling
Not being prepared	Not following dieta, contraindicated medications, pre-existing conditions, too soon after trauma, facilitators not educating participants about risks
Brew ingredients	Presence of Datura or tobacco, non-traditional admixtures
Unethical facilitators	Sexual abuse, financial exploitation, legal concerns, “witch doctors”
Lack of follow-up care	No process for integration, risks of self-harm
Dogmatic practices	Strict religious practices, gender issues
Inexperienced facilitators	Not having a shaman, lack of trust due to inexperience, unable to handle psycho-spiritual complications
Use of cannabis	Smoking marijuana during ceremony

Helpful Experience Themes

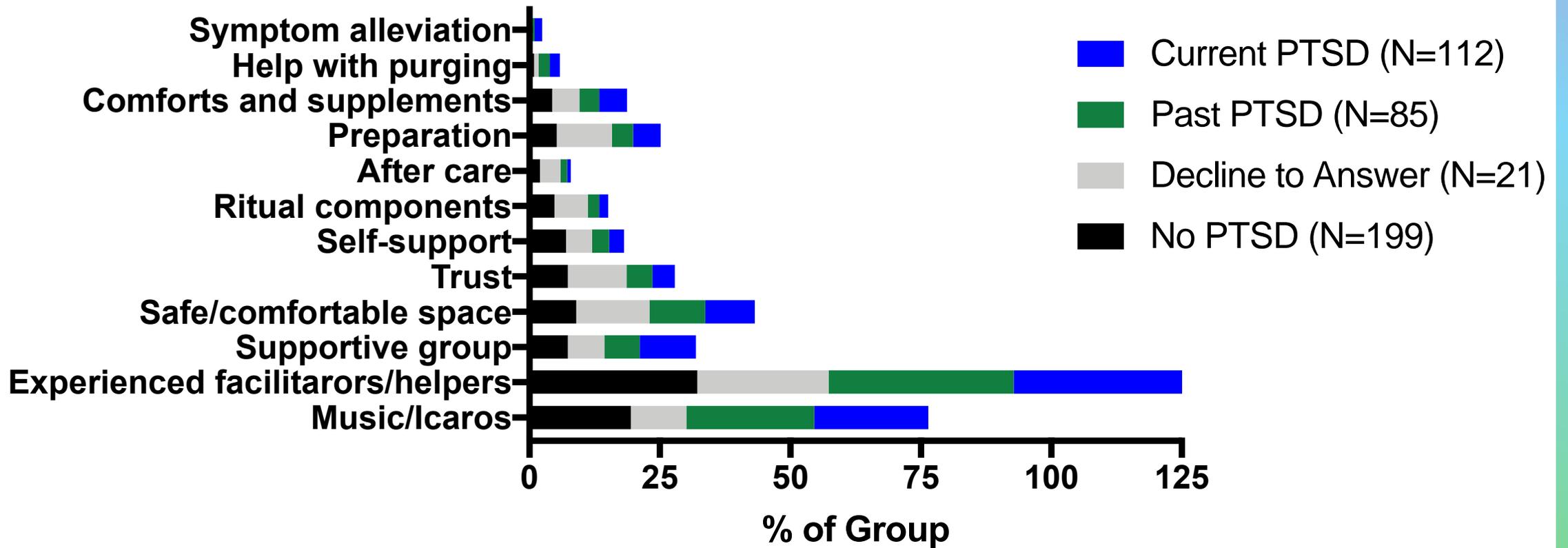


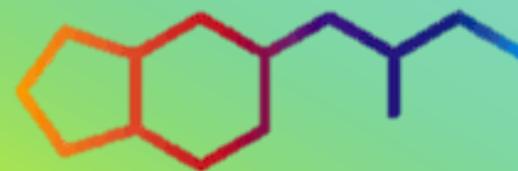
Table 2. Common themes related to helpful aspects of an ayahuasca experience.

THEMES	DETAILS
Soothing Sounds	Shaman singing icaros, playing instruments, sounds of the jungle, familiar music, being able to sit in silence
Experienced facilitators and helpers	Having a shaman, having support from helpers, one-on-one attention
Supportive, like-minded group	Doing ceremony with others in their community, people they are comfortable with
Safe/comfortable space	Having a space to lay down, pillows, blankets, spaces to be alone, being in nature, darkness/limited light
Trust	Trusting the facilitators, trusting ayahuasca, being able to let go/surrender
Self-support	Meditation, journaling, yoga, prayer, connection to spirits/guides, self-love
Ritual components	Smudging/cleansing of space, sacred items (talismans, an altar), mapacho smoke
After care	Post-session meetings with shaman, with group
Preparation	Pre-session meetings, setting intentions, following dieta, experience with other psychedelics
Comforts and supplements	Agua Florida, ginger tea for nausea, citrus, flower baths, scented oils, pets
Help with purging	Helpers to provide and clear purge buckets, toilet paper/tissue, easy access/help to bathroom, being comfortable purging in front of others
Symptom alleviation	Claims of being healed by ayahuasca from symptoms of trauma (e.g. PTSD, depression)

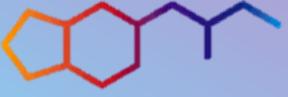
DATA ANALYSES ONGOING (N=963)

- Differences in mystical experiences between ayahuasca and DMT
- More in-depth qualitative coding of subjective experiences
- Exploration of trauma caused by poor ceremony facilitation
- Changes in substance use and psychological symptoms

MDMA



MDMA



- 3,4-Methylenedioxyamphetamine
- Empathogen and entactogen
- MDMA effects:
 - Decreased fear
 - Clear-headed, alert state of consciousness
 - Serotonin, Oxytocin

History of MDMA



- 1912 - MDMA first synthesized and patented (1914) by Merck Pharmaceuticals in Germany.
 - \pm 3,4-methylenedioxyamphetamine
- 1976- Alexander Shulgin re-synthesized MDMA
 - Claudio Naranjo: MDA and MDMA in groups
- 1977 – Leo Zeff tried MDMA and distributed it to other therapists
 - MDMA was called “Adam”
- 1980- Ann Shulgin
- 1985 – MDMA is classified as a Schedule 1 drug
- 1990s - MDMA becomes popular in the RAVE culture

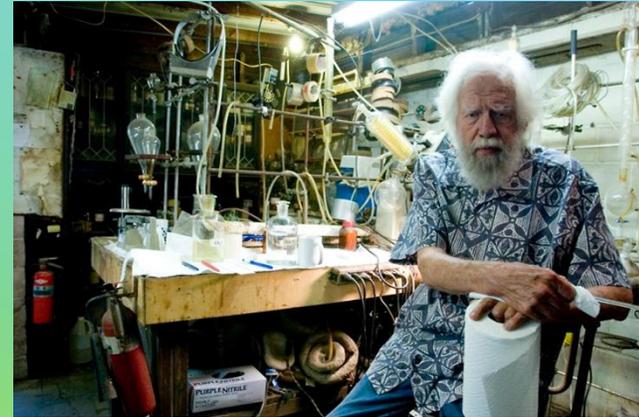
MDMA in the Brain and Body

- Effects last 6-8 hours
 - Onset of effects takes 30-60 minutes
 - Peak effects 90-150 minutes
- Increases serotonin, dopamine, oxytocin and norepinephrine
- Decreases activity in the left and right amygdalae
- Increases activity in the prefrontal cortex



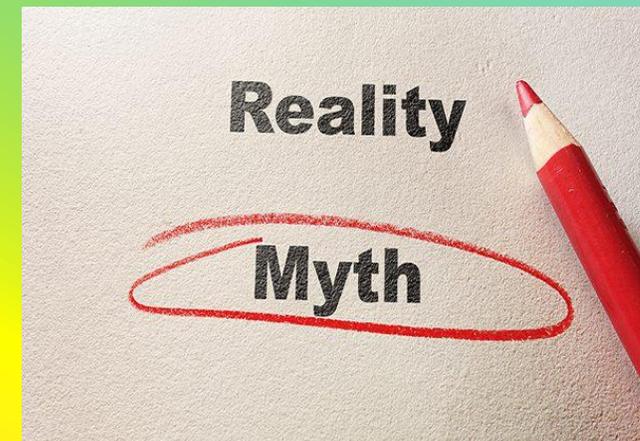
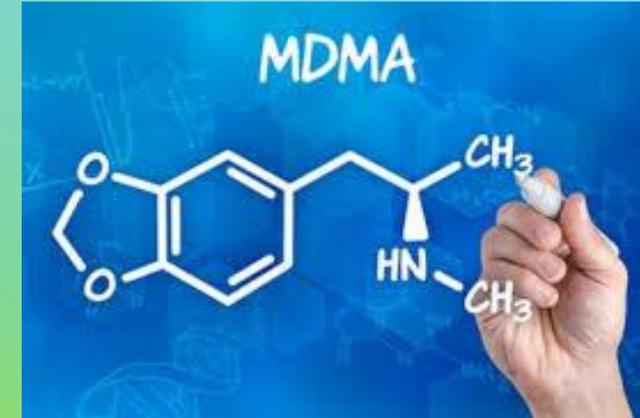
Subjective Experience

- Pro-social effects
 - Feelings of intimacy and love
 - Compassion and empathy
 - Empathogen
 - Entactogen
- Reduced fear and anxiety
- Enhanced sensations
 - Visual and auditory
- Ecstasy
 - Feelings of euphoria
 - Mystical and spiritual experience
 - Holotropic state of consciousness



Myths about MDMA

- Severely damaging to your brain
 - “Holes in your brain”
- Highly addictive
- Depletes serotonin permanently
- “Molly” is pure MDMA



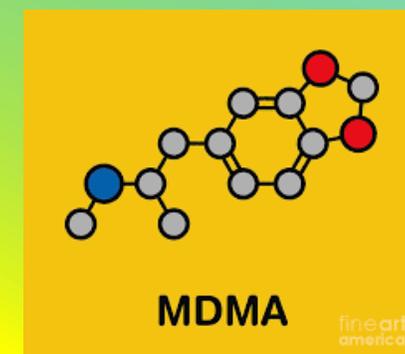
Therapeutic Process

- Preparation sessions
 - Establish therapeutic alliance
 - Discuss use of touch, music, and intentions
- MDMA-assisted session
 - Non-directive approach
 - Directive approach
- Integration sessions
 - Making sense of experiences
 - Applying insights to form new thought patterns and habits of thinking
 - Prepare for next MDMA session

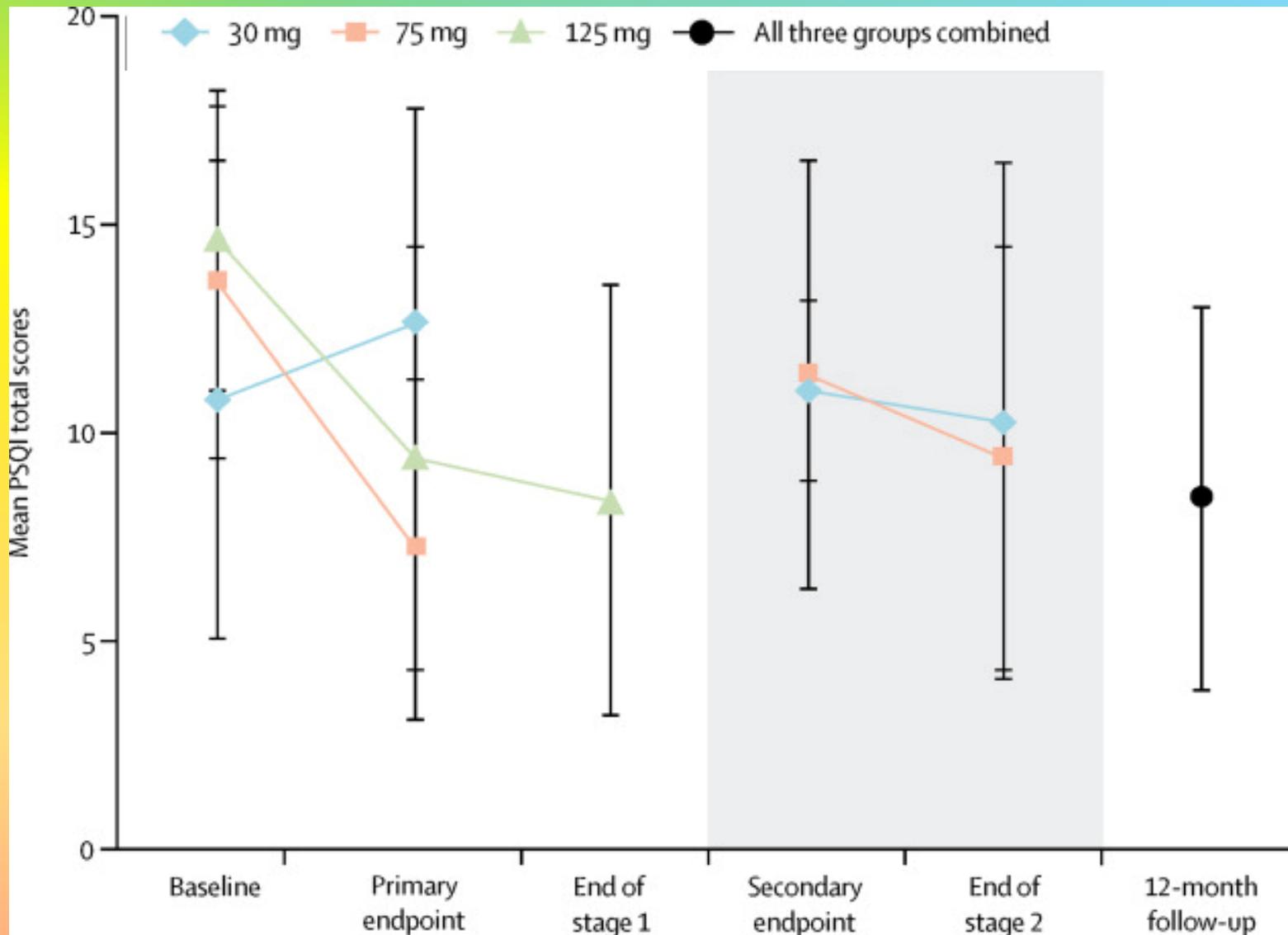
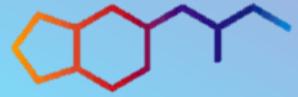


FDA Breakthrough Therapy Status

- FDA approved by 2023 for patients diagnosed with PTSD
- Expanded Access
- Phase 2 results
 - 107 participants
 - 61% no longer qualified for PTSD after three sessions of MDMA-assisted psychotherapy two months following treatment
 - 12-month follow-up, 68% no longer had PTSD
- Memory reconsolidation and fear extinction



MDMA-Assisted Psychotherapy



MDMA-Assisted Psychotherapy



Post-Traumatic Stress Disorder

Study	NCT #	Location	Population	MDMA doses	Active MDMA sessions completed ^b	Long-term follow-up	Publications
MP-1	NCT00090064	Charleston, South Carolina	Crime, veterans	0 mg ($n = 8$), 125 mg ($n = 15$)	1 ($n = 2$) 2 ($n = 11$) 3 ($n = 9$)	CAPS ($n = 16$) LTFUQ ($n = 19$)	(Mithoefer et al. 2011 , 2013)
MP-2	NCT00353938	Biberist, Switzerland	Various	25 mg ($n = 5$), 125 mg ($n = 9$)	3 ($n = 12$)	CAPS ($n = 11$) LTFUQ ($n = 0$)	(Mithoefer et al. 2019 ; Oehen et al. 2013)
MP-4	NCT01958593	Vancouver, Canada	Various	0 mg ($n = 2$), 125 mg ($n = 4$)	3 ($n = 6$)	CAPS ($n = 6$) LTFUQ ($n = 6$)	(Mithoefer et al. 2019)
MP-8	NCT01211405	Charleston, South Carolina	Veterans, firefighters, police officers	30 mg ($n = 7$), 75 mg ($n = 7$), 125 mg ($n = 12$)	1 ($n = 1$) 3 ($n = 18$) 5 ($n = 5$) 6 ($n = 1$)	CAPS ($n = 24$) LTFUQ ($n = 24$)	(Mithoefer et al. 2018 , 2019)
MP-9	NCT01689740	Be'er Ya'aqov, Israel	Various	25 mg ($n = 3$), 125 mg ($n = 7$) ^a	2 ($n = 9$)	CAPS ($n = 9$) LTFUQ ($n = 9$)	(Mithoefer et al. 2019)
MP-12	NCT01793610	Boulder, Colorado	Various	40 mg ($n = 6$), 100 mg ($n = 9$), 125 mg ($n = 13$)	3 ($n = 26$)	CAPS ($n = 25$) LTFUQ ($n = 25$)	(Mithoefer et al. 2019 ; Ot'alora et al. 2018)

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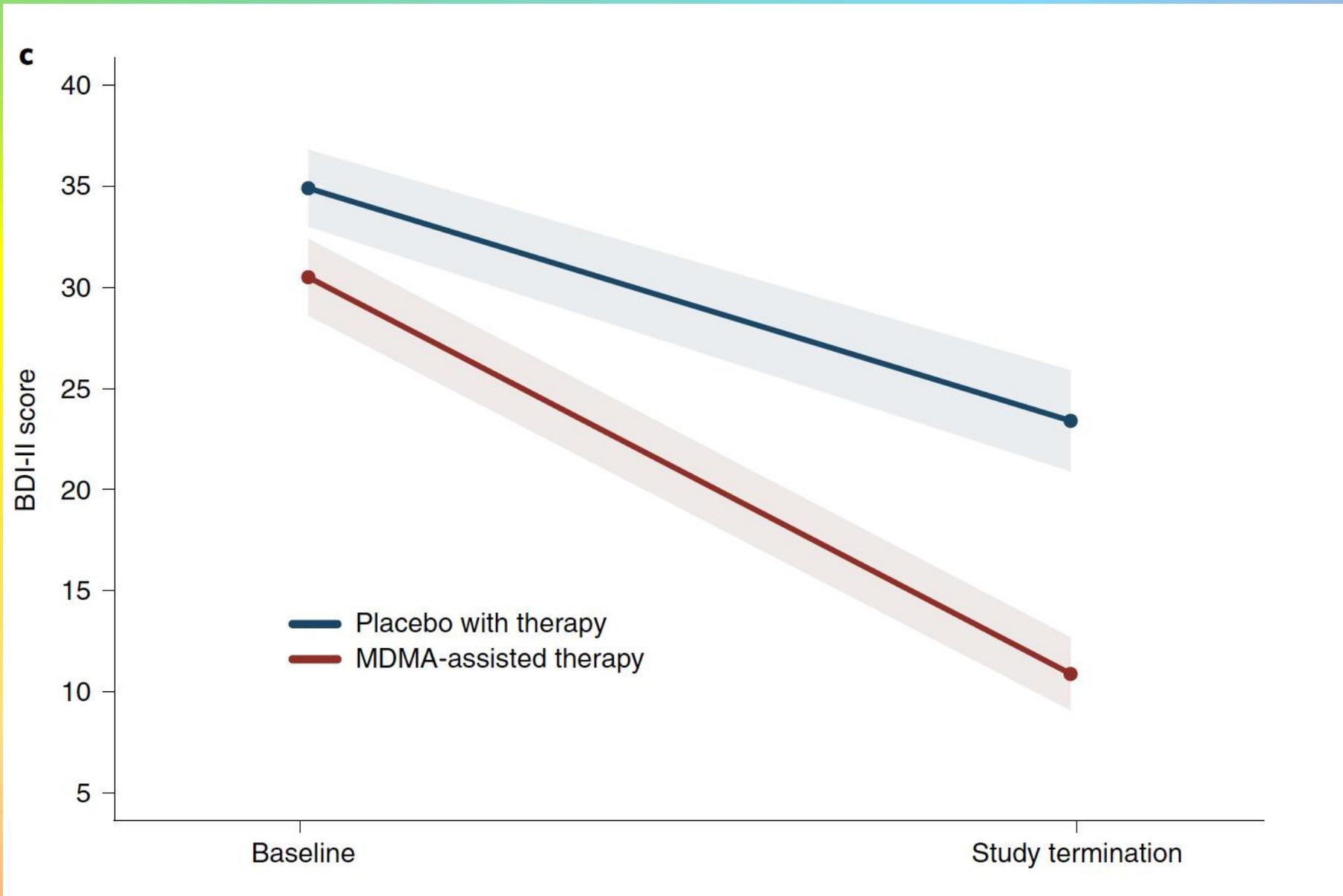
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MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study



MDMA and Social Anxiety in Autism

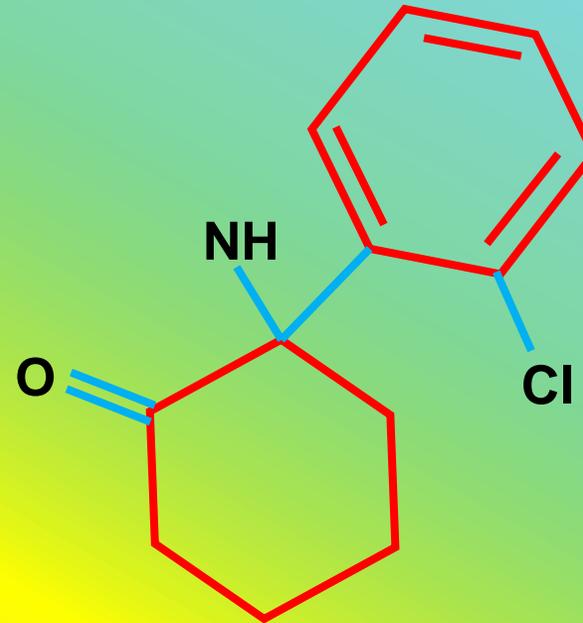
- Danforth et al. (2018)
 - 12 participants (8=MDMA and 4=placebo)
 - 75mg-125mg of MDMA (two MDMA sessions)
 - Results
 - Significant difference in Liebowitz Social Anxiety Scale (LSAS) scores for MDMA group compared to placebo at one-month endpoint
 - Also at 6-month follow up
- Discussion
 - Increased comfort with prolonged eye contact
 - Increased ability to verbally express emotions



Less Anxiety and More Confidence

- Eleven of 12 participants reported marked reductions in anxiety responses to triggers previously distressing for them
 - Such as making a presentation, speaking on the telephone, entering new social settings, or interacting with authority figures.
- Relationships with family and friends improved due to increased social skills.
- Some participants reported they were able to initiate dating with another person for the first time in their life.
- It appears that MDMA-assisted therapy helped participants feel calmer and more confident when interacting with other people in social situations

Ketamine



Ketamine

- Racemic mixture consisting of (S)- and (R)-ketamine
- Dissociative (NMDA antagonist)
- In use since 1970s as an anesthetic
 - analgesic
 - anti-inflammatory
 - anti-depressant*

*** Current FDA-approved uses do not pair with psychotherapy**

Randomized Controlled Trial > Am J Psychiatry. 2018 Dec 1;175(12):1205-1215.

doi: 10.1176/appi.ajp.2018.18020138. Epub 2018 Aug 29.

Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism

Nolan R Williams¹, Boris D Heifets¹, Christine Blasey¹, Keith Sudheimer¹, Jaspreet Pannu¹, Heather Pankow¹, Jessica Hawkins¹, Justin Birnbaum¹, David M Lyons¹, Carolyn I Rodriguez¹, Alan F Schatzberg¹

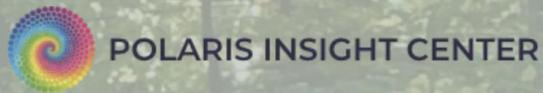
> Mol Psychiatry. 2019 Dec;24(12):1779-1786. doi: 10.1038/s41380-019-0503-4.
Epub 2019 Aug 29.

Attenuation of antidepressant and antisuicidal effects of ketamine by opioid receptor antagonism

Nolan R Williams^{# 1}, Boris D Heifets^{# 2}, Brandon S Bentzley^{# 3}, Christine Blasey^{# 3 4}, Keith D Sudheimer³, Jessica Hawkins³, David M Lyons³, Alan F Schatzberg⁵

* Effects can be bl...
suggesting role of

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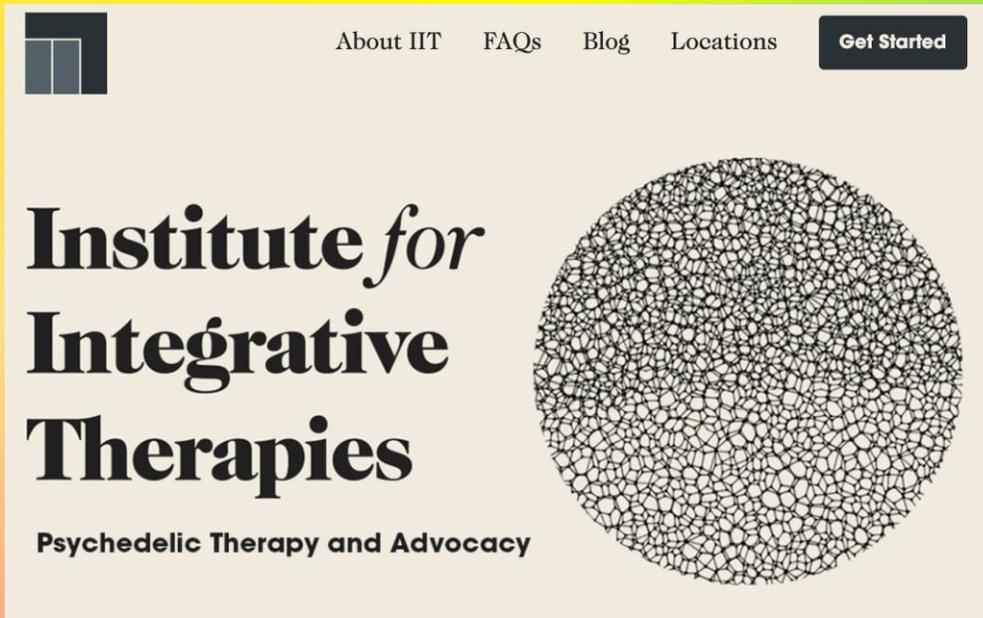
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THANK YOU FOR YOUR ATTENTION!

QUESTIONS??