Therapeutic Applications of Psychedelics

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Disclosures

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

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

## Psychedelics ≠ Psychotomimetic

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

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia Spectrum</th>
<th>5-HT$_{2A}$ Agonists</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory modalities</td>
<td>Mainly AH (multimodal in some cases)</td>
<td>Mainly VH (multimodal in some cases)</td>
<td>Different</td>
</tr>
<tr>
<td>Content</td>
<td>No geometric hallucinations</td>
<td>Geometric hallucinations</td>
<td>Different</td>
</tr>
<tr>
<td></td>
<td>Complex hallucinations (mostly ordinary entities)</td>
<td>Complex hallucinations (ordinary and extraordinary entities)</td>
<td></td>
</tr>
<tr>
<td>Meaning</td>
<td>Strong existential/metaphysical meaning</td>
<td>Strong existential/metaphysical meaning</td>
<td>Similar</td>
</tr>
<tr>
<td>Reality monitoring/insight</td>
<td>Poor reality monitoring and insight</td>
<td>Reality monitoring and insight often preserved</td>
<td>Different</td>
</tr>
<tr>
<td>Duration</td>
<td>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.</td>
<td>Transient states, lasting a few hours. Long-term perceptual effects are rare.</td>
<td>Different</td>
</tr>
</tbody>
</table>

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

RSNs, resting-state networks; DMN, default mode network; CEN, central-executive network; SN, salience network.
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
Publication Trends: 1950-2017

All publications

Publications Mentioning Therapy

Papers in PubMed

Year

Marijuana
Ketamine
MDMA
LSD
Psilocybin
Mescaline
Iboga
Ayahuasca
Publication Trends: 1950-2017

- Marijuana
- LSD
- Psilocybin
- Mescaline
- Ketamine
- MDMA
- Iboga
- Ayahuasca

All Papers

Mention therapy
Usana Institute Receives FDA Breakthrough Therapy Designation for Psilocybin for the Treatment of Major Depressive Disorder

Michael Pollan
Author of The Omnivore’s Dilemma
Objective Effects

Default Mode Network

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

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

**Graphs:**

- 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
- PTSD
- Depression
- Anxiety
- Addiction
- OCD
- 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

Full reference list at: nielsonlab.umn.edu
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 $\text{5HT}_{2A} + \text{5HT}_{2C}$
   - Mescaline (Peyote, San Pedro)

2. Tryptamines: non-selective for serotonin receptors
   - $\text{5HT}_{1A} + \text{5HT}_{1B} + \text{5HT}_{1D}$
   - $\text{5HT}_{2A} + \text{5HT}_{2C}$
   - $\text{5HT}_{5} + \text{5HT}_{6} + \text{5HT}_{7}$
   - Psilocybin, Ayahuasca (DMT), Ibogaine (low affinity)

3. Lysergamides: non-selective for serotonin, dopamine and norepinephrine receptors
   - $\text{5HT}_{1A} + \text{5HT}_{1B} + \text{5HT}_{1D} + \text{5HT}_{2A} + \text{5HT}_{2C} + \text{5HT}_{5} + \text{5HT}_{6} + \text{5HT}_{7}$
   - $D_{1} + D_{2} + D_{3} + D_{4}$
   - $\alpha_{1} + \alpha_{2} + \beta_{1} + \beta_{2}$
   - LSD
Function of 5-HT2AR Agonism?

- 5-HT - ↑ plasticity ↑ & environmental sensitivity ↑ & key role in brain development
- 5-HT2AR functioning ↑ key development periods
- 5HT2AR agonism → learning/unlearning/cog-flex ↑
- 5-HT2AR agonism → neuroplasticity (cortex) ↑
- 5-HT2AR agonism → system regression
Function of 5-HT2AR Agonism?

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- 5-HT2AR agonism → neuroplasticity (cortex) ↑
- 5-HT2AR agonism → system regression
- Range of stressors → 5-HT2AR functioning ↑
Psychodelics Promote Structural Plasticity

increased: neurite growth, spine density, synaptogenesis
Psilocybin induces rapid changes of dendritic spines in the hippocampus

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1Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, USA
2Interdepartmental Neuroscience Program, Yale University School of Medicine, New Haven, Connecticut, USA
3Medical Scientist Training Program, Yale University School of Medicine, New Haven, Connecticut, USA
4Department of Neuroscience, Yale University School of Medicine, New Haven, Connecticut, USA
5Lead contact
*Correspondence: alex.kwan@yale.edu
https://doi.org/10.1016/j.neuron.2021.06.008

- Longitudinal 2p imaging
  - Increase spine density for >1 month
- Learned helplessness
  - Ameliorate stress-related behavioral deficit
- mEPSC recording
  - Promote excitatory neurotransmission

Psilocybin
Psychedelic Neurobiology - Mechanisms

University of Minnesota Department of Psychiatry & Behavioral Sciences

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.

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:
Mushrooms (Psilocybin)

4-phosphoryloxy-N,N-dimethyltryptamine
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-HT2A 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

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<thead>
<tr>
<th>NCT Number</th>
<th>Title</th>
<th>Conditions</th>
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<td>A Double-Blind Trial of Psilocybin-Assisted Treatment of Alcohol Dependence</td>
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<tr>
<td>NCT04141501</td>
<td>Clinical and Mechanistic Effects of Psilocybin in Alcohol Addicted Patients</td>
<td>Alcohol Use Disorder</td>
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<td>Effects of Psilocybin in Advanced-Stage Cancer Patients With Anxiety</td>
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<td>NCT00957359</td>
<td>Psilocybin Cancer Anxiety Study</td>
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<td>Psilocybin for the Treatment of Cluster Headache</td>
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<td>Psilocybin-facilitated Treatment for Cocaine Use</td>
<td>Cocaine-Related Disorders</td>
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<td>A Study of Psilocybin for Major Depressive Disorder (MDD)</td>
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<td>Psilocybin vs Escitalopram for Major Depressive Disorder: Comparative Mechanisms</td>
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<td>Psychopharmacology of Psilocybin in Cancer Patients</td>
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<td>Psilocybin for Depression in People With Mild Cognitive Impairment or Early Alzheimer's Disease</td>
<td>Distress</td>
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<td>NCT02950467</td>
<td>Psilocybin-assisted Group Therapy for Demoralization in Long-term AIDS Survivors</td>
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<td>NCT03181529</td>
<td>Effects of Psilocybin in Major Depressive Disorder</td>
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<td>Psilocybin - Induced Neuroplasticity in the Treatment of Major Depressive Disorder</td>
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<td>Psilocybin-facilitated Smoking Cessation Treatment: A Pilot Study</td>
<td>Nicotine Dependence</td>
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<td>NCT03355483</td>
<td>Efficacy of Psilocybin in OCD: a Double-Blind, Placebo-Controlled Study,</td>
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<td>NCT03380442</td>
<td>Psilocybin and Depression</td>
<td>Severe Depression</td>
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<td>NCT03775200</td>
<td>The Safety and Efficacy of Psilocybin in Participants With Treatment Resistant Depression</td>
<td>Treatment Resistant Depression</td>
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</table>
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”

Mushrooms (Psilocybin)

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

Davis et al (2020). *JAMA Psychiatry*
Mushrooms (Psilocybin)

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

Davis et al (2020). *JAMA Psychiatry*
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

Psilocybin dosing, day 1

Psilocybin dosing, day 2

Mean Change

Day

Carhart-Harris et al (2021). *NEJM*
B Change from Baseline in WEMWBS Score

Psilocybin dosing, day 1
Psilocybin dosing, day 2

Mean Change

0 5 10 15 20

Day

0 7 14 21 28 35 42

Psilocybin
Escitalopram

Carhart-Harris et al (2021). NEJM
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
- Decreased cancer-related existential distress
- Increased spiritual well-being and quality of life
- Improved attitudes towards death
- Psilocybin experiences were highly meaningful and spiritual
- No serious adverse events occurred

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

4 sessions with different doses (VLD, LD, MD, HD)

- Decreases in OCD symptoms were observed in all subjects
- 66.7% maintained a >50% decrease in Yale-Brown Obsessive Compulsive Scale (YBOCS) scores at 24 hours
- 2 reported symptom reduction up to one week after last psilocybin ingestion
- Psychologically and spiritually enriching
- No serious adverse events

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

https://thethirdwave.co/psychedelics/ibogaine/
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-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

Thomas et al (2013). *Current Drug Abuse Reviews*
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 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

Palhano-Fontes et al (2019). *Psychological Medicine*
Ayahuasca treating PTSD

Ayahuasca in Peru

Dr. Jessica Nielson, University of California, San Francisco
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. 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 psychotherapy and marijuana. 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. 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. 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. 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 neocortex 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. 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. The memory and its associated emotions become trapped in the hippocampus, so that whenever the adverse memory is triggered...
Erowid Ayahuasca Experience Categories

Modified from Nielson and Megler, 2014
Ayahuasca in the Media

Ayahuasca: Coming to a Clinic Near You?

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

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

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

Psychedelic drug ayahuasca improves hard-to-treat depression

Are Psychedelics the New Prozac?
Ayahuasca in the Media

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.

The Dark Side of Ayahuasca

Canadian man lynched over shaman’s death in Peru

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 town yesterday to identify the body and to find out how he had died.

Shipibio 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
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
Survey responses as of 12/29/2017 N=1,088

- Excluded
  - Completed survey N=539
  - Incomplete survey N=549
- Did not withdraw consent N=521
- Withdrew consent N=18

Final Cohort N=520

< 18 years old N=1

47% PTSD

QUALITATIVE OUTCOMES
Qualitative Analysis – Grounded Theory

Ayahuasca experience

Dangerous? Helpful?

Yes, no, unsure

Explain

Rater 1
(A,B,C,D) Identify themes

Rater 2
(A,B,C,D) Identify themes

Rater 3
(C,D)

A
Dangerous Experiences?

B
Helpful Experiences?

Reported PTSD Diagnosis

C
Open-Ended Responses by Condition

Reported PTSD Diagnosis

Nielson, Megler, Cavnar. Chapter in Ayahuasca Healing and Science (in press)
Dangerous Experience Themes

Use of cannabis
Inexperienced facilitators
Dogmatic practices
Lack of follow up care
Unethical facilitators
Brew Ingredients
Not prepared
Access to purging facilities
Physical complications
Unsafe setting, no supervision
Internal fears
Other people

No PTSD (N=87)
Decline to Answer (N=10)
Past PTSD (N=43)
Current PTSD (N=59)

Nielson, Megler, Cavnar. Chapter in Ayahuasca Healing and Science (in press)
Table 1. Common themes related to dangerous aspects of an ayahuasca experience.

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

Helpful Experience Themes

- Symptom alleviation
- Help with purging
- Comforts and supplements
- Preparation
- After care
- Ritual components
- Self-support
- Trust
- Safe/comfortable space
- Supportive group
- Experienced facilitators/helpers
- Music/Icaros

% of Group

Legend:
- Current PTSD (N=112)
- Past PTSD (N=85)
- Decline to Answer (N=21)
- No PTSD (N=199)

<table>
<thead>
<tr>
<th>THEMES</th>
<th>DETAILS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soothing Sounds</td>
<td>Shaman singing icaros, playing instruments, sounds of the jungle, familiar music, being able to sit in silence</td>
</tr>
<tr>
<td>Experienced facilitators and helpers</td>
<td>Having a shaman, having support from helpers, one-on-one attention</td>
</tr>
<tr>
<td>Supportive, like-minded group</td>
<td>Doing ceremony with others in their community, people they are comfortable with</td>
</tr>
<tr>
<td>Safe/comfortable space</td>
<td>Having a space to lay down, pillows, blankets, spaces to be alone, being in nature, darkness/limite light</td>
</tr>
<tr>
<td>Trust</td>
<td>Trusting the facilitators, trusting ayahuasca, being able to let go/surrender</td>
</tr>
<tr>
<td>Self-support</td>
<td>Meditation, journaling, yoga, prayer, connection to spirits/guides, self-love</td>
</tr>
<tr>
<td>Ritual components</td>
<td>Smudging/cleansing of space, sacred items (talismans, an altar), mapacho smoke</td>
</tr>
<tr>
<td>After care</td>
<td>Post-session meetings with shaman, with group</td>
</tr>
<tr>
<td>Preparation</td>
<td>Pre-session meetings, setting intentions, following dieta, experience with other psychedelics</td>
</tr>
<tr>
<td>Comforts and supplements</td>
<td>Agua Florida, ginger tea for nausea, citrus, flower baths, scented oils, pets</td>
</tr>
<tr>
<td>Help with purging</td>
<td>Helpers to provide and clear purge buckets, toilet paper/tissue, easy access/help to bathroom, being comfortable purging in front of others</td>
</tr>
<tr>
<td>Symptom alleviation</td>
<td>Claims of being healed by ayahuasca from symptoms of trauma (e.g. PTSD, depression)</td>
</tr>
</tbody>
</table>
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-Methylenedioxymethamphetamine
  - 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. — ±3,4-methylenedioxymethamphetamine
- 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

## Post-Traumatic Stress Disorder

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

Jerome et al (2020). *Psychopharmacology*
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
Ketamine

- Dissociative (NMDA antagonist)
- In use since 1970s as an anesthetic analgesic anti-inflammatory anti-depressant*

* Effects can be blocked with naltrexone (both anti-depressant and anti-suicidality), suggesting role of opioid receptors in ketamine's uses for depression.
Ketamine – assisted psychotherapy (KAP) - training

We provide online didactic and in-person experiential trainings in KAP.

https://www.polarisinsight.com/training-retreats/

https://www.fluencetraining.com/postgraduate-certificate-in-ketamine-assisted-psychotherapy

https://pratigroup.org/kap-training/
Ketamine – assisted psychotherapy (KAP) - local

https://www.iit-mn.com/

https://www.catalystinsightcollective.com/
WHAT’S NEXT??
Other Psychedelic Therapy Trainings

MDMA Therapy Training Program

The MDMA Therapy Training Program is a clinical training program that facilitates learning in the theory, skills, and practice of MDMA-assisted therapy. The theoretical approach is based on a philosophy that every person has within them an intrinsic wisdom and ability to heal, and that this inner healing wisdom blossoms naturally in an environment of safety and support.

https://mapspublicbenefit.com/training/
Other Psychedelic Therapy Trainings

IPI Online Psychedelic-Assisted Therapy Training

Get Certified as a Psychedelic-Assisted Therapy Provider (PATP)*

*Optional in-person ketamine experiential retreat

Year-Long Program
January 2022 – November 2022

Accelerate your therapy practice with the power of psychedelic medicine. Psychotherapy is undergoing another revolution: the fifth-wave of psychotherapy has arrived. With the aid of psychedelic medicines, many clients have an opportunity to break through long-standing trauma and mood issues in a matter of sessions rather than struggling for years. Deepen your skillset and learn how to harness the incredible power of psychedelic therapy. Join the revolution now.

https://psychiatryinstitute.com/mpi-year-long-psychedelic-assisted-therapy-training/
About the Certificate in Psychedelic-Assisted Therapies & Research

https://www.ciis.edu/research-centers/center-for-psychedelic-therapies-and-research/about-the-certificate-in-psychedelic-assisted-therapies-and-research
General Psychedelic Science & Therapy Education

Foundations in MDMA Safety, Therapeutic Applications & Research

Psychedelic.Support Free Courses

Experts in harm reduction and psychedelic therapy want you to be informed! Sign up for our newsletter and gain access to high quality courses on psychedelic fundamentals, harm reduction, and more.

https://psychedelic.support/education/
Acknowledgements

Eric Peterson, MA, LADC, co-founder Catalyst Insight Collective

Alex Larson, MA, LADC, LPCC, lead MA counselor at Wilder Recovery Services

Silvia Franco M.D. Psychiatry PGY-4 Mt. Sinai St. Luke’s/West
THANK YOU FOR YOUR ATTENTION!
QUESTIONS??