Psychedelics in Substance Use Disorder: The Future?

Presented By:

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Disclosures

The following session leaders have no relevant financial relationships with ineligible companies to disclose:

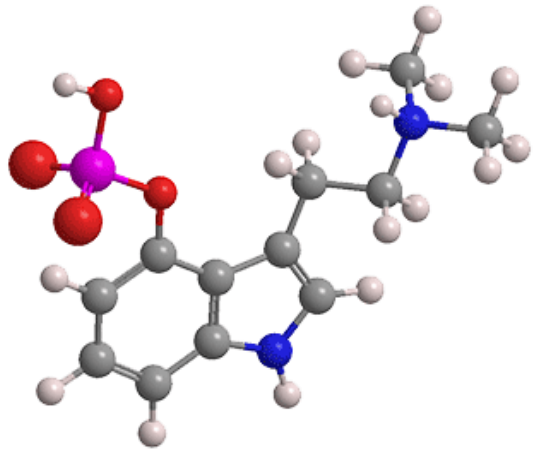
Clement Chen – none

Saatchi Patell – none

Objectives

- Review the current evidence-based treatment for OUD
- Explain the effects and properties of psychedelics
- Explore current research in the use of psilocybin for OUD

Background



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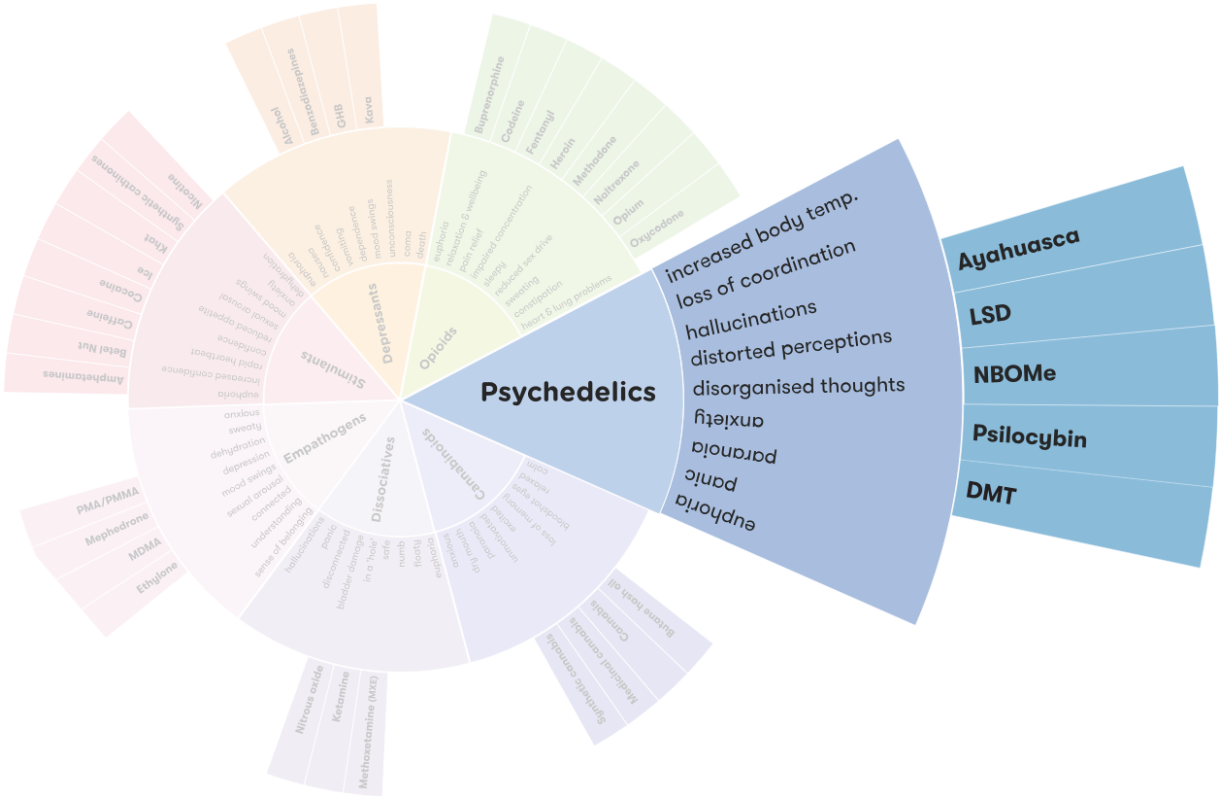
What are Psychedelics aka "Hallucinogens?"



- Help with spiritual processes
- "Mystical experience"
  - Sensory alterations – visual
  - Distortions in shape, color, time, and space
- Psychedelic journey
  - "An inverse PTSD"
  - Opposite of a dream

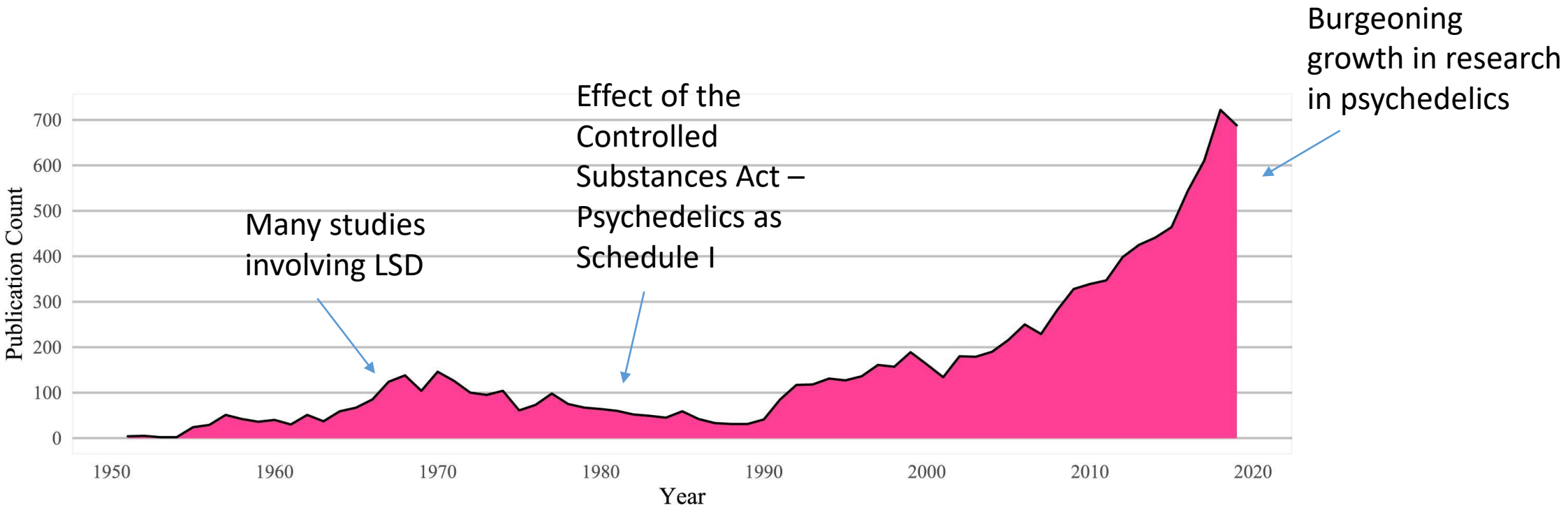
Image from: https://adf.org.au/drug-facts/psychedelics/#wheelhttps://www.newyorker.com/magazine/2015/02/09/trip-treatment
https://www.newyorker.com/magazine/2015/02/09/trip-treatment

Specific Example of a Mystical Experience

- *"In my mind's eye, I felt myself instinctively taking on the posture of prayer in my head. I was on my knees, hands clasped in front of me and I bowed to this force. I wasn't scared or threatened in any way. It was more about* ***reverence****. I was showing my respect. I was humbled and honored to be in this presence. This presence was a feeling, not something I saw or heard. I only felt it, but it felt* ***more real than any reality I have experienced****. And it was a familiar place too. One I had felt before. It was when I surrendered to this, that I felt like I let go. I was gone…or I should say this earthly part of me was. It was still on the couch in some sort of suspended animation awaiting my return. I was* ***in the void****. This void had a* ***strange and indescribable quality to it*** *in that there was nothing to it but this feeling of* ***unconditional and undying Love****. It felt like my soul was basking in the feeling of this space. I have no idea how long this lasted.* ***Time and space did not exist there*** *…it was all different manifestations of this Love feeling I found myself wrapped in."*
- Effect of feeling more hopeful when confronting the disease in the mystical experience

Barrett FS, et al. *Curr Top Behav Neurosci.* 208;36:393-430.

A Little History…



Petranker R, et al. *Front Psychol.* 2020 Jul 10;11:1681.

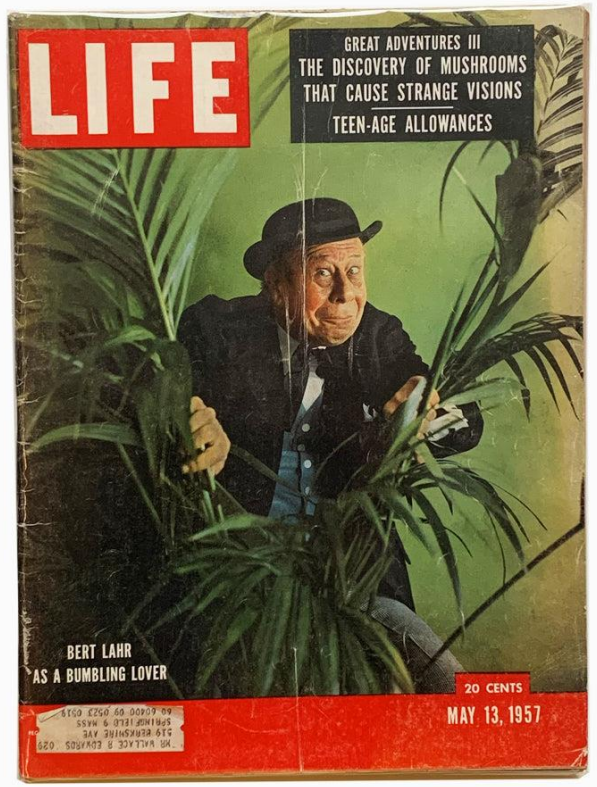
A Little History…

Algeria, 6000-9000 BC

- Likely role in shaping philosophies and religion over time
- "Entheogens"
- Elucinian mysteries in Greece "of all the divine things that exist among men, it is both the most awesome and the most luminous."
- Soma in ancient India “Good fruit containing food not any intoxicating drink, we drink you. You are elixir of life, achieve physical strength or light of god, achieve control over senses;
- Aztec shamans used mushrooms, known as Teonancatl (‘"god’s flesh") in religious ceremonies

https://www.psychiatrypodcast.com/psychiatry-psychotherapy-podcast/episode-104-psilocybin-therapy-part-1-history-pop-culture-safety-and-side-effects-mdma-studies-and-early-research

A Little History Continued…



1957 - R. Gordon Wasson – mycologist introduced in Mexico by a shaman to psilocybin

1958 – Albert Hofman – first to isolate and synthesize psilocybin

1960 -Timothy Leary – founded the Harvard Psilocybin Project

1962 – Walter Pahnke – double-blind experiment before Good Friday Service

- "Sacredness" and a "sense of peace"

Images from: https://donlonbooks.com/products/life-magazine

Fast Forward…

- 2006 – Tony Bossis, Stephen Ross, and Jeffrey Guss
  - NYU School of Medicine experimental trial to treat anxiety with psilocybin + therapy

Types of "Psychedelics"

- Primarily seritonergic hallucinogens
  - Indolealkylamines: LSD, psilocybin, DMT (in ayahuasca)
  - Phenylethylamines: mescaline ("peyote")
- MDMA (NMDA and serotonin triggering massive NT release)
- Cannabinoids
- Primarily NMDA antagonists
  - Arylcycloalkylamines: PCP, ketamine
- Anticholinergics: deadly nightshade, jimsonweed

Common Misunderstandings of Classic Psychedelics

- Very low risk of addiction
- Does not cause craving/withdrawal
- No direct effects on the brain-reward pathway (dopamine)

Psilocybin: from ancient magic to modern medicine

David E Nichols [1]

Affiliations + expand

PMID: 32398764 DOI: 10.1038/s41429-020-0311-8

Abstract

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is an indole-based secondary metabolite produced by numerous species of mushrooms. South American Aztec Indians referred to them as teonanacatl, meaning "god's flesh," and they were used in religious and healing rituals. Spanish missionaries in the 1500s attempted to destroy all records and evidence of the use of these mushrooms. Nevertheless, a 16th century Spanish Franciscan friar and historian mentioned teonanacatl in his extensive writings, intriguing 20th century ethnopharmacologists and leading to a decades-long search for the identity of teonanacatl. Their search ultimately led to a 1957 photo-essay in a popular magazine, describing for the Western world the use of these mushrooms. Specimens were ultimately obtained, and their active principle identified and chemically synthesized. In the past 10-15 years several FDA-approved clinical studies have indicated potential medical value for psilocybin-assisted psychotherapy in treating depression, anxiety, and certain addictions. At present, assuming that the early clinical studies can be validated by larger studies, psilocybin is poised to make a significant impact on treatments available to psychiatric medicine.

Nichols DE. *J Antibiot (Tokyo).* 2020 Oct;73(10);679-86.

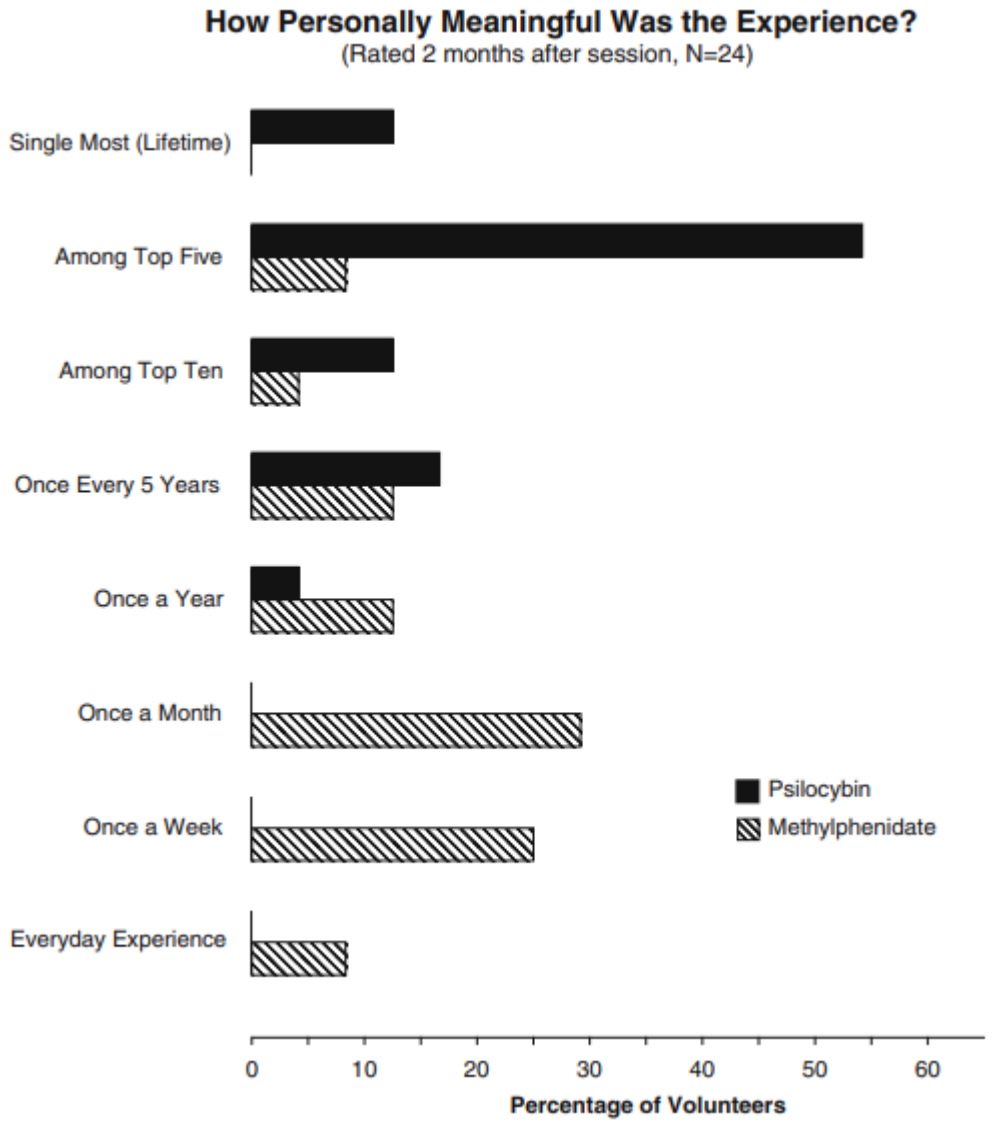
Initial Study

Psychopharmacology
DOI 10.1007/s00213-006-0457-5

ORIGINAL INVESTIGATION

Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance

R. R. Griffiths · W. A. Richards · U. McCann · R. Jesse



Patients had greater life satisfaction and better well-being 2 months after

- Unity, sacredness, ineffability, peace/joy, and transcendence
- Increased ratings of mood, social effects, and behavior even at 14-month follow-up

Griffiths RR, et al. *Psychopharmacology (Berl):* 2006 Aug;187(3):268-83.

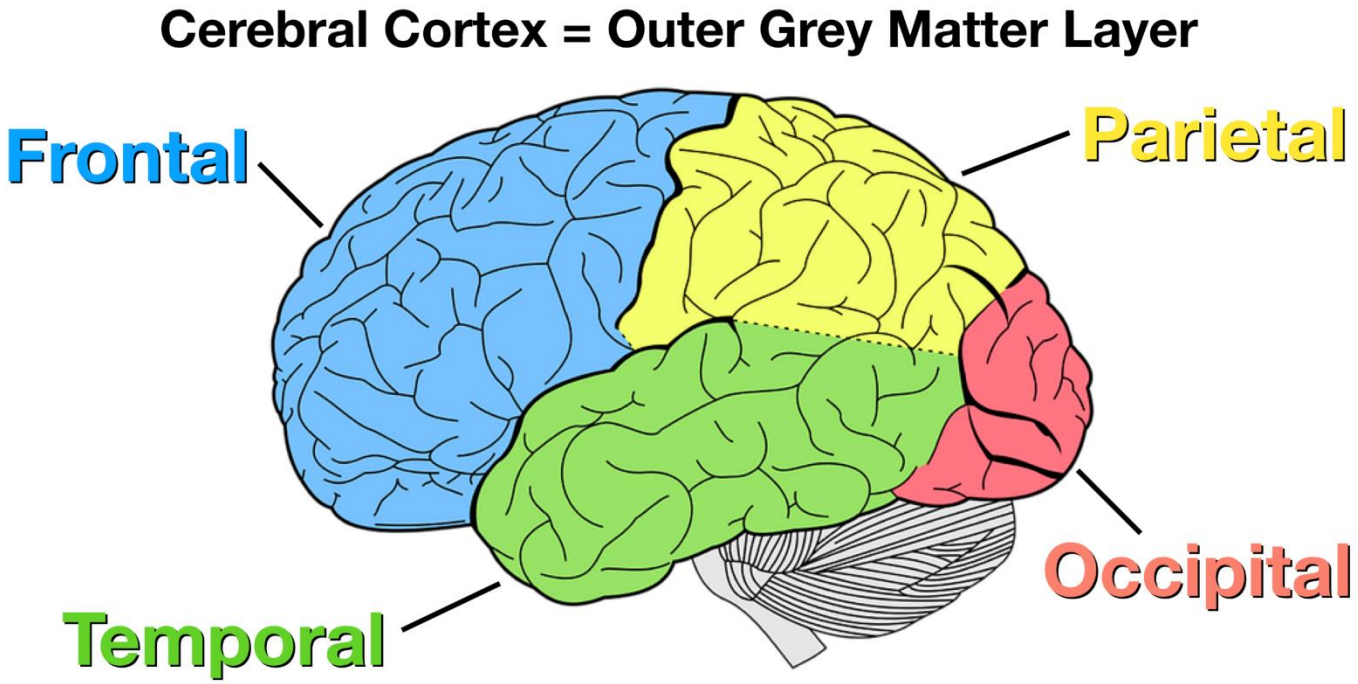
A Focus on Psilocybin – "Magic Mushrooms"

- Tryptamine alkaloid, 2A serotonin receptor agonist, similar to LSD
- Triggers sensory alterations especially alterations in visual perception
  - Distortions of shapes and colors
- Ingested generally as tea or added to foods
- No significant association between lifetime use of psychedelics and substance-induced psychosis and other psychiatric disorders

Krebs TS, et al. *PLoS One.* 2013 Aug; 19;8(8):e63972.
Rucker JH, et al. *Neuropharmcology.* 2018 Nov;142:200-18.

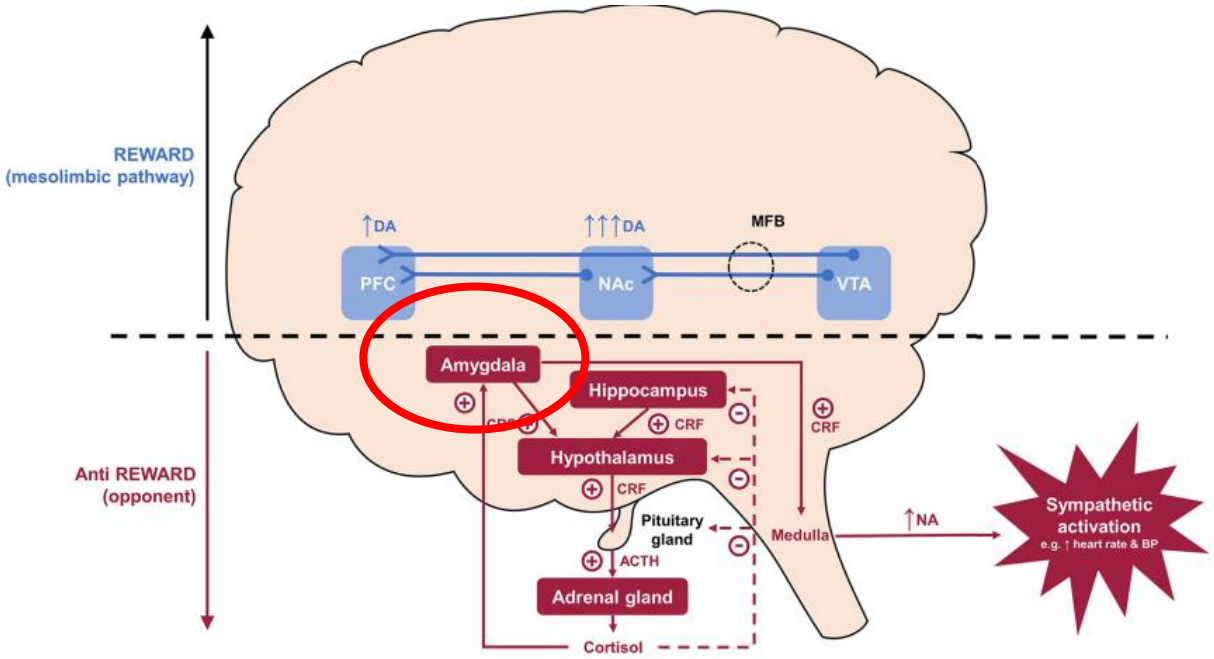
Neurobiology

Serotonin expression (5-HT2a) distributed across the cerebral cortex



https://www.ezmedlearning.com/blog/cerebral-cortex-lobe-anatomy

Amygdala



- Involved in processing of emotions and memories
- Decreased amygdala reactivity associated with better mood
  - Strong link with SUD and amygdala hyperactivity

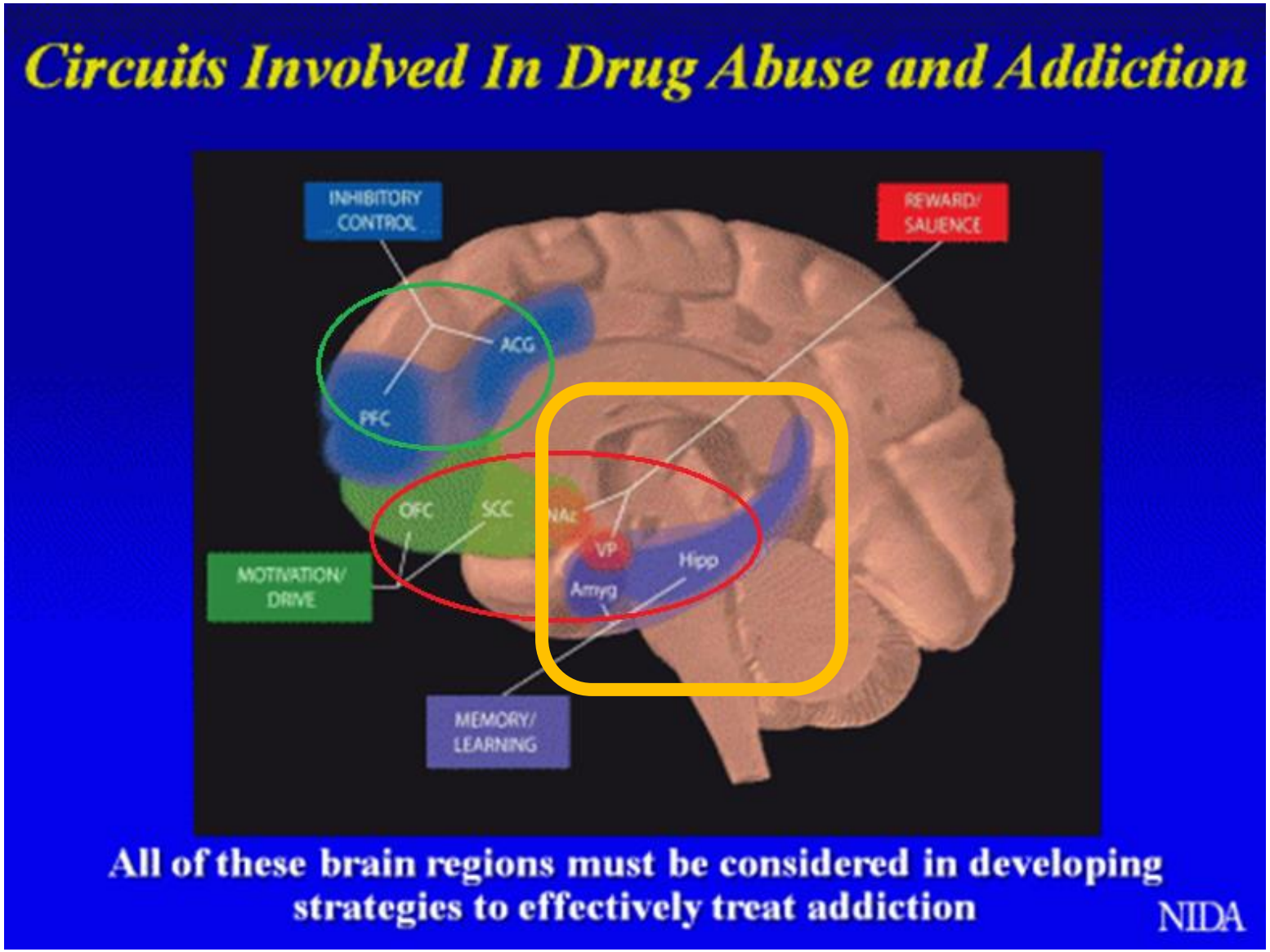
Kakko J, et al. *Front Psychiatry.* 2019 Aug 30:10:592.

Neurobiology

Unbalanced 5-HT1A and 5-HT2A receptor expression in the prefrontal cortex and hippocampus

Psilocybin decreases amygdala activity – reducing stress, steering brain activity from negative emotional state

5-HT2a agonism has strong effects on overcoming behavioral inflexibility



De Veen BTH, et al. *Expert Rev Neurother.* 2017 Feb;17(2):203-12.

Psilocybin Mechanism of Action

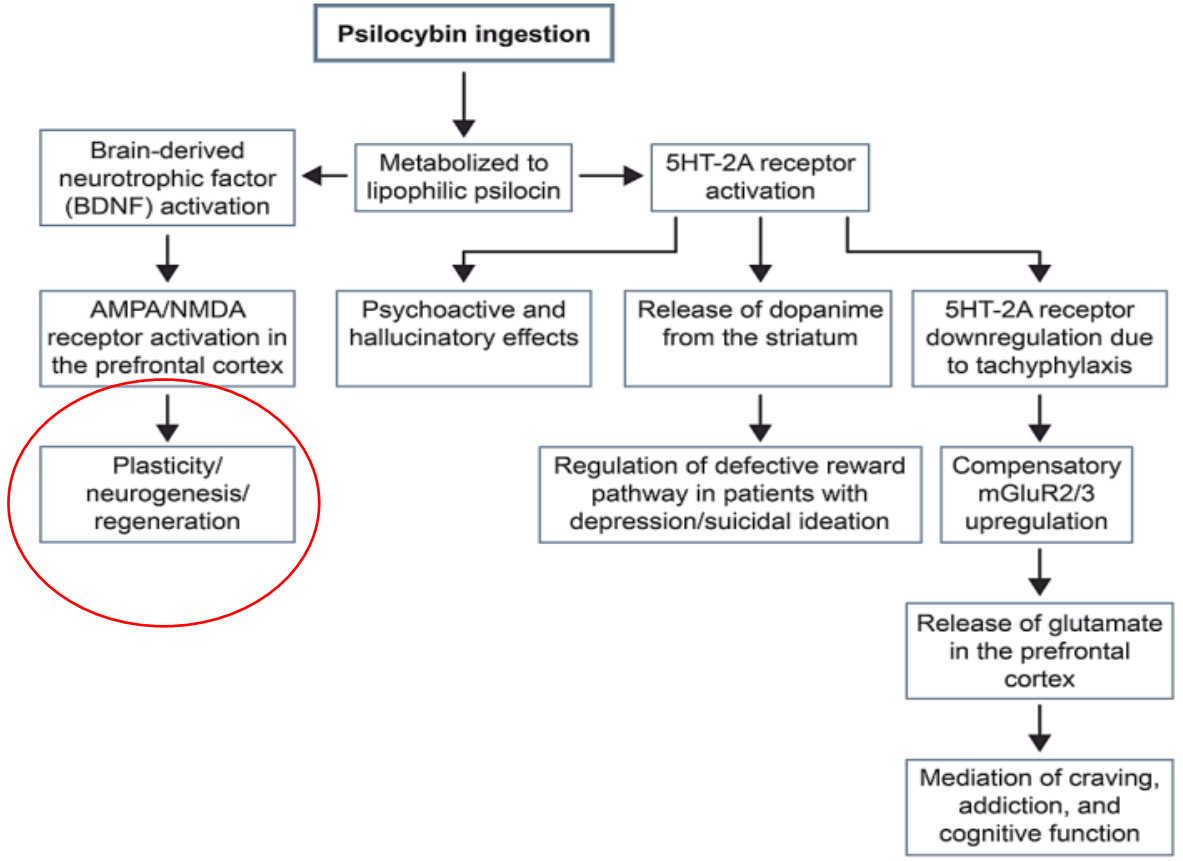
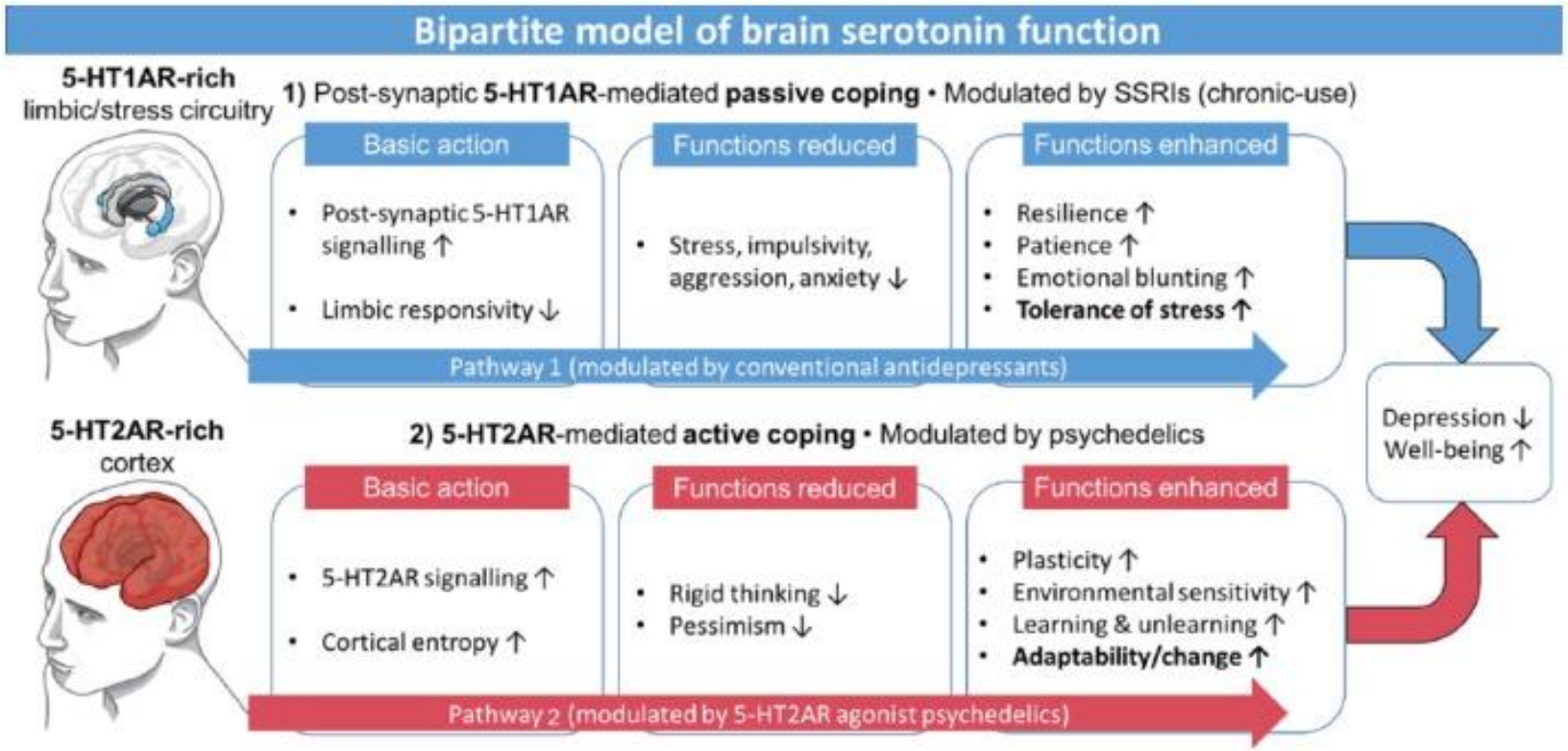


FIGURE 1: Psilocybin mechanism of action.

mGluR2/3: metabotropic glutamate receptors; AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; NMDA: N-methyl-D-aspartate; BDNF: brain-derived neurotrophic factor; 5HT-2A: 5-hydroxytryptamine 2A

Ziff S, et al. *Cureus.* 2022 Feb 5;14(2):e21944.

Comparison of Effects



Carhart-Harris RL, et al. *J Psychopharmacol.* 2017 Sep;31(9):1091-1120.

Adverse Effects

- Hypertension
- Tachycardia
- Nausea/vomiting
- Low risk
  - Hyperthermia
  - Respiratory failure
  - Coma
- *In general, low toxicity across multiple studies

- Altered perceptions → long-lasting hallucinations
  - Panic or fear
- Psychosis-induction
  - Uncommon but can exacerbate psychiatric conditions
  - Delirium
  - Caused by the psychedelic?

- However, low risk of physiological and psychological dependence

De Veen BTH, et al. *Expert Rev Neurother.* 2017 Feb;17(2):203-12.

Summary

- Calms the stressor network
- High distribution of 5-HT2a receptor in the cerebral cortex and amygdala
- Improvements from a negative emotional state and cognitive inflexibility and compulsivity

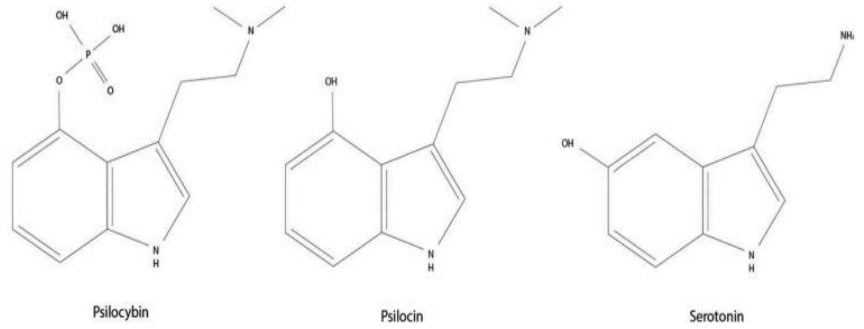


Figure 1. Chemical structures of psilocybin, psilocin, and its endogenous analogue serotonin. Edited from Stebelska [52].

De Veen BTH, et al. *Expert Rev Neurother.* 2017 Feb;17(2):203-12.
https://www.newyorker.com/magazine/2015/02/09/trip-treatment

What is the Fervor of Psychedelics All About in SUD?

Relief of anxiety and "existential distress"

https://hub.jhu.edu/2018/09/26/psilocybin-scheduling-magic-mushrooms/

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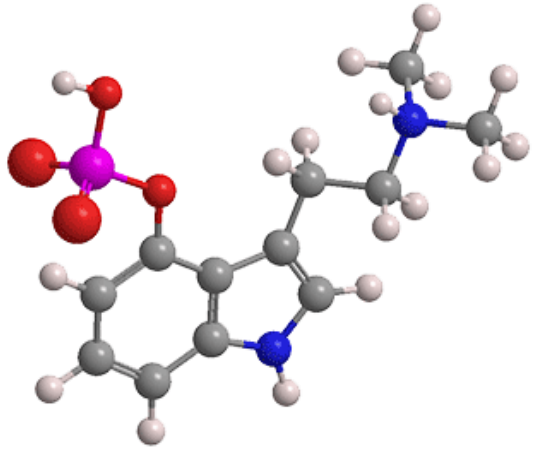
Current Research on Psychedelics in SUD: A Focus on OUD



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Psilocybin Studies in Mental Health Griffith, et al.

- Randomized, double-blind crossover trial
- Effect of psilocybin + psychotherapy in 51 patients with life-threatening cancer on symptoms of depression/anxiety
- Low dose – 1-3mg/70 kg; high dose – 22-30mg/70 kg
- 5 weeks between sessions and 6-months follow-up
- High-dose had significant decrease in clinician and self-rated measures of anxiety and depression
- 6-month follow-up: 80% of participants had effects continued

Griffiths RR, et al. *J Psychopharmacol.* 2016 Dec;30(12):1181-97.

Ross, et al.

- Randomized, double-blind, placebo-controlled crossover trial of 29 patients
- Cancer-related anxiety and depression
- Single dose of psilocybin (0.3mg/kg) or niacin (placebo)
- Significant anxiolytic and antidepressant effects were noted, including decreases in hopelessness, improved spiritual wellbeing, and quality of life
- 60-80% of patients had sustained benefits after 6 months

Ross S, et al. *J Psychopharmacol.* 2016 Dec;30(12):1165-80.

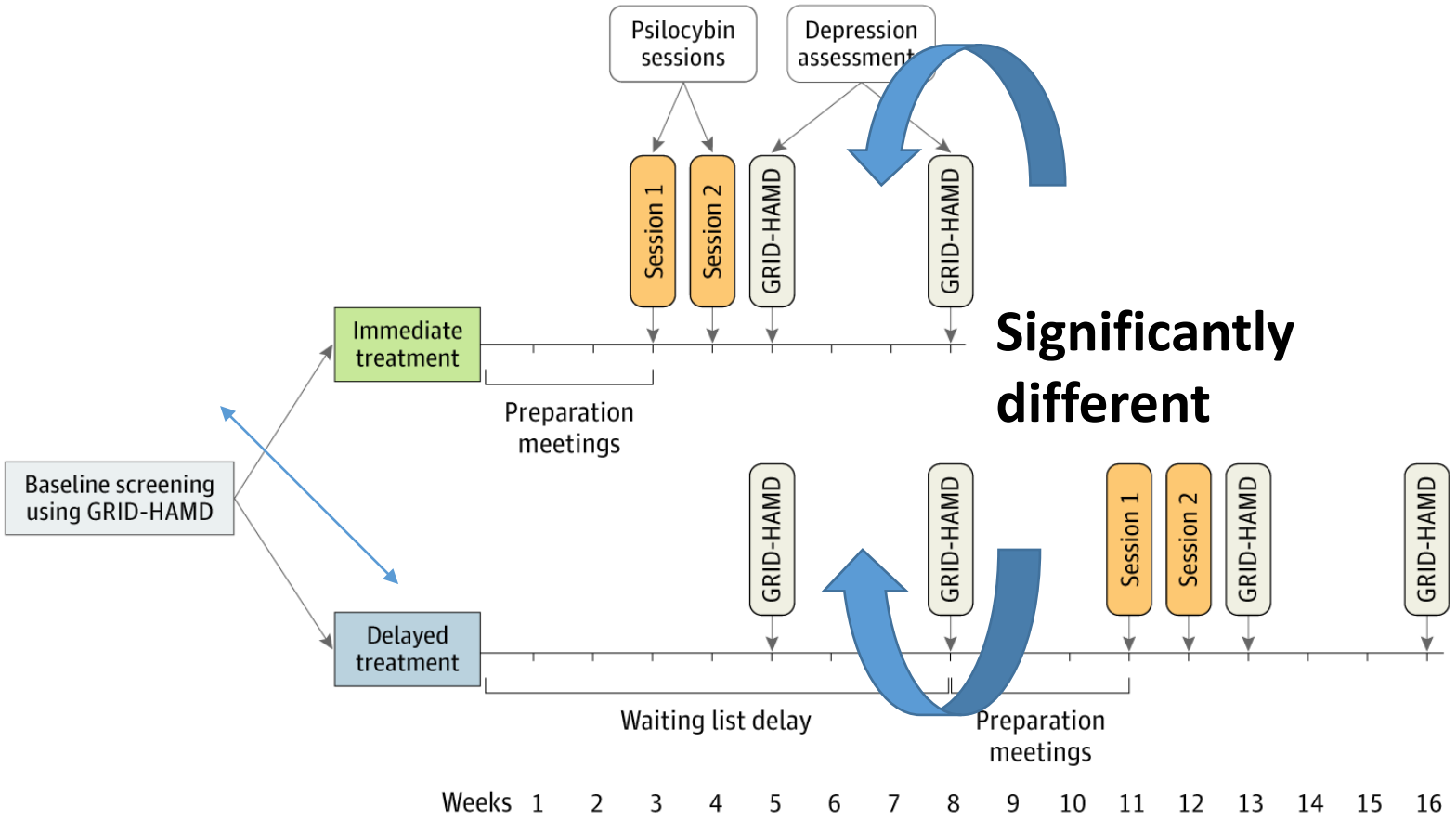
Carhart-Harris, et al.

- Open label trial of 12 patients with moderate to severe treatment resistant depression who received 2 doses of psilocybin (10mg-->7 days-->25 mg) with psychological support before, during, and after.
- Measured depressive symptoms (QIDS—subjective/patient-reported) at 1 week (mean QIDS difference −11·8, 95% CI −9·15 to −14·35, p=0·002) and 3 months (−9·2, 95% CI −5·69 to −12·71, p=0·003)
- Follow up 6 month study showed that:
  - positive effect continued ((Cohen's d = 1.4, $p < 0.001$)
  - Reduction in depressive symptoms was predicted by the quality of the psychedelic experience

Carhart-Harris RL, et al. *Lancet Psychiatry.* 2016 Jul;3(7):619-27.
Carhart-Harris RL, et al. *Psychopharmacology (Berl).* 2018 Feb;235(2):399-408.

Davis, et al.

- RCT of 24 patients with MDD who received 2 sessions of either immediate or delayed psilocybin-assisted supportive therapy.
- 71% of patients had a clinically significant response (>=50% reduction GRID HAM-D, scored blinded)

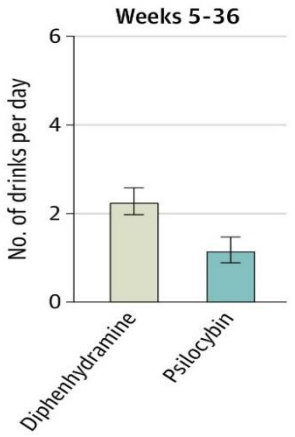


Davis AK, et al. *JAMA Psychiatry.* 2021 May 1;78(5):481-89.

Psilocybin Studies in SUD

- Smoking – open-label study
  - Johnson, et al – 15 patients receiving CBT for first 4 weeks; 3 sessions (20mg/kg --> 30mg/kg for subsequent sessions) starting at week 5
  - Structured 15-week treatment protocol
  - 80% abstinent at 6-month follow-up
  - Follow-up: majority still abstinent 12 months and 30 months
- Alcohol
  - Bogenschutz, et al. - double-blind RCT of 12 weeks psychotherapy and assigned to receive psilocybin vs. diphenhydramine during 2 day-long medication sessions at weeks 4 and 8.
  - 32-week follow-up after first dose of medication
  - 95 participants; % of heavy drinking days significantly less for psilocybin vs. Diphenhydramine (9.7% vs. 23.6%), as well as mean daily alcohol consumption.

- Reasons:
  - "Changing orientation toward the future, so that long-term benefits outweighed immediate desires"
  - "Changing life priorities/values"



Johnson MW, et al. *Am J Drug Alcohol Abuse.* 2017 Jan;43(1):55-60.
Bogenschutz MP, et al. *JAMA Psychiatry.* 2022 Oct 1;79(1):953-62.

Jones, et al – Associations Between Classic Psychedelics and OUD

Opioid dependence and abuse criteria	Frequency (unweighted N)	aOR (95% CI) (psilocybin as independent variable)[1]
1. Significant time spent getting/using	2249	**0.83* (0.70, 0.98)**
2. Use more than intended	1030	**0.71* (0.54, 0.93)**
3. Decreased effects/need more for same effect	2901	**0.82* (0.70, 0.96)**
4. Unable to cut back	914	0.80† (0.62, 1.04)
5. Emotional/physical health problems	1383	**0.73** (0.60, 0.90)**
6. Fewer important activities	1320	**0.71** (0.58, 0.87)**
7. 3 + Withdrawal symptoms	1724	0.86 (0.71, 1.05)
8. Significant work/home/school problems	1063	**0.66** (0.50, 0.86)**
9. Use in physically hazardous situations	910	**0.66** (0.49, 0.88)**
10. Recurrent legal trouble	454	0.72 (0.45, 1.15)
11. Social/interpersonal issues	906	0.75† (0.56, 1.01)

Table 3. Associations between psilocybin and the 11 DSM-IV criteria for opioid dependence and abuse. [1]†p < 0.10; *p < 0.05; **p < 0.01; ***p < 0.001; *aOR* adjusted odds ratio, *CI* confidence interval. Significant values that indicate lowered odds of OUD criteria are in bold.

- Association between classic psychedelics (lifetime use) and past year diagnosis of OUD
- N > 214k in NSDUH survey (several limitations)
- Psilocybin, peyote, mescaline, and LSD
- Only psilocybin associated with lower odds of OUD (30% lower)
- Demographic differences: marital status, educational level, age, sex, race/ethnicity, and yearly household income

Jones G, et al. *Sci Rep.* 2022 Apr 7;12(1):4099.

Main Challenges for Studying

- Schedule I controlled substance
  - No public funding
- Requires FDA approval
- Needs special DEA license
- No financial incentive if only given once or twice a session

Understanding the Treatment Concerns

- Small sample sizes
- Lack of randomized, **double-blind** controlled studies
  - Difficulty achieving
  - Control arm
- Selection and expectation bias
- Set and setting
  - Prepare in anticipation of the session, session itself, and integration of the "psychological material" that arise"
- Significant training amongst staff and patients needed
- Lack of studies examining recurrence rates (relapse)
- Genetic differences
- Representation in studies
- Causative effect of psilocybin or other factors? (difficult controlling for factors)

Ziff S, et al. *Cureus.* 2022 Feb 5;14(2):e21944.
Phelps J. *J Humanist Psycho.* 2017;57:450-87.

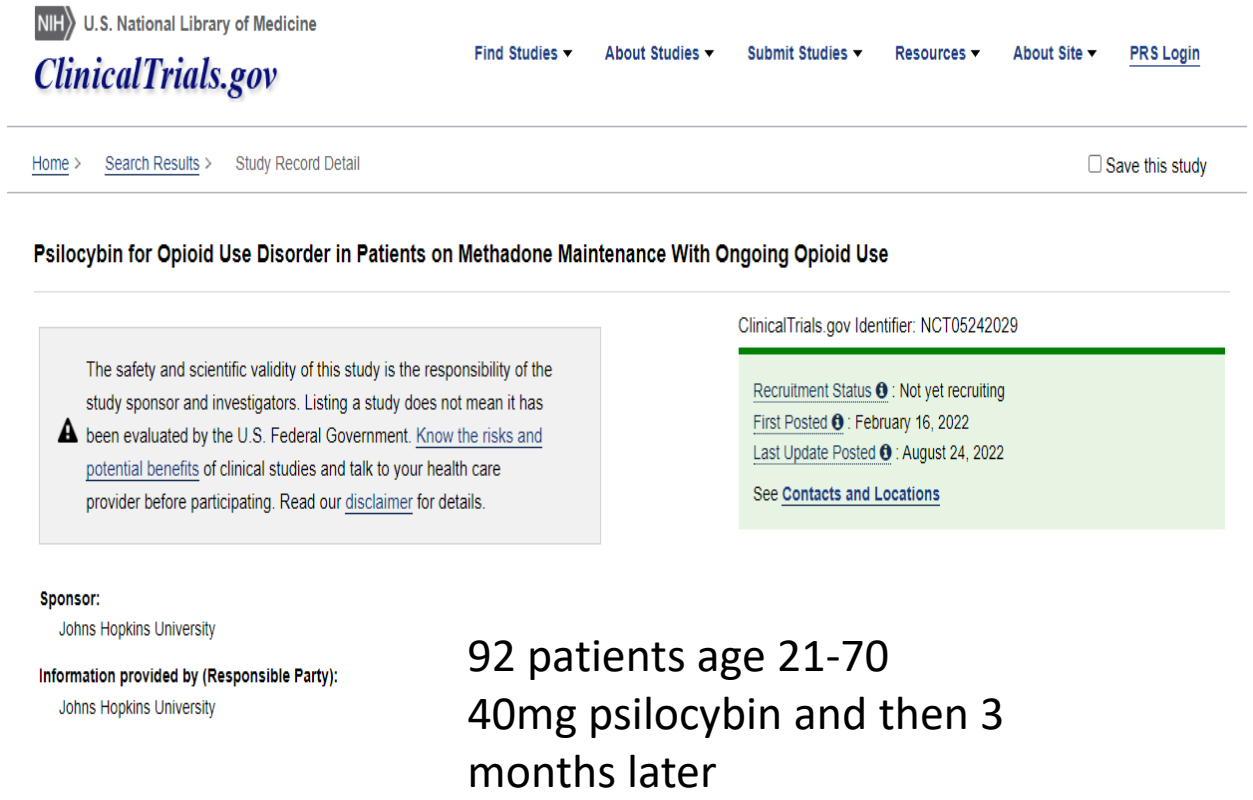
Understanding the Recreational Concerns

- Many different mushrooms with different amounts/potency
- Purity of the psilocybin
- Contaminants with other drugs is a possibility
- Set and setting

Are there Next Steps?

Opening the dialogue

Future Study: Psilocybin for OUD in Methadone Maintenance with Ongoing Opioid Use: Phase 2



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Psilocybin for Opioid Use Disorder in Patients on Methadone Maintenance With Ongoing Opioid Use

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT05242029

Recruitment Status : Not yet recruiting
First Posted : February 16, 2022
Last Update Posted : August 24, 2022

See Contacts and Locations

Sponsor:
Johns Hopkins University

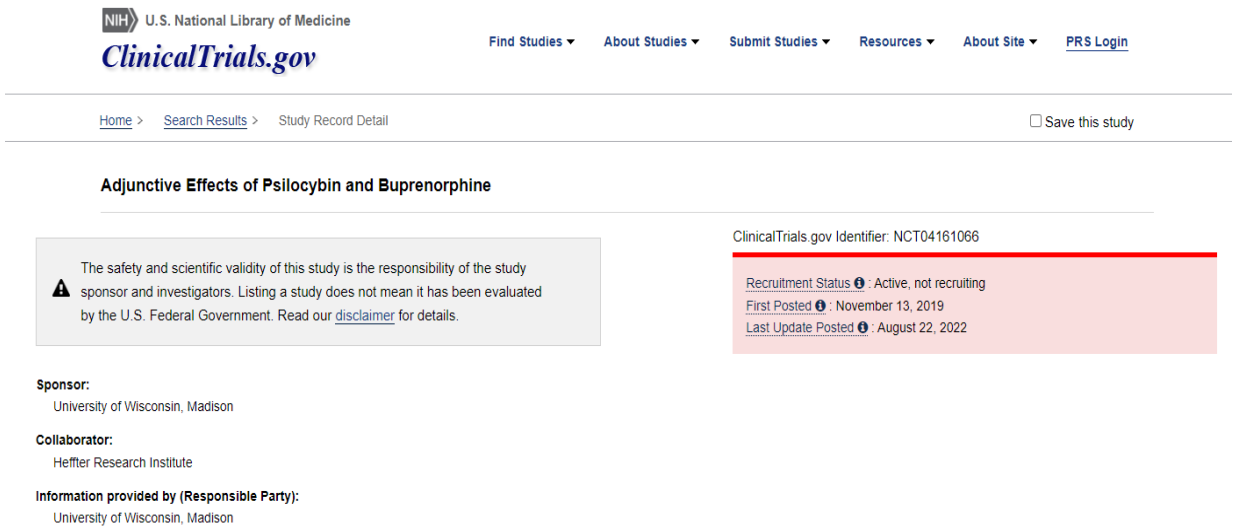
Information provided by (Responsible Party):
Johns Hopkins University

92 patients age 21-70
40mg psilocybin and then 3 months later

- Primary outcomes: reductions in illicit opioid use and quality of life
  - 2nd: improvements in Mood, tobacco use reduction, improvements in chronic pain/sleep
- RCT – double-blind, placebo-controlled of 2 doses admin under supportive conditions

https://clinicaltrials.gov/ct2/show/NCT05242029

Ongoing Study: Adjunctive Effects of Psilocybin and Buprenorphine: Open-Label, Pilot Study



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Adjunctive Effects of Psilocybin and Buprenorphine

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04161066

Recruitment Status : Active, not recruiting
First Posted : November 13, 2019
Last Update Posted : August 22, 2022

Sponsor:
University of Wisconsin, Madison

Collaborator:
Heffter Research Institute

Information provided by (Responsible Party):
University of Wisconsin, Madison

- Primary outcome: Characterize adverse events associated with adding 2 psilocybin doses to a stable bupe/naloxone regimen
- Secondary Outcomes: Evaluate the effectiveness of psilocybin on buprenorphine maintenance therapy and vice versa
- 10 patients

https://clinicaltrials.gov/ct2/show/NCT04161066

Other Studies

- Methamphetamine?
  - Randomized Trial of 30 patients; 2 sessions of psilocybin vs. Standard of care in rehab
  - Ongoing
- Cocaine?
  - Double-blind and placebo-controlled randomized clinical trial of psilocybin vs. Diphenhydramine on cocaine use disorder
  - Ongoing

https://clinicaltrials.gov/ct2/show/NCT04982796
https://clinicaltrials.gov/ct2/show/NCT02037126

Evidence-Based Treatment

- Focus on evidence-based treatment → MOUD
- Much of the issues not due to efficacy but rather due to access and barriers to care
- Cultural shift → Mindfulness? → more psychedelic research in mental health and SUD?
  - Primary psychedelics
  - Other psychedelics
- Re-scheduling of psychedelics?
- Psychedelics are currently not evidence-based and thus cannot be recommended

Questions & Discussion

Thank you to everyone who joined and participated today!