Psilocybin

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Disclosures

- Nothing to disclose

Overview

- Introduction
- What is Psilocybin?
- Promises of Psilocybin Research
- Overview of Psychedelic Treatment Model
- Pitfalls of Psilocybin Research
- What’s on the horizon?

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A Caveat

- In today's conversation, we are exclusively speaking about psilocybin within a research context.
- Psilocybin is currently a Schedule I drug and is illegal in most of the United States. However, many cities and states are moving toward decriminalization of psilocybin (as opposed to legalization).
- There are state-based programs in Oregon and Colorado that allow for some supervised adult use of psilocybin outside of the research context.

What are Psychedelic Medicines?

- "1. Pertaining to a classic psychedelic, i.e. psychoactive substances that **have a primary mechanism of action activation of 5-HT2A**

- 2. Pertaining to **substances that induce an non-ordinary state of consciousness (NOSC) characterized** by enhanced attentional scope, reduced self-referential thinking, and hyper-associative processing and… embedded within a supportive framework that includes preparation for and integration of the NOSC"

What is Psilocybin?

- Active ingredient in “magic mushrooms” (synthetic psilocybin used within our clinical trials)
- Binds to the 5HT2A serotonin receptor that leads to a non-ordinary state of consciousness for several hours
- Can be associated with feelings of expansiveness, connection, awe as well as at times of anxiety or fear
- Used in clinical research in the psychedelic treatment model
- Standard dose for many US clinical trials is 25mg (considered a “macro” dose)

History of Psilocybin Research

- Psilocybin has a long history of indigenous use in Central America for ceremonial or healing purposes and was first studied by US scientists in the mid-1950s.
- Clinical research with psilocybin and the chemically similar LSD took root in the 1950s to 1960s establishing the relative clinical safety and therapeutic potential in a variety of mental health conditions.
- However, given the political climate of the 1960s and counter cultural embrace of recreational psychedelic use, Richard Nixon signed the Controlled Substance Act in 1970 outlawing ongoing investigation into the therapeutic potential of these medicines.

History of Psilocybin Research at Johns Hopkins

- In the early 2000s, researcher Roland Griffiths began exploring the use of psilocybin in healthy volunteers.
- In the 2010s, his work expanded to include participants with anxiety in the setting of a life threatening diagnosis of cancer as well as major depressive disorder.
- In 2019, the center for psychedelics and consciousness research (CPCR) was founded at JHU, the worlds first psychedelic research center.

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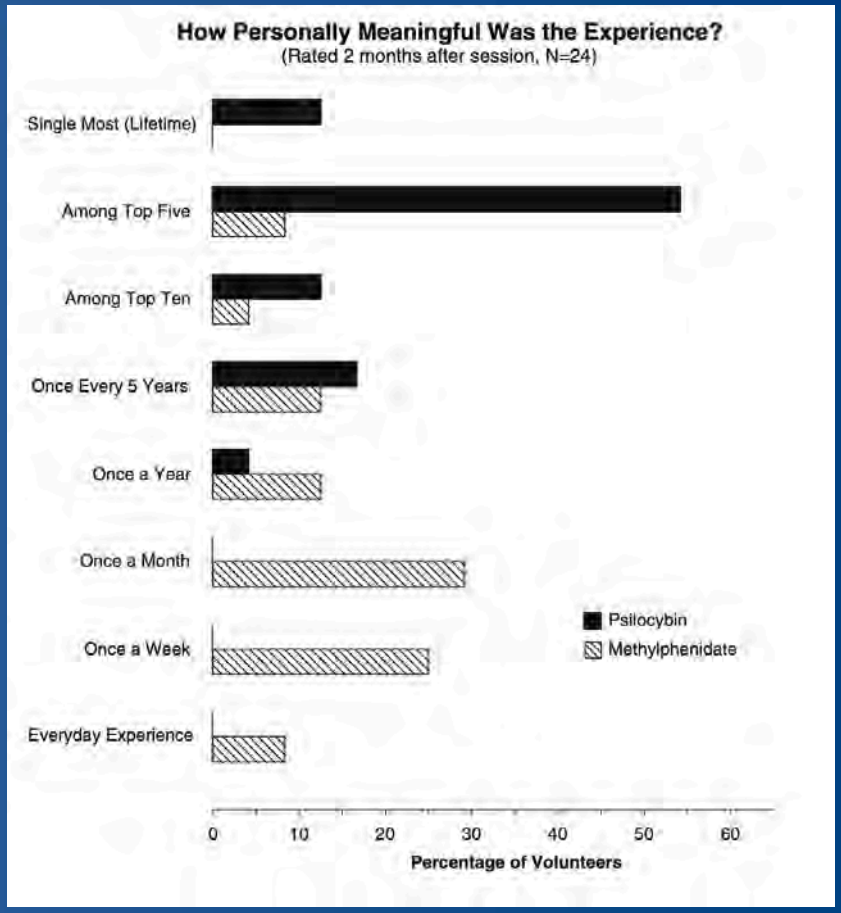
So what exactly is going on here?

How is a psilocybin treatment course different?

Screening → Preparation → Dosing Session → Integration → Follow Up

What did these early studies show?

- Early studies demonstrated the feasibility of working with psilocybin in contemporary research contexts as well as the profound effect it often had on the lives of participants
- Many participants rated their psilocybin experience among some of the most meaningful moments of their lives



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

Psychopharm

Journal of Psychopharmacology
2016, Vol. 30(12) 1181–1197

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Roland R Griffiths[1,2], Matthew W Johnson[1], Michael A Carducci[3], Annie Umbricht[1], William A Richards[1], Brian D Richards[1], Mary P Cosimano[1] and Margaret A Klinedinst[1]

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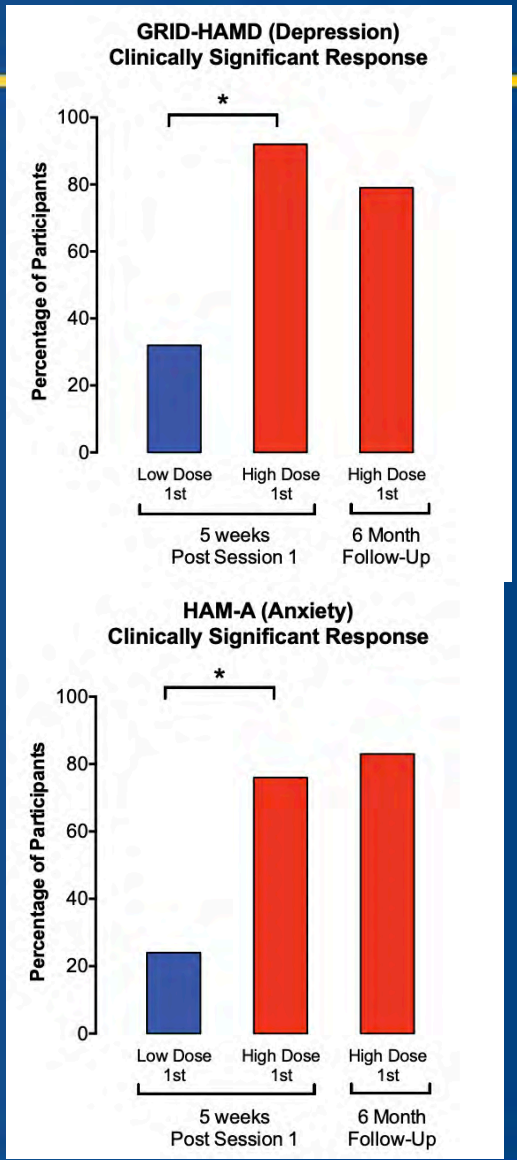
- Randomize, double-blind cross-over design study
- N= 51 patient with life-threatening cancer diagnosis
- Participants received high dose and very low dose psilocybin as a control across a multi-week study period, follow-up occurred initially and at 6 months
- "High-dose psilocybin produced large decreases in clinician and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety. At 6-month follow-up, these changes were sustained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety."



Psilocybin for the Treatment of Substance Use Disorders

- Tobacco use disorder (2014) : Pilot study of N=15 smokers with CBT + Psilocybin. 12/15 abstinent after the intervention. 13/15 abstinent at 12 months.
  - For comparison, varenicline (Chantix) abstinence rate of 20-22% at 1 year

- Alcohol use disorder (2022): Double blind, RCT with psilocybin N=93, significantly lower heavy drinking days in psilocybin treated group at 32 weeks

- Ongoing research in Cocaine User Disorder, Opiate use disorder, Cannabis use disorder

Agboola SA, Coleman T, McNeill A, Leonardi-Bee J. Abstinence and relapse among smokers who use varenicline in a quit attempt-a pooled analysis of randomized controlled trials. Addiction. 2015 Jul;110(7):1182-93. doi: 10.1111/add.12941. PMID: 25846123.

Psilocybin for the Treatment of Depression

- A new drug application (brought by Compass Pathways versus Usona) for Psilocybin will likely be submitted for use in major depressive disorder or treatment resident depression in the next 3-5 years pending the completion of Phase 3 trials

- Several positive initial trials indicate a likely benefit with psilocybin in those suffering for depressive disorders

- First comparative trial showed similar efficacy to SSRI medications

Positive Treatment Outcomes with Psilocybin

- Psychological distress (anxiety/depression) in cancer patients
  - Grob et al. 2011
  - Ross et al. 2016
  - Griffiths et al. 2016

- Obsessive Compulsive Disorder
  - Moreno et al. 2006
  - Kelmendi et al. 2024

- Treatment-resistant MDD
  - Carhart-Harris et al. 2016
  - Davis et al. 2020
  - Carhart-Harris et al. 2021
  - COMP360 2022
  - Raison et al., 2023

- Substance use disorders
  - Tobacco
    - Johnson et al 2014
  - Alcohol
    - Bogenschutz et al 2015, 2022

Current Clinical Research at the CPCR

- Obsessive Compulsive Disorder
- Major Depressive Disorder (MDD)
- Alcohol Use Disorder and depression
- Chronic low back pain and depression
- Post-treatment Lyme disease
- Opiate Use Disorder
- Cannabis Use Disorder
- Mild Cognitive Impairment and depression
- ALS and psychological distress
- Post-traumatic stress disorder (PTSD)
- Healthy Participant Studies (Music, Microdosing, etc)

Potential… but also Pitfalls

- Safety
- Ethics
- Access
- Hype

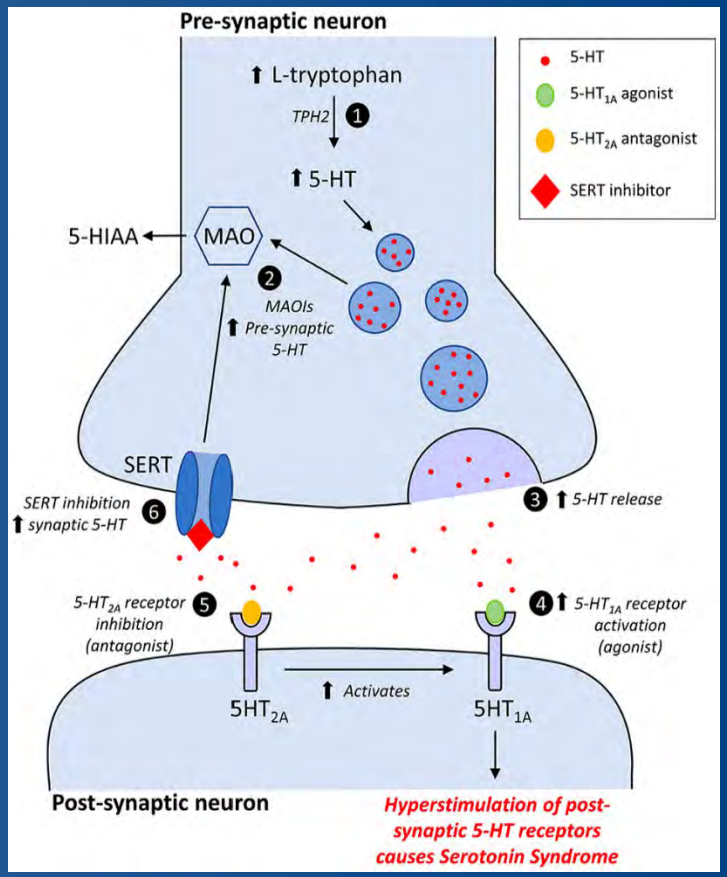
Safety

- The full safety profile of psilocybin and other psychedelic medicines is still under investigation
- Psilocybin is mostly non-reinforcing (i.e. does not lead to significant dependence)
- Psilocybin has overall low toxicity (LD50 >100x doses used in clinical trials)
- However, challenging psychological experiences can occur following psilocybin, especially in unsupported or recreational contexts.
- Certain psychiatric conditions (Bipolar I disorder and Schizophrenia) are likely exacerbated by psychedelic interventions.

Serotonin Syndrome

- Results primarily from overactivation of 5HT2A post-synaptic receptors, causing second messenger signaling that drives toxic response
- Strong agonism of the 5HT2A receptor could hypothetically put someone at risk for serotonin toxicity, but most psychedelics including psilocybin bind significantly less strongly than 5HT itself
- Clinical risk is most related from increased <u>intrasynaptic</u> 5HT from medications that increase 5HT in the synaptic cleft

- Psilocybin:
  - Does NOT increase intrasynaptic serotonin
  - 5HT2A agonist BUT doesn't bind strongly compared to 5HT (so even with high doses, low risk of serotonin syndrome)



Drug-Drug Interactions

- No CYP activity and no intrasynaptic increase in 5HT
- Antipsychotics: No known toxicity. Haldol (D2 only) results in increased dysphoria but no impact on most subjective effects. Risperidone does act on 5HT2A receptors (in addition to D2) and has been shown to blunt subjective effects.
- SSRI/SNRI: No known toxicity. "When blocking SERT pharmacologically with [2-weeks pre-treatment] escitalopram (Becker et al. 2021), there is no attenuation of psilocybin's psychedelic effects and in fact reduced measures of anxious distress and participant complaints." This is also supported by Compass360 data showing comparable outcomes in patients maintained on SSRIs during trials. This is in contrast to reports of SSRIs blunting the subjective effects of psilocybin, proposed mechanism is down-regulation of 5HT2A receptors with long-term SSRI use.
- Buspirone: No known toxicity. Possible indirect activity with 5HT2A receptor that may decreased acute subjective effects.
- Trazodone: No toxicity. Inhibition of 5HT2A receptor activity may decrease acute subjective effects (see case report of trazodone+psilocybin).
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Adverse Events

- ". In contemporary research settings, there were no reports of deaths by suicide, persistent psychotic disorders, or hallucinogen persisting perception disorders (HPPD) following administration of high-dose classic psychedelics. However, there was significant heterogeneity in the quality of AE monitoring and reporting. Of 68 analyzed studies published since 2005, only 16 (23.5%) described systematic approaches to AE assessment, and 20 studies (29.4%) reported all AEs, as opposed to only adverse drug reactions." (Jama, Hinkle et al. 2024)
- Hallucinogen persisting perception disorders (HPPD) has been reported with recreational use of psychedelic medicines
- Common Side Effects: Acute elevations in blood pressure as well as headache

Microdosing?

- Microdosing, or taking sub-perceptual doses of psilocybin or similar psychedelic medicines, has become a popular recreational practice
- Despite the perception that lower doses of this medication is safer, repeated small doses (as opposed to infrequent macro-doses) of medicines such as psilocybin could put someone at risk for valvular heart disease (due to activation at the 5HT2B receptor)
- We are still learning about these risks, however, there are legitimate concerns about microdosing
- Additionally, microdosing has yet to be established as clinically beneficial

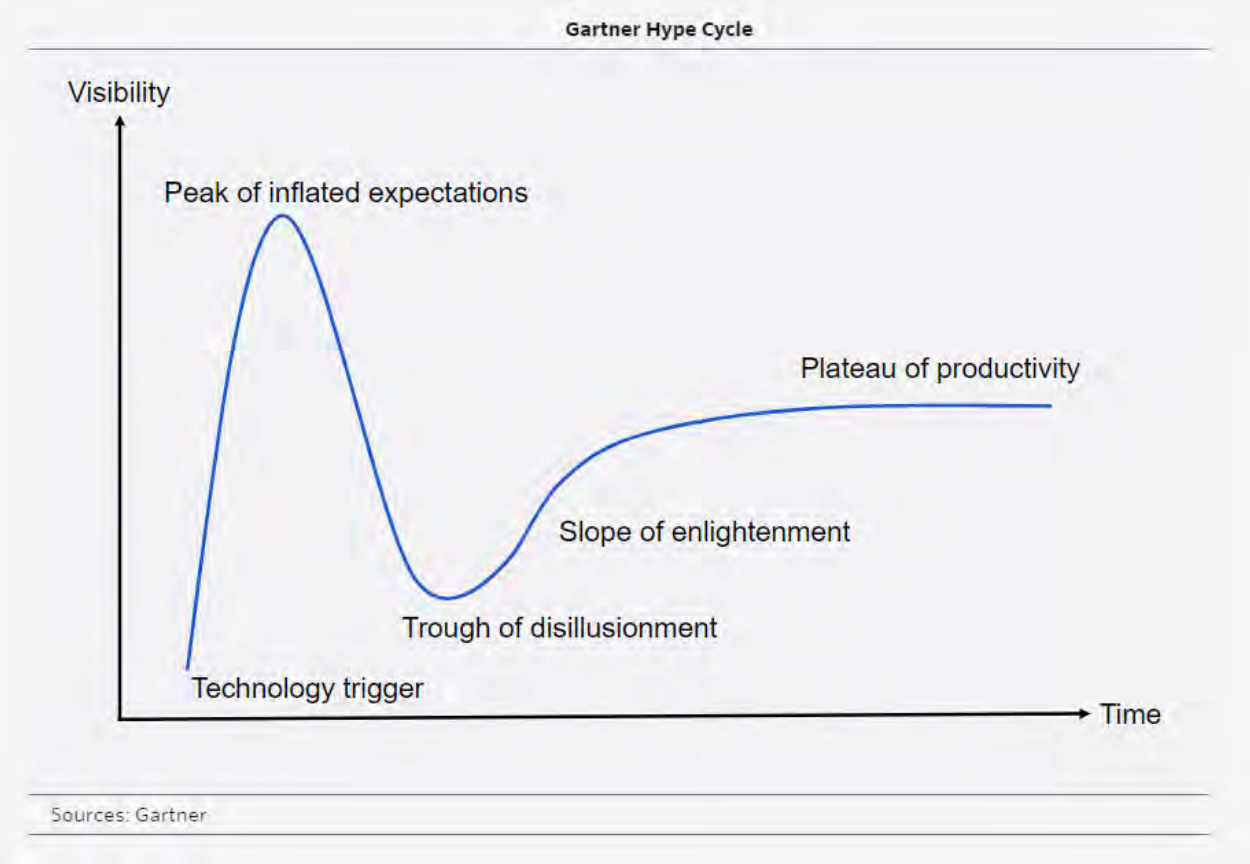
Ethics

- There is an emerging field of psychedelic ethics
- Key domains include:
  - therapeutic boundaries and touch
  - informed consent
  - provider or researcher bias
  - inclusion of diverse participant populations in research
  -appropriation of indigenous cultural practices within the medical or scientific frame

Access to Care

- Currently, limited access to clinical trials based on study inclusion/exclusion criteria
- If psychedelic medicines are approved, how will these interventions be paid for and by whom?
  - Current model of two providers with extensive medical monitoring plus psychological support/psychotherapy may not be feasible within the established mental healthcare field

The Hype Cycle



Inclusion in Clinical Trials and Current Research

- A number of current clinical trials are ongoing at our center
  - OCD, AUD-MDD, OUD, PTSD, ALS, MCI, CUD, CLBP-D…
- Common exclusion criteria
  - A personal history or first degree relative with bipolar disorder (I or II) or schizophrenia
  - Active or recent suicidal ideation
  - A history of significant cardiovascular disease, seizure d/o, stroke, or substance use

Challenging Experiences Consultation Clinic

- Johns Hopkins Personalized Care now offers Psychiatric Services
- Dr. Azin Bekhrad works with the CPCR providing consultation with individuals struggling with psychiatric concerns related to psychedelic experiences
- abekhra1@jhmi.edu

Thank you!

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Health Disparities

AI

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