Psilocybin use in psychiatric disorders

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Agenda

- History.
- Pharmacology of Psilocybin.
- Psilocybin- assisted psychotherapy.
- Psilocybin use in psychiatric disorders.

History

- Psilocybin is a naturally occurring compound produced by more than 200 species of mushrooms.
- Psilocybin-producing mushrooms are distributed in Asia, Australia, US, Canada, Central and South America.

History

- Psilocybin belongs to a group of drugs known as psychedelics (or hallucinogens) that cause perceptual change in a state of full wakefulness and alertness.

- The term ‘psychedelic’ is derived from the Greek words ψυχή (psyche, ‘soul, mind’) and δηλοῦν (deloun, ‘to manifest’), hence the term ‘mind manifesting’ or “ mind-altering”

- It was first coined by British psychiatrist Humphry Osmond in 1957.

History

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- The term ‘psychedelic’ is derived from the ancient Greek words psychē (ψυχή, translated as “soul” or “mind”) and dēlein (δηλειν, translated as “to reveal” or “to manifest”). Therefore, psychedelic literally translates as ‘mind manifesting’ or ‘soul revealing’

- It was first coined by British psychiatrist Humphry Osmond in 1957.

History

- The psychedelics can be divided into four classes based on their pharmacological profiles and chemical structures:

1. Classic psychedelics (serotonin 2A [5-HT_{2A}] receptor agonists) e.g. psilocybin, LSD, ayahuasca.

2. Empathogen or Enactogen (mixed serotonin and dopamine reuptake inhibitors and releasers) e.g. MDMA.

History

3. Dissociative hallucinogen, such as ketamine . Act mainly as NMDA receptor antagonists

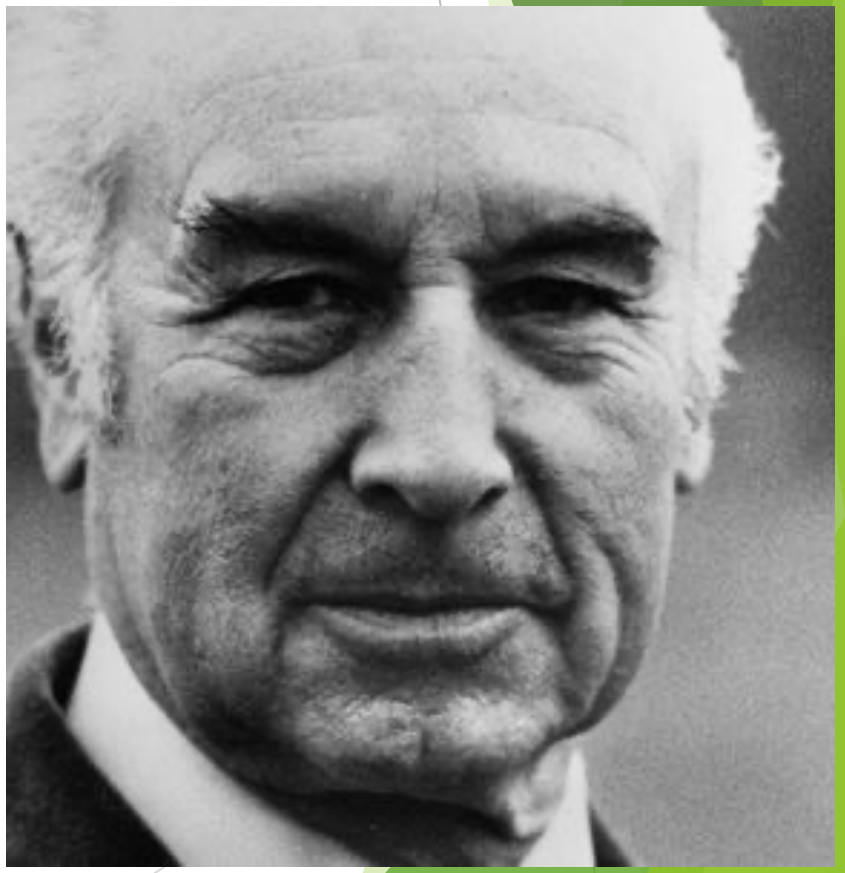
4. Atypical hallucinogens – affect multiple neurotransmitter systems.

History

- Classic psychedelic compounds like psilocybin, mescaline have been used in religious ceremonies and for healing purposes in indigenous societies in South and Central America for centuries.

History

- In 1938 Swiss chemist Albert Hofmann ((11 January 1906 – 29 April 2008) synthesized the first synthetic hallucinogen, lysergic acid diethylamide (LSD), while working with the pharmaceutical company Sandoz.

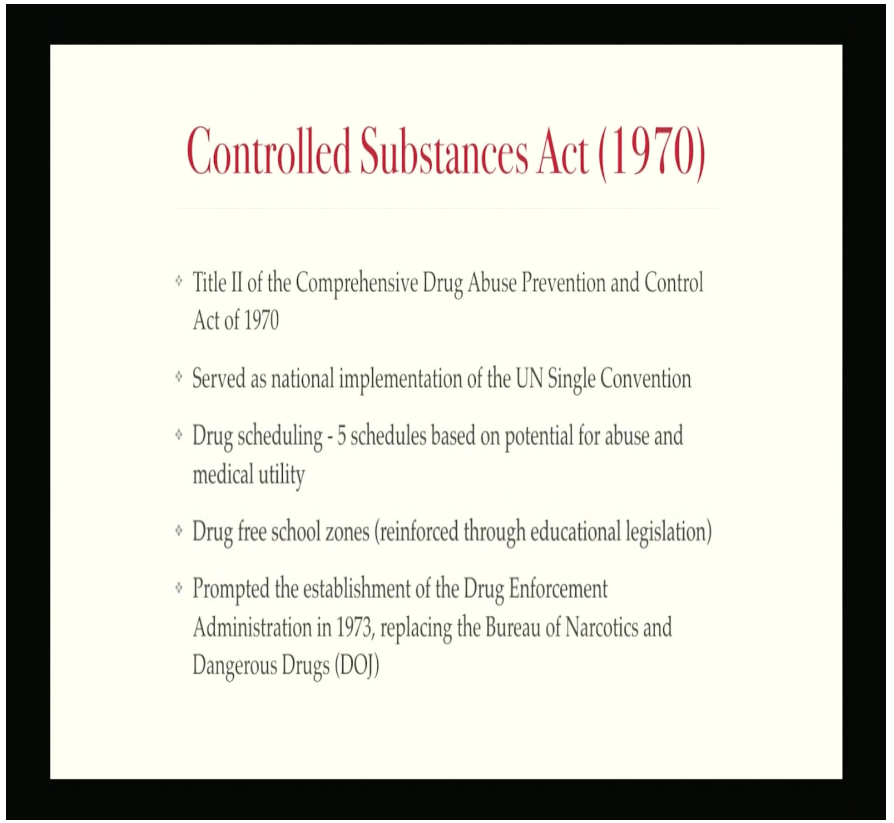


In 1947, Sandoz began to market LSD under the trade name Delysid as an adjunctive psychotherapy medication and as an agent for experimental study on the nature of psychosis.

- In 1957 Albert Hofmann extracted psilocybin from mushroom Psilocybe Mexicana.
- In 1960s Sandoz, Ltd. market their drug Indocybin™(pills containing 2 mg of psilocybin) which was used for clinical research.

History

- In 1960s : illicit production of LSD increased as it was being used widely in medically unsupervised settings.
- In 1965, governments in Europe and the United States raised concerns about the general public's use of LSD and psilocybin.
- Psychedelic substances became illegal with the passing of the Controlled Substances Act in 1970. (classified as Schedule 1 drugs).



Transition to Modern-Day Clinical Studies

- Over the course of the past decade, there has been a resurgence of research on the potential therapeutic benefits of psychedelic compounds, with the number of published review articles and clinical trial reports steadily increasing.

- Research on these compounds has been supported by diverse organizations ranging from the United Kingdom Medical Research Council, a nationally funded health agency, to the Multidisciplinary Association for Psychedelic Studies (MAPS), a nonprofit organization that was founded in 1986 to increase the knowledge base of psychedelic substances.

Transition to Modern-Day Clinical Studies

- These organizations have helped fund many pivotal trials and often work with regulatory agencies, including the FDA and the European Medicines Agency, to ensure that studies comply with the regulatory guidelines for eventual approval of clinical use.

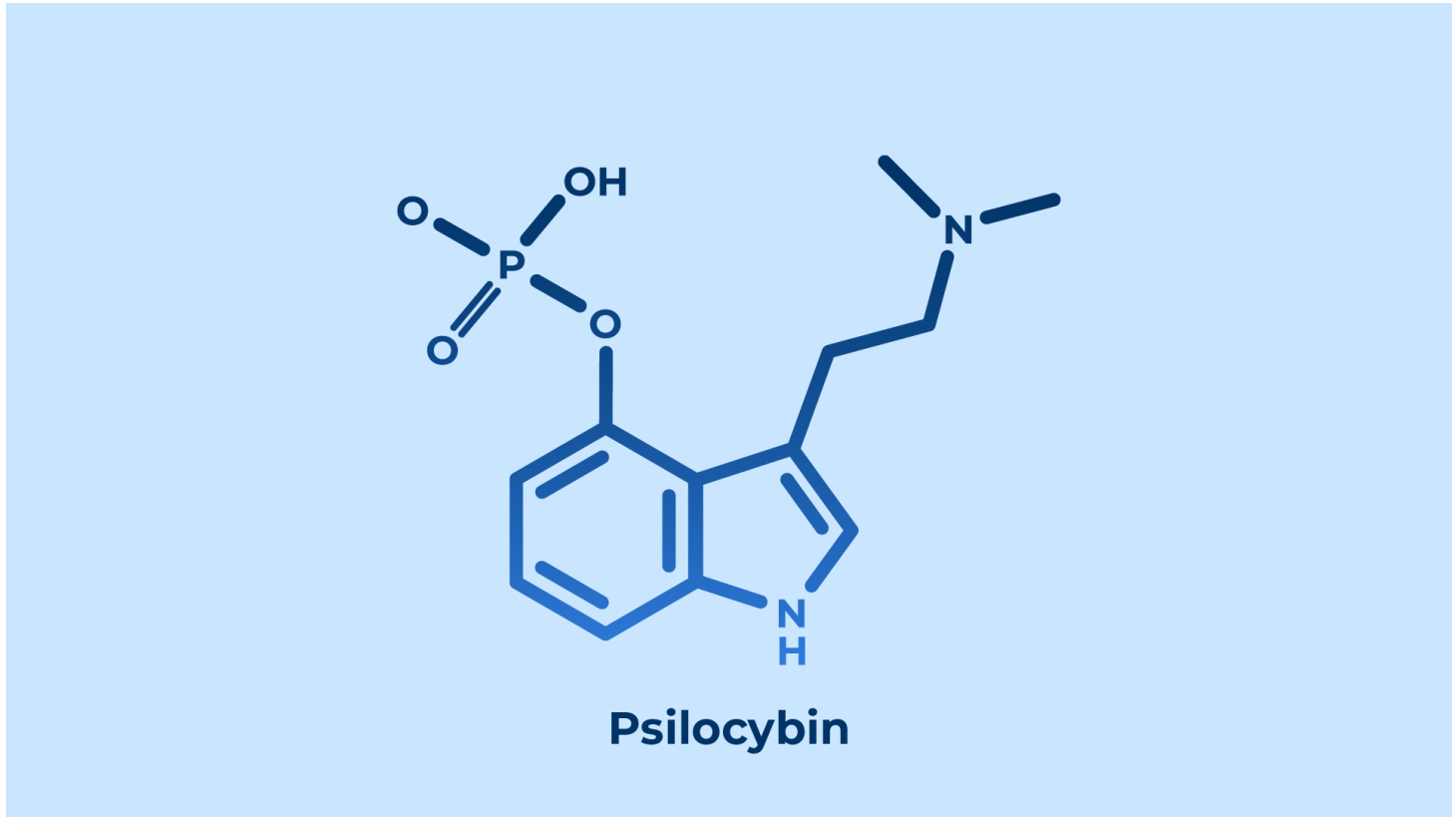
- Modern psychedelic drug research has been conducted at leading academic research universities around the world, including Johns Hopkins University, New York University, University of California, Los Angeles, Imperial College London, University of Zurich, and University of Basel

- Recently, Johns Hopkins University and Imperial College London established centers for psychedelic research, which aim to investigate the effects of psychedelic drugs on the mind, the brain, and psychiatric disorders.

- To date, over 27,000 scientific articles have been published on psychedelic drugs, with over 1000 particularly on psilocybin

- Currently, psilocybin is the most studied psychedelic .

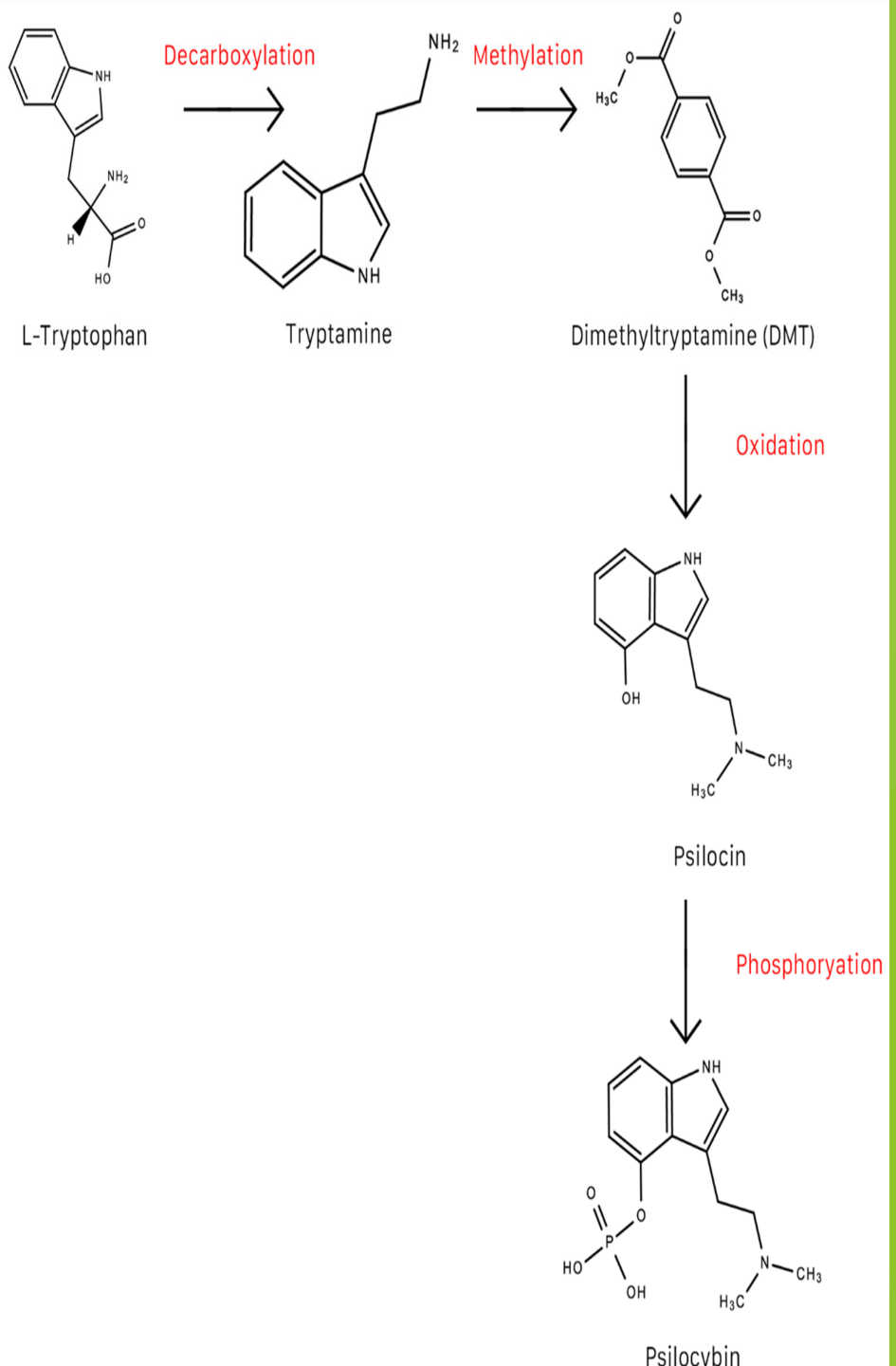
Pharmacology of Psilocybin

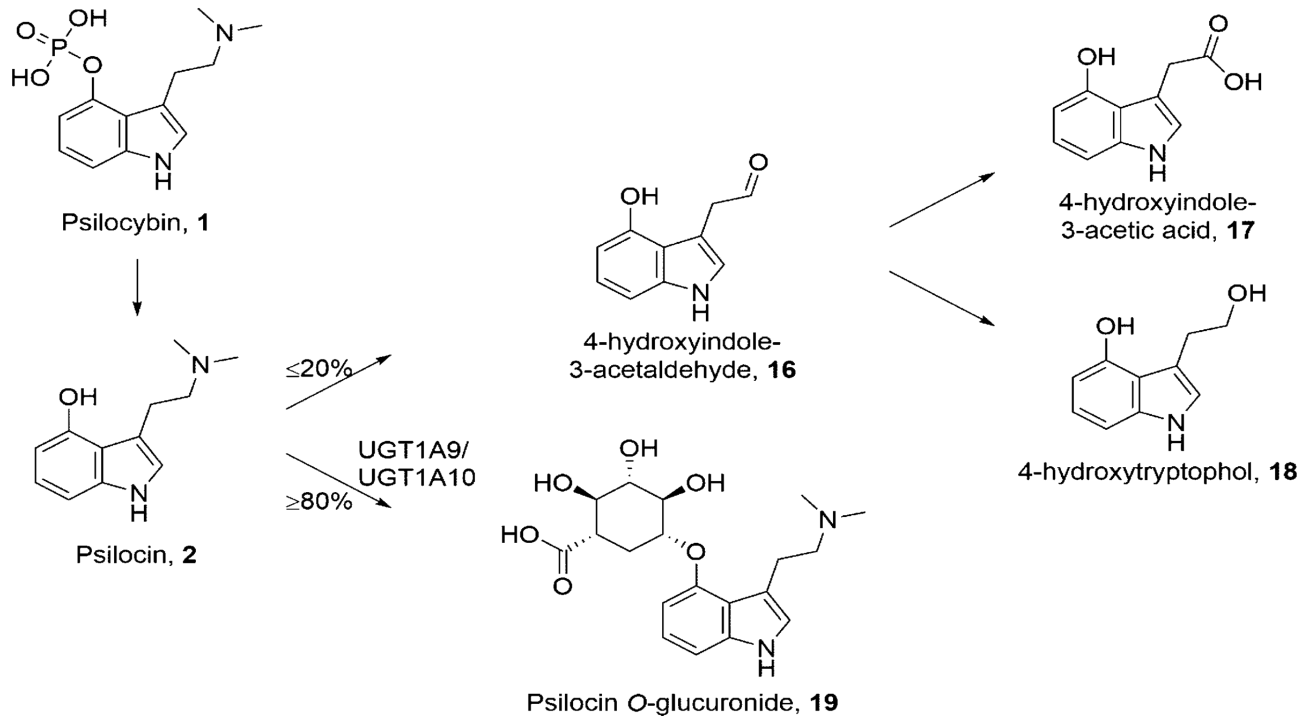


Psilocybin

Pharmacology of psilocybin

- Psilocybin is synthesized from the amino acid tryptophan.
- In human, psilocybin is rapidly dephosphorylated to psilocin by alkaline phosphatase in the liver and nonspecific esterase in the intestinal mucosa.
- Psilocybin does not cross blood brain barrier and is considered a prodrug of psilocin.
- Psilocin is lipophilic , cross blood brain barrier.



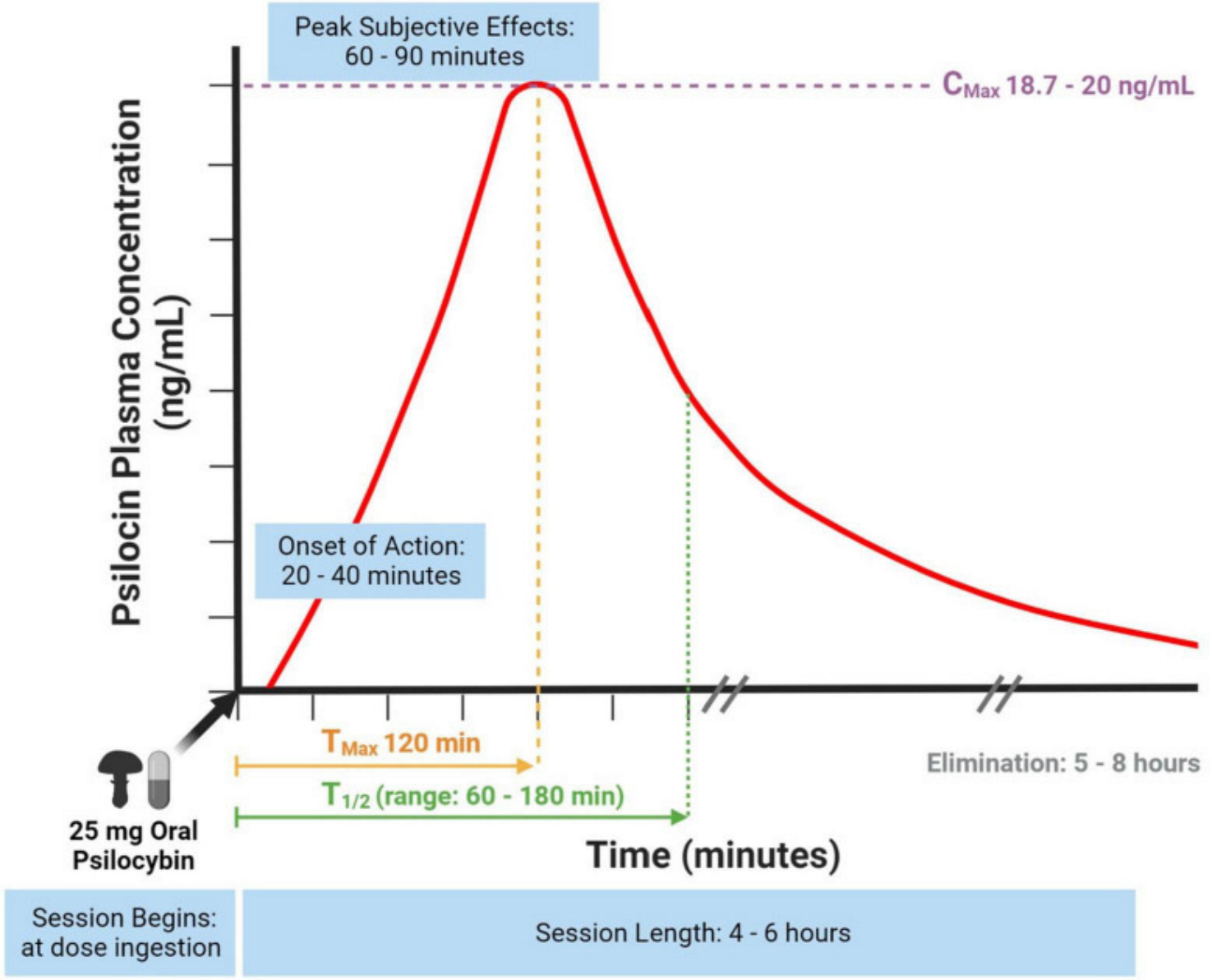


- Psilocin metabolism metabolism primarily occurs via UDP-glucuronyl transferase enzymes , UGT1A9 and UGT1A10. (Phase II = 80%).
- It also undergoes deamination and demethylation to form inactive metabolites.(Phase I =20%)

Pharmacology of Psilocybin

- Its metabolites are then renally excreted.
- The elimination half-life of psilocin is approximately 3 h (+/- 1.1h) in healthy adults.
- After 24 hour , almost all psilocybin and psilocin are excreted from the body.

- After oral ingestion, psilocybin effect start anywhere between 20 to 40 minutes, peaks 60-90 minutes after ingestion and then subside six hours post-ingestion.



- The psychological effects of psilocybin are highly variable and depend on dose, setting and mindset of the user.

- Effect of psilocybin can be :
  - Somatic : Mydriasis, Rhinorrhea, hypersalivation, increased systolic blood pressure , slight elevation in body temperature and transient headache.

  - Perceptual: perceptual enhancement, illusion, distortion, visual hallucination (bright and colorful shapes seen with eye closed (lower dose) and with eyes open (at higher dose) , synesthesia.

- Cognitive : increased empathy, enhanced objective and situational analysis, music appreciation, ego loss, time distortion.

- Emotional : intensification of emotion, unique state of euphoria, negative emotions forgiveness uncontrollable laughter, Mystical-experience (increased spirituality, sense of interconnection between humanity and a higher power).

Pharmacodynamics

- Psilocybin interacts mainly with serotonergic receptors (5-HT1A, 5HT1D, 5HT2A and 5HT2C)
- The psychedelic effect of psilocybin are mediated by agonism at serotonergic 5-hydroxytryptamine 2A (5-HT-2A) receptors
- Administration of the 5-HT2AR antagonist, ketanserin, to healthy humans attenuated hallucinatory effects following psilocybin administration In comparison, antagonism at other 5-HT2 receptors, such as the 5-HT2C receptors, did not completely attenuate psilocybin-induced hallucinatory effects.

Pharmacodynamics

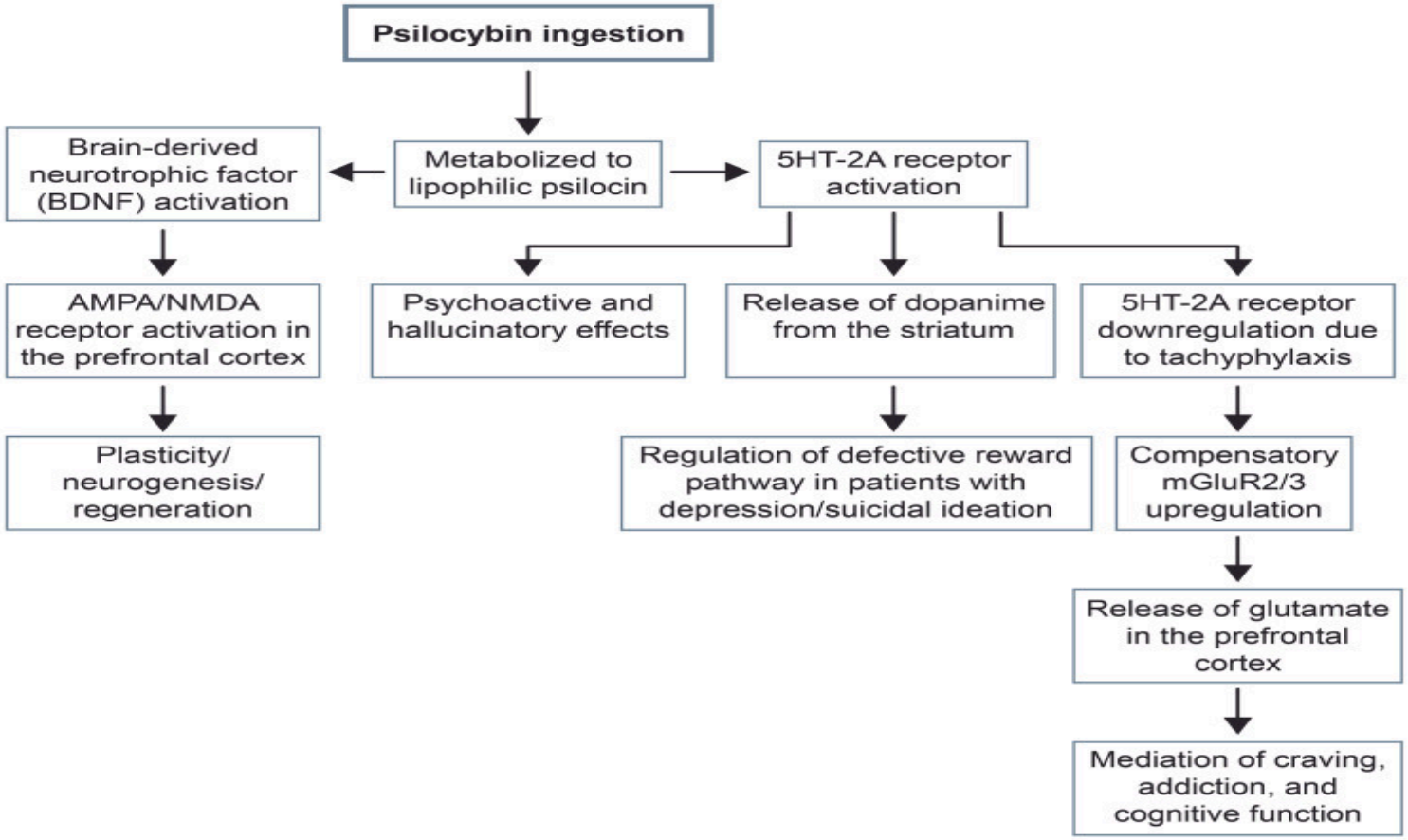
- Psilocybin also inhibits the sodium-dependent serotonin transporter (SERT) , deactivation of SERT results in higher concentrations of serotonin remaining in the synaptic cleft following stimulated serotonin release, allowing repeated firing of serotonergic postganglionic neurons.

- In contrast to many other psychedelic (like LSD) , Psilocybin has no affinity for dopamine D2 receptors.

- However, it has moderate affinity for dopamine D3 receptors which likely contribute to its ability to mediate addictive tendencies.

- Additionally, psilocin also has activity at at Histamine 1 (H1) receptor, alpha-2A and 2B receptors.

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

Adverse effects

- In general, psilocybin has the most favorable safety profile of all psychedelic drugs.
- Psilocybin has a wide margin of safety with lethal doses estimated to be more than 1000-fold higher than therapeutic doses.
- In clinical trials, Single doses of psilocybin have been used in controlled settings without serious side effects.

Adverse effects

- All adverse events were reported to be transient and mild
- The most common being headache, elevated blood pressure, nausea, and anxiety.

Adverse effects

- In uncontrolled settings such as in recreation, psilocybin use may lead to what is referred to as a “bad trip”.

- Bad trip is an undesired or even traumatic physical and emotional experiences characterized by altered visual perception, extreme distress, fear, lack of coordination, derealization, depersonalization, panic-attacks, traumatic flashbacks, paranoia and short-term psychosis.

Adverse effects

- The risk of seizures caused by psilocybin ingestion is very low but may be increased in times of heightened physiological stress, including dehydration and extreme fatigue.

- Hallucinogen Persisting Perception Disorder (HPPD): rare clinical condition in which patients who have had previous exposure to a hallucinogenic substance continue to experience perceptual distortions months to years after complete cessation of the initial substance use.

Adverse effects

- Damage to the cardiac valves is possible with frequent long-term use due to psilocin’s 5-HT2B receptor activity at the heart, which induces the proliferation of cardiac fibroblasts, resulting in a stiffening of the cardiac valves.

Contraindications

- Severe cardiovascular disease including uncontrolled blood pressure, heart failure, coronary artery disease or previous heart attack or stroke.
- History of epilepsy and other seizure disorders
- History of schizophrenia, psychosis, bipolar disorder, and borderline personality disorder are generally contraindicated for psilocybin.
- Pregnancy and breastfeeding are also contraindicated given insufficient scientific evidence to assess risk.

Drug interactions

- Concomitant use with serotonergic drugs may lead to a rare, but serious, condition called serotonin syndrome in which excessive serotonin signaling can lead to a potentially life-threatening adverse drug reaction.

- For this reason , clinical trial protocols often require the tapering and washout of these medications due to the concern of serotonin syndrome.

- As psilocin is primarily metabolized by UGT 1A10 and 1A9 medications that can inhibit or induce these enzymes must be held or tapered prior to administration of psilocybin
  - (examples UGT 1A10/1A9 inhibitors include diclofenac (a Non-steroidal anti-inflammatory drug) and probenecid (a uric acid reducer).
  - Estradiol upregulates expression of UGT1A9 , therefore Hormonal replacement therapy , OCP may induce psilocybin metabolism.

- Drugs that block 5HT2A such as second-generation antipsychotics and chlorpromazine will attenuate psilocybin’s subjective effect.


Quiet
Please...
Important
Work In
Progress
PSILOCYBIN
SESSION CURRENTLY
IN PROGRESS

Psilocybin-Assisted Therapy

- Psilocybin therapy combines the pharmacological effects of psilocybin with psychological support.
- The psychological support element of the therapy is essential for both effectiveness and safety.

Psilocybin-Assisted Therapy

- Psilocybin-assisted psychotherapy can be divided into three types of sessions: preparatory, medication (one to three sessions with moderate to high doses of a psilocybin), and integration sessions.

Preparations:

- Preparation focuses on establishing the therapeutic alliance between the therapist and participant.

- During the preparatory sessions, the therapists engage the patient to explore his or her life history and help the patient understand his or her symptoms with an emphasis on the potential for emotional and psychological growth.

- They also educate the patient about what to expect during the psychedelic session

The psilocybin session:

- Psilocybin is administered in a comfortable room with a reclining chair or bed in an environment that is decorated and appointed so that it will feel familiar and not intimidating.
- After drug ingestion, the patient is encouraged to focus his or her attention inward and is offered the option of listening to music and wearing eye shades.

- For the next 6–8 hours, the therapists listen empathically to the patient and maintain a nonthreatening, neutral therapeutic stance.

- The therapists' goal is to facilitate a sense of safety, trust, and openness

Integration

- Immediately after the psilocybin session and in the following days, a process of integration is facilitated by the therapist.

- During the integration sessions, the therapists work with the patient to interpret the content of the psychedelic experience into meaningful long-term change through identifying insights or interpreting thoughts or ideas that arose during the psychedelic session

- It is believed that the therapeutic effect is a result of the interaction between the drug and the mindset of the patient (together often referred to as “set”), the external conditions (often referred to as “setting”), and the therapist(s)

- It is believed that a therapeutic set and setting make adverse outcomes less likely even when challenging and painful experiences arise.

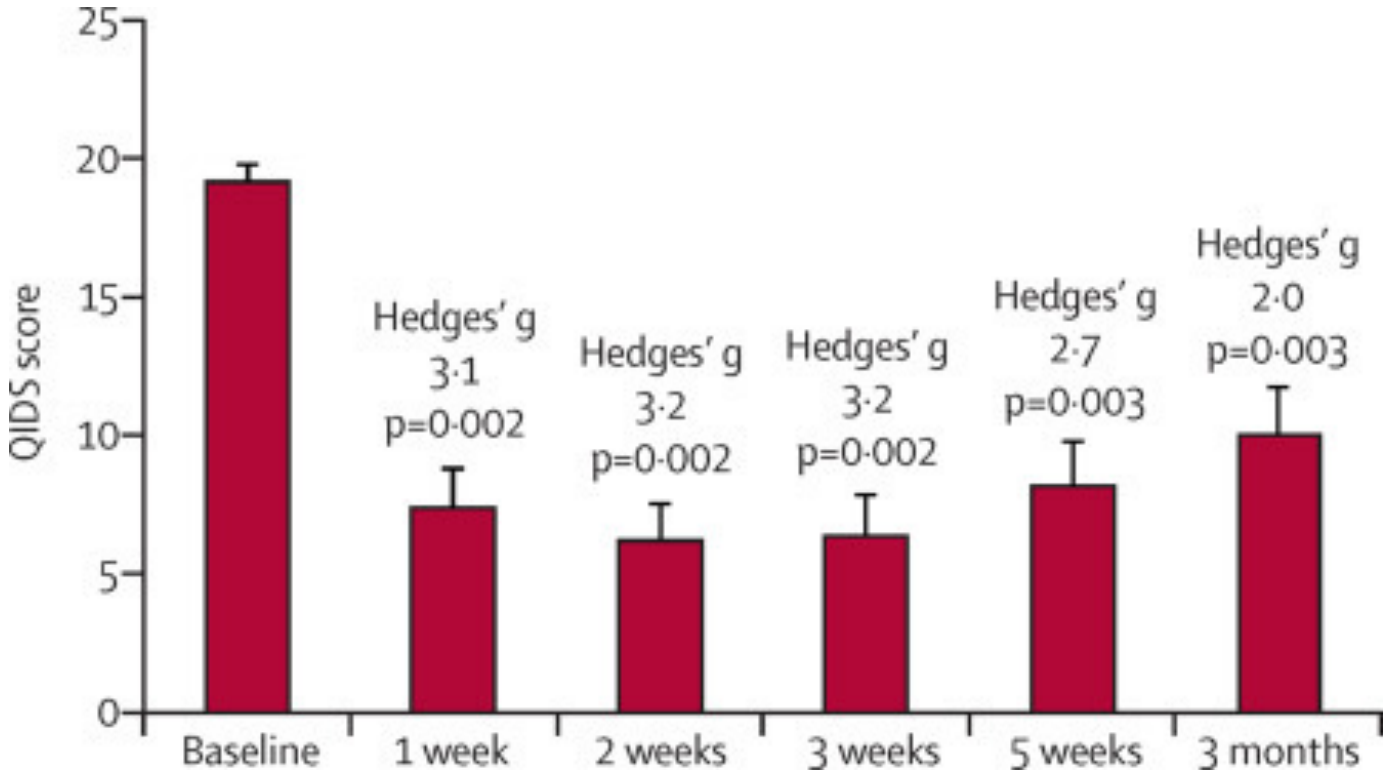
Psilocybin therapy in psychiatric disorders

- Recently, there has been a resurgence in psilocybin research in the United States and Europe in the treatment of refractory mood disorders, refractory obsessive-compulsive disorder, end-of-life anxiety, and tobacco and alcohol use disorders.

Psilocybin therapy in Major Depressive Disorder

- In a recent open-label pilot study evaluating the feasibility and efficacy of psilocybin-assisted psychotherapy in 12 patients with moderate to severe treatment-refractory depression.
- Participants were given two oral doses of psilocybin in association with psychotherapy sessions.
- Participant received a low dose (10 mg) of psilocybin at the first session and a higher dose (25 mg) at the second session.

Carhart-Harris et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 2016.



- Depression scores (measured by the Quick Inventory of Depressive Symptomatology (QIDS) were significantly decreased from baseline to 1 week and 3 months after treatment.

- Remission was achieved by eight patients (67%) at 1 week and five patients (42%) at 3- month after psilocybin session.
- In the same sample, functional MRI (fMRI) scans were performed at baseline and again the morning after the high-dose psilocybin-assisted psychotherapy session.
- One day before and 1 day after their psilocybin sessions, patients were shown images of faces with fearful, happy, or neutral expressions.

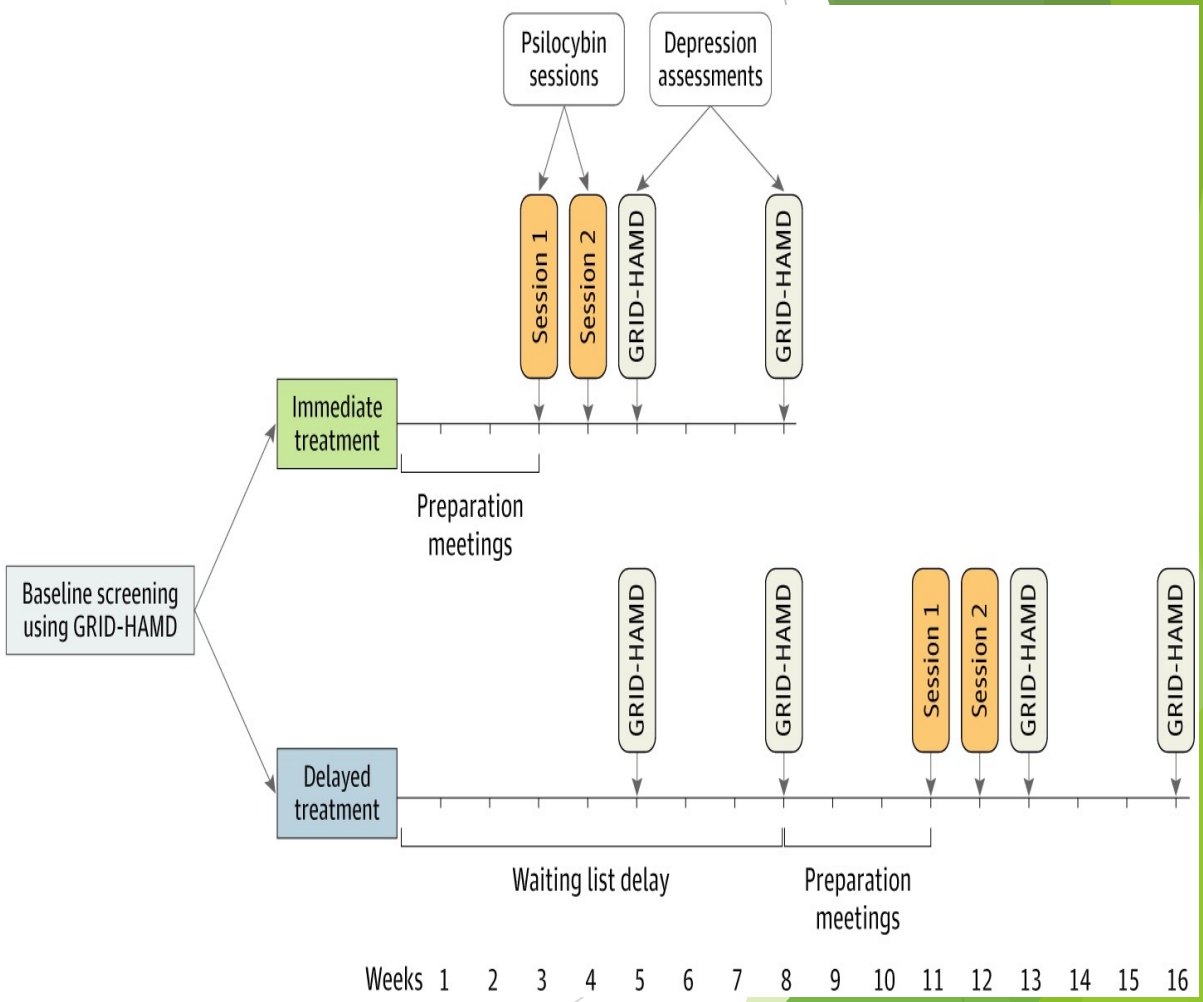
- Patients who received psilocybin showed increased amygdalar responses to fearful compared with neutral faces 1 day after treatment, and this response predicted positive clinical outcome 1 week later.
- Heightened amygdalar activity following psilocybin administration was interpreted as evidence of a different antidepressant mechanism of action than that of patients treated with selective serotonin reuptake inhibitors (SSRIs), who have shown diminished amygdalar response to emotional stimuli.

- Further fMRI research has demonstrated that psilocybin acutely disrupts default mode network connectivity, inducing temporary neuroplastic states that may make an individual more susceptible and receptive to psychotherapy.

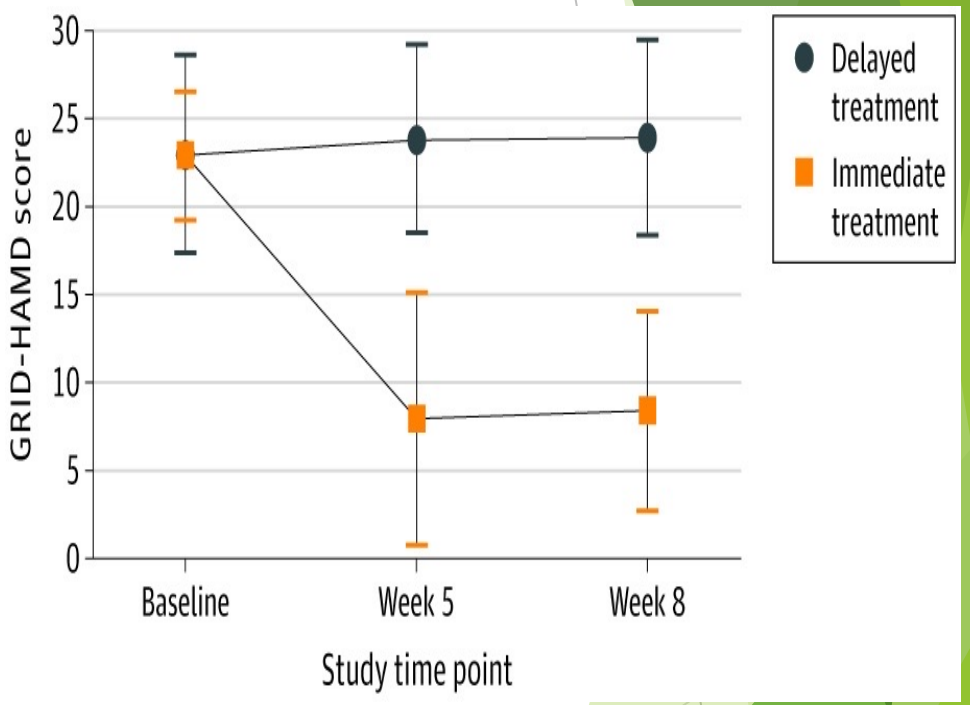
- By disrupting connection between some parts of the brain, psilocybin allows new connections in the brain to be formed (pharmaco-physiological interaction).

Effect of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA PSYCHIATRY 2021.

- 24 patients with moderate to severe MDD were randomly assigned to psilocybin or a waiting list.
- The psilocybin group received a single dose (20mg/70kg) at week 3 and a second dose (30mg.70kg) at week 4 plus psychological support, which included preparation for ingesting psilocybin, support during psilocybin session and discussion of psilocybin experience in subsequent sessions.

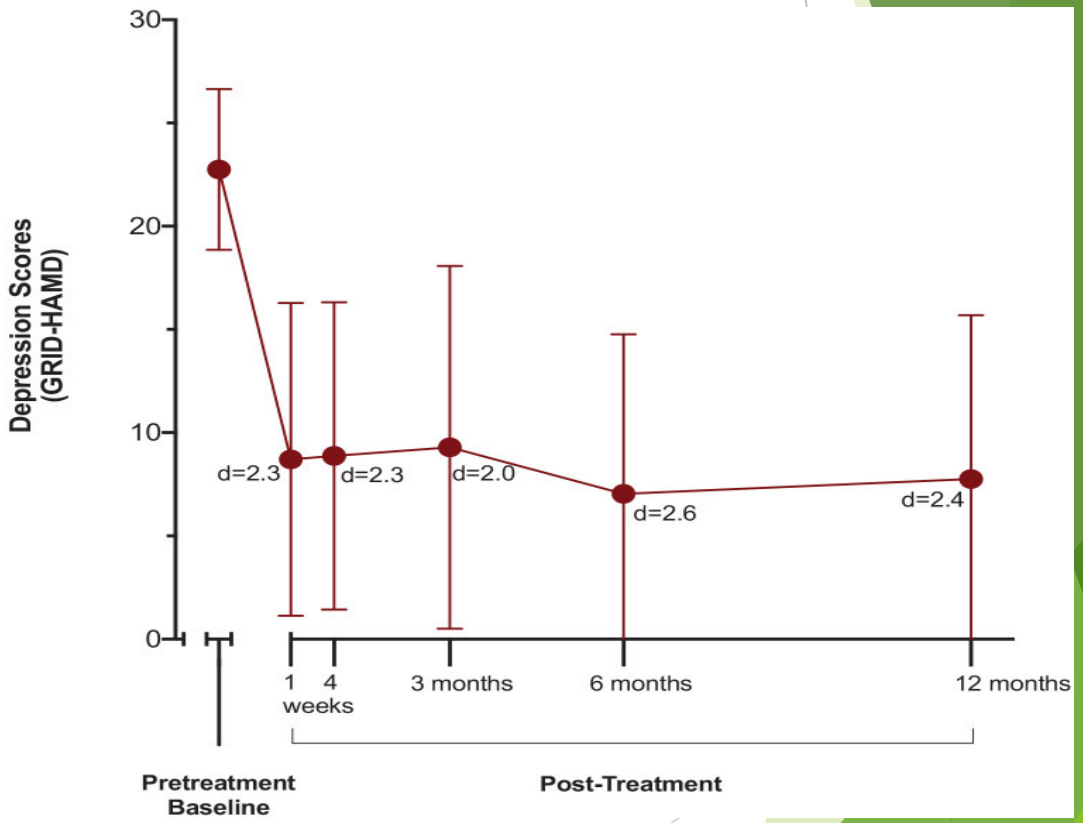


- Rapid and significant decrease in depression score one day after psilocybin session, at week 5 and week 8.
- The effect sizes reported in this study were approximately 2.5 times greater than the effect sizes found in psychotherapy and more than 4 times greater than the effect sizes found in psychopharmacological depression treatment studies.
- The intensity of mystical-type experience reported after psilocybin sessions was associated with decreased depression score.



Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. J Pychopharmacol 2022 Feb

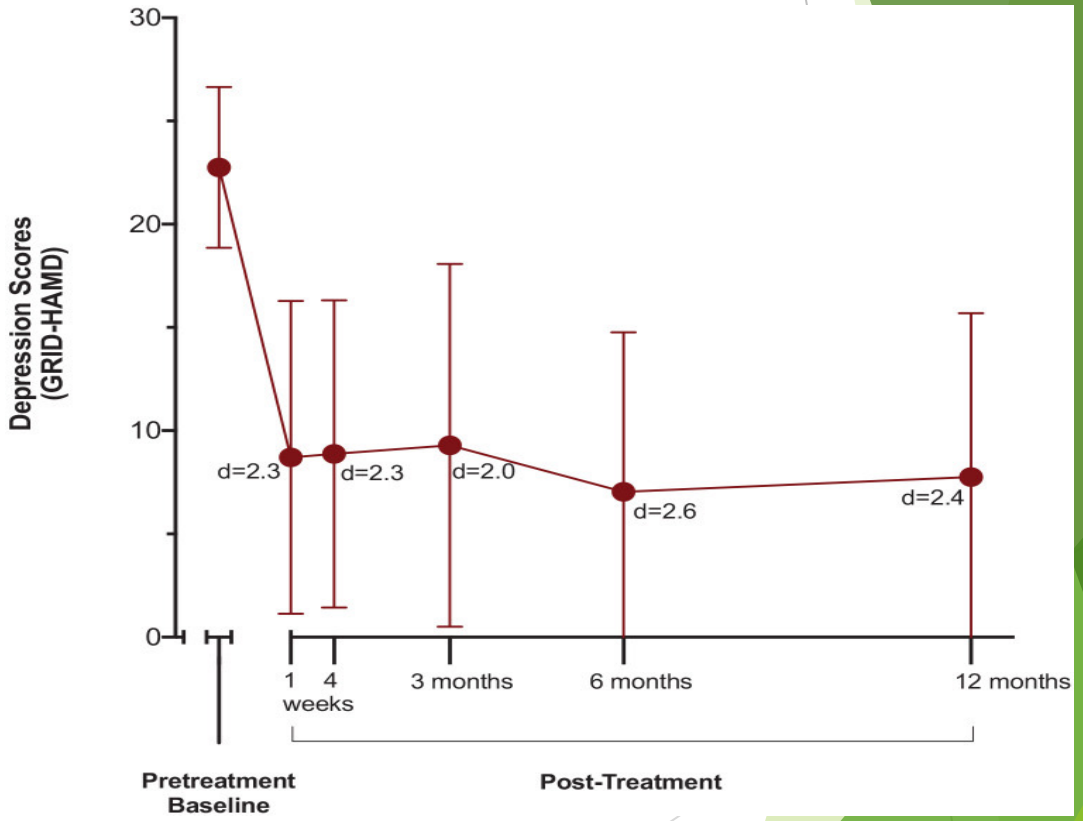
- Same subjects of the previous study were followed over a period of 12 months.
- Large decreases from baseline in GRID-HAMD scores were observed at 1-, 3-, 6-, and 12-month follow-up (Cohen *d* = 2.3, 2.0, 2.6, and 2.4, respectively).
- Treatment response (⩾50% reduction in GRID-HAMD score from baseline) and remission were 75% and 58%, respectively, at 12 months.



Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. J Pychopharmacol 2022 Feb

- There were no serious adverse events judged to be related to psilocybin in the long-term follow-up period.

- Participant ratings of personal meaning, spiritual experience, and mystical experience after sessions predicted increased well-being at 12 months,but did not predict improvement in depression.



- In 2018, the FDA granted psilocybin a “breakthrough therapy” for treatment-resistant depression, giving it priority consideration in the regulatory process.

- Breakthrough therapy designation is a process designed to expedite the development and review of drugs intended to treat a serious or life-threatening condition for which preliminary clinical evidence suggests substantial improvement over available options.

- In phase 2b trial, a single dose of synthetic psilocybin 25 mg (COMP360 made by Compass Pathway) in combination with psychotherapy was given to patients with TRD.

- Results were impressive with 29% of patients were in remission and 37% had at least 50% reduction in depression scores 3 weeks after psilocybin session.

- Currently COMP360 is being studied in Phase III trial.

- Upon successful completion of Phase III trials, the company may submit a New Drug Application asking the FDA to consider psilocybin for marketing approval.

Cancer-Related Psychiatry Distress

- Recent trials have also shown that psilocybin may be effective for treating anxiety disorders and emotional suffering associated with end-stage cancer.

- A large double-blind randomized crossover study by Griffiths et al. (N=51) investigated the effects of psilocybin, administered in two sessions, on depression and anxiety syndromes in 51 patients with terminal cancer who also had a DSM-IV diagnosis of an anxiety or mood disorder.

Cancer-Related Psychiatry Distress

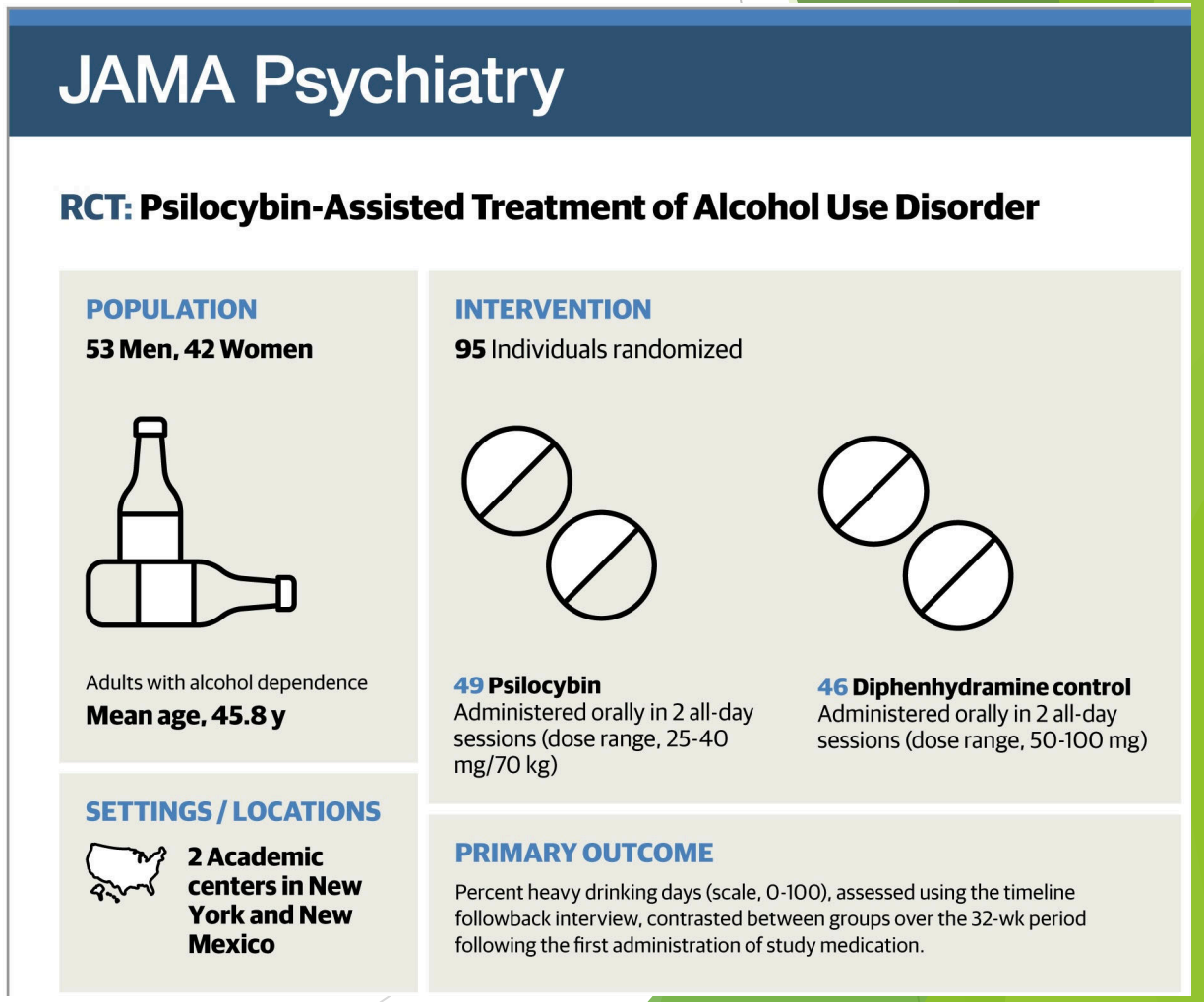
- Participants received a high dose (22 mg/70 kg) or a low dose (1 mg or 3 mg/70 kg) of psilocybin, with the low dose serving as an active control.
- Participants were crossed over to receive the alternative dose in a second session 5 weeks later.

- Before the first psilocybin session, participants met with study monitors to discuss “meaningful aspects” of their lives. During dosing sessions, therapists provided a supportive presence and encouraged participants to “trust, let go, and be open” to the experience, but otherwise were nondirective.

- The data showed that high-dose but not low-dose psilocybin produced large and significant decreases in depression and anxiety symptoms after 5 weeks, and this effect persisted through 6-month follow-up.

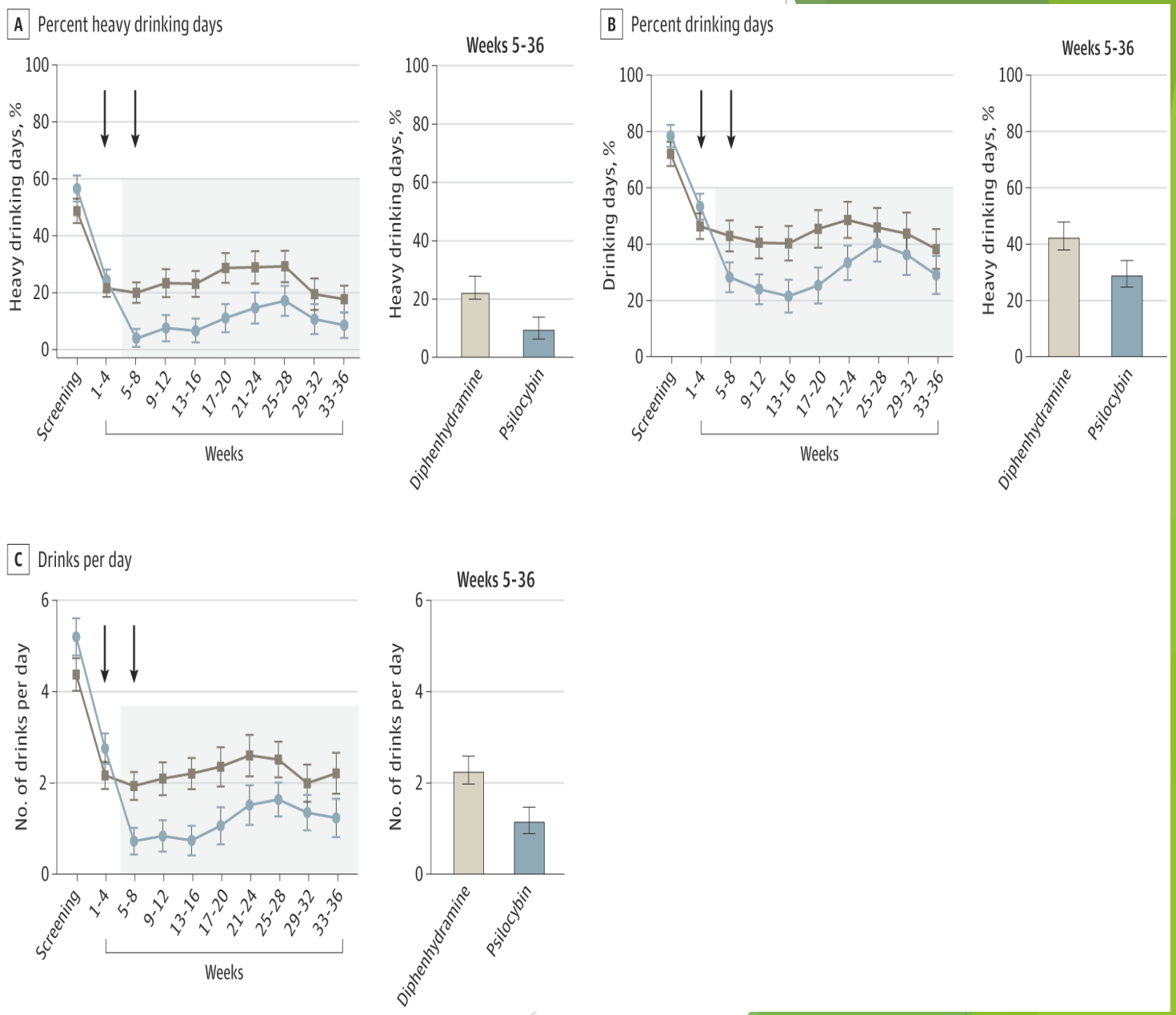
Psilocybin therapy in Alcohol Use Disorder

- When combined with psychotherapy, psilocybin appears to be effective for alcohol use disorder.
- In a trial, 95 subjects who were receiving 12 weeks of cognitive behavioral and motivational enhancement therapy were randomly assigned to receive two doses of psilocybin or diphenhydramine (active placebo).



- Over the 32-week follow-up period, subjects in the psilocybin group reported a lower percentage of heavy drinking days than those in the diphenhydramine group (9.7 versus 23.6, respectively; mean difference 13.86, 95% CI 3.0-24.7)

- Furthermore, subjects in the psilocybin group had fewer mean drinks per day than the diphenhydramine group (1.2 versus 2.3, respectively; mean difference 1.1, 95% CI 0.27-0.92)



Tobacco Use Disorder

- There is preliminary evidence that psilocybin may be efficacious in the treatment of tobacco use disorder
- An open-label study enrolled 15 participants participants who wanted to quit smoking in a 15-week course of smoking cessation treatment coupled with psilocybin administration.
- The first 4 weeks of treatment consisted of cognitive-behavioral therapy, assigning a target quit date, and keeping a smoking diary.

Tobacco Use Disorder

- Psilocybin was administered at weeks 5 and 7, with an optional third psilocybin session at week 13.
- Smoking abstinence was verified using exhaled carbon monoxide (CO level ≤6 ppm) and urinary cotinine measurements (level <200 ng/mL).
- At the 6-month follow-up, 12 of the 15 participants (80%) were laboratory-verified as abstinent; 10 participants (67%) remained abstinent at 12 months, and nine (75%) at 2.5 years.

Tobacco Use Disorder

- The observed smoking cessation rate substantially exceeds rates commonly reported for other behavioral and/or pharmacological therapies (typically <35%).
- No serious adverse events were caused by psilocybin.

Tobacco use Disorder

- NIH-funded Study :
  - Double-blind, randomized clinical trial of the 5-HT2A receptor agonist psilocybin for smoking cessation.
  - 66 participants (22 at each site), randomized to receive either: 1) oral psilocybin (30 mg in session 1 and either 30 mg or 40 mg in session 2); or 2) oral niacin (150 mg in session 1 and either 150 mg or 200 mg in session 2), with sessions 1 week apart.
  - This is a three year study, expected to be completed in 2024.
  - It represents the first NIH-funded psychedelic study in over 50 years.

Other psychiatric disorders:

- Two ongoing phase 2 randomized clinical trials are investigating psilocybin's effects in patients with a diagnosis of obsessive-compulsive disorder (ClinicalTrials.gov identifiers 03300947 and 03356483).

- Additional studies are investigating psilocybin for the treatment of
  - cocaine use disorder (ClinicalTrials.gov identifier 04052568)
  - opioid use disorder (ClinicalTrials.gov identifier 04161066)
  - anorexia nervosa (ClinicalTrials.gov identifier 04052568)
  - depression in early Alzheimer's disease (ClinicalTrials.gov identifier 04123314).

Summary

- Psilocybin offers a wide range of possible therapeutic benefits with Addiction medicine, depression, and end-of-life mood disorders are among the areas with the most evidence of benefit.

- The FDA's breakthrough designation of psilocybin for the treatment of depression reflects the drug's potential to treat resistant psychiatric disorders.

- Several sessions of psilocybin-assisted psychotherapy can lead to antidepressant effects that persist for weeks to months.

- This modality of treatment might provide a therapeutic advantage over current standards of care, such as transcranial magnetic stimulation, electroconvulsive therapy, or ketamine infusion therapy, each of which requires multiple visits per week to achieve antidepressant effect and often requires multiple visits per month to sustain remission.

- Psilocybin assisted therapy may constitute a major new area of medicine that might eventually alleviate suffering across multiple psychiatric disorders.

Questions ??

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Thank you