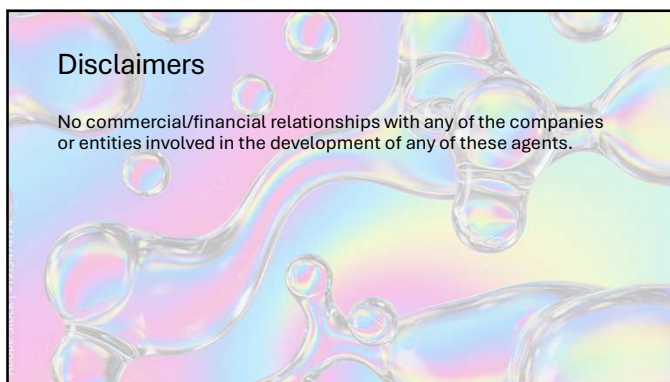




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2



3

Outline

The goal of this presentation is to enlighten participants about:

- What is a Hallucinogen/Psychedelic drug?
 - What are the types and classes, class characteristics?
- What is the evidence base for therapeutic efficacy?
 - And, for precautions?
- The regulatory processes
 - Federal- FDA and DEA
 - States

4

Historical and cultural background

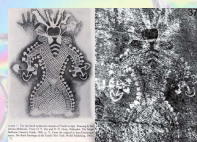
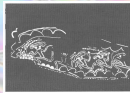
Oldest use of psychoactive substances

- 11000 BC, Israel- Beer (*Hordeum* spp)
- 8600 BC, Peru- San Pedro (*Trichocereus* spp)
- 8440 BC, Texas- Mescalbean (*Sophora secundiflora*)
- 8200 BC, Japan- Hemp (*Cannabis*)
- 7000 BC, Thailand- Betel (*Areca catechu*)
- 6000 BC, Egypt- Henbane (*Hyoscyamus* spp)
- 6000 BC, Egypt- Waterlilies (*Nymphaea* spp)
- 6000 BC, Sahara- Psilocybian mushrooms
- 6000 BC, Peru- Coca (*Erythroxylum* spp)
- 5800 BC, Georgia- Wine (*Vitis vinifera*)
- 5600 BC, Italy- Opium poppy (*Papaver somniferum*)

5

Historical and cultural background

The earliest evidence of psychedelic use can be found in a cave in a region of the Sahara desert, Algeria. In this cave is a mural depicting what is referred to as the 'mushroom man' or 'mushroom shaman', a bee-headed figure with mushrooms sprouting out of his body; mushrooms identified as *Psilocybe mairei*, native to the region. The mural is 7,000 to 9,000 years old.



6

Historical and cultural background

Evidence of hallucinogens in ritual practices

In 1995, spelunkers stumbled upon a funerary cave in Menorca from 3000 years ago. Archeologists found sealed, decorative containers full of strands of hair that had been dyed red. The hairs were tested and found to contain atropine, scopolamine, and ephedrine.

These Bronze Age people likely consumed those compounds by eating certain plants, including mandrake, henbane, horn apple, and joint pine. Scientists concluded that these individuals had been ingesting the drugs over the span of at least a year.

These were thought to be used ceremonially because the containers that held the hair were decorated with concentric circles.



7

Historical and cultural background

Evidence of hallucinogens in ritual practices

- Ergotamines: discovery of fragments of *Claviceps purpurea* (Fr.) Tul. sclerotia in a temple of the 4th–2nd century BC dedicated to the two Eleusinian Goddesses, Demeter and Persephone, excavated at a site in Spain. Ergot sclerotia fragments were found inside a vase along with remains of beer and yeast, and within the dental calculus in a jaw of a 25-year-old man, providing evidence of their being chewed (Juan-Stresseras, 2002). This finding seems to strongly support the hypothesis of ergot as an ingredient of *Kykeon*, the visionary drink of the Eleusinian Mysteries of ancient Greece.
- In 2008, archaeologists excavating a cave in southwestern Bolivia discovered a 1,000-year-old ritual bundle formerly belonging to a shaman of a pre-Incan civilization. Scrapings from the artifacts inside revealed traces of psychotropic compounds—benzoylcgonine, bufotenine (an alkaloid in psychedelic snuff powder), psilocin, harmine, and dimethyltryptamine (an active ingredient in ayahuasca).
- Ritual use of peyote in the Americas dates back more than 5000 years, to prehistoric times. Traces of peyote in a ritual context have been found in Mexico and in the Shumla Cave in Texas, together with other shamanic artefacts: ritual deer scapula rattles, bone rods and scrapers, and tubes containing incense.

8

Defining the Hallucinogens

- AKA Psychedelics, Entheogens, Psychoplastogens, Psychotomimetics
- Two classes:
 - Classic or Dissociative with distinct MOAs and Intoxication syndromes
- Other chemicals/substances can cause hallucinosis through other mechanisms, e.g. anticholinergic delirium. These are not considered to be Hallucinogens.
 - Angel's Trumpet (*Brugmansia* species) contains potent tropane alkaloids—specifically **scopolamine**, **atropine**, and **hyoscyamine**—that cross the blood-brain barrier and competitively block muscarinic acetylcholine receptors in the central nervous system, triggering a severe anticholinergic toxidrome

9

Defining the Hallucinogens

Classic

- Tryptamines
 - Indoleamines- Psilocybin/Psilocin, DMT (Dimethyltryptamine, Ayahuasca)
 - Ergolines-Lysergide/LSD,
- Phenylalkylamines- Mescaline (Peyote)
- Agonists at 5HT-2A
- Effects: perceptual shifts, ego dissolution, deactivation of the DMN, increases in BDNF, increases neuroplasticity

Dissociative

- PCP, Ketamine, Nitrous Oxide, Dextromethorphan (DXM), Salvia Divinorum
- Antagonists at NMDA receptors
- Effects: distortions of sight, sound, or reality; dissociation; maybe memory
- Alters BDNF and neuroplasticity

10

Hallucinogen-related Disorders- Intoxication

Classic

- Behavioral changes: paranoia, ideas of reference, fear of losing one's mind, anxiety/depression, impaired judgment
- Perceptual changes (intensification of perceptions, depersonalization, derealization, illusions, hallucinations, synesthesia)
- At least 2 of: Pupillary dilation, blurred vision, tachycardia, sweating, palpitations, tremors, incoordination

Dissociative

- Behavioral changes: belligerence, assaultiveness, impulsiveness, unpredictability, p/m agitation, impaired judgment, and
- At least 2 of: Nystagmus, HTN or tachycardia, numbness or diminished pain response, ataxia, dysarthria, muscle rigidity, seizures or coma, hyperacusis

11

MOA and Theory

Soylemez KK, de Boo EM, Susuzlu A, Lusher J. The Role of Psychedelics in Contemporary Psychological and Interdisciplinary Inquiry. *J Pers Med*. 2025 Sep 28;15(10):450. doi: 10.3390/jpm15100450. PMID: 41149813; PMCID: PMC12565330.

- The mechanisms of the therapeutic effects extend beyond the psychopharmacology.
- First, the importance of both "set" (personality, preparation, expectation, and intention of the user) and "setting" (physical, social, and cultural environment in which the therapy takes place) in determining the effects of psychedelics has been discussed in the literature.
- Patients undergoing psychedelic-assisted psychotherapy often undergo preparatory and integration therapy sessions in safe, comfortable, and trusting settings. In many studies, hallucinogen use also often takes place with the aid of music, and participants are often advised to stay with and describe the subject matter which comes to mind.
- Second, psychedelics can assist with loosening of ego defenses, release of unconscious materials and affective load, increased insight into the impact of experiences on the creation of maladaptive ego defenses, facilitation of transference, and synthesizing (traumatic) experiences into a more flexible character structure.
- One theory postulates that psychedelics relax the typical constraints higher-order brain systems impose on emotion, cognition, and sensory perception through their action on the 5-HT_{2A} receptor, allowing people to better modulate pathological fixed beliefs and opening them to considering information they would otherwise be biased to ignore or discount.

12

MOA and Theory- DMN

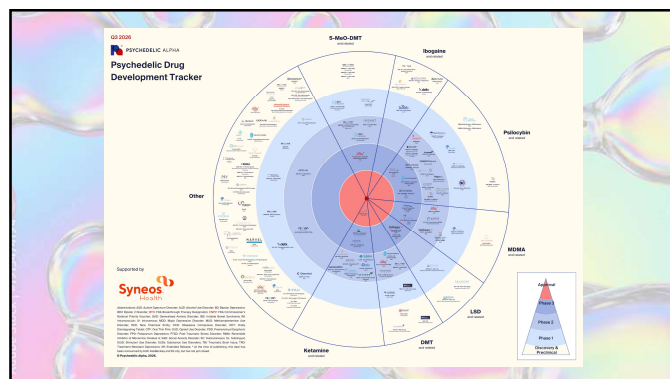
- In a functional magnetic resonance imaging (fMRI) study, activity in brain areas associated with the Default Mode Network (DMN) reduced following psilocybin administration.
- The DMN encompasses the medial prefrontal cortex, anterior and cingulate cortices and is functionally associated with activities which are self-referential, considering one's place in the world.
- Activity in the DMN is high when attention is focused inwardly on the self, and when dreaming.
- One proposed hypothesis is that psilocybin alters functional connectivity within the DMN, which suggests possible re-structuring of pathways associated with internalizing disorders such as depression.
- Commonly reported effects following psilocybin-assisted psychotherapy (PAP) include enhanced introspection, self-acceptance, and compassion, which are also key mechanisms in the cognitive reappraisals of trauma memories.

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MOA and Theory

- REBUS (Realized Beliefs Under Psychedelics)- Pathologically rigid beliefs are disrupted through the actions on networks.
- CSTC (Cortico-thalamic-striatal-cortico) Theory- Thalamic gating
- Cognitive flexibility
- Mindfulness and dualism
- Social connection
- Spiritual bypassing

14



15

Psilocybin/Psilocin

- Although psilocybin has been noted to act on multiple serotonin receptors such as 5-HT_{1A}, 5-HT_{2B}, 5-HT_{1D}, and 5-HT_{2C}, it likely exerts anxiolytic, antidepressant, and hallucinogenic effects by acting as a partial agonist at the 5-HT_{2A} receptor. 5-HT_{2A} agonism has been associated with the enhancement of acquired fear extinction, positive mood, and attenuation of negative facial. Though exact mechanisms are unclear, 5-HT_{2A} agonism has also been associated with hallucinogenic effects via modulation of dopamine release in the striatum and the cortex. Psilocybin also increases dopamine, though not directly, within the mesolimbic dopaminergic pathway.
- Psilocybin usage has been associated with reduced amygdala reactivity to negative stimuli measured on fMRI, decreased threat response, as well as to increased amygdala responsiveness to positive emotional stimuli.
- Psilocybin facilitates fear extinction and promotes neuroplasticity via neuritegenesis and spinogenesis both in vivo and in vitro, which may also contribute to antidepressant and anxiolytic effects. These neuroplastic changes are thought to be mediated through tropomyosin receptor kinase B (TrkB), mammalian target of rapamycin (mTOR) and 5-HT_{2A} signalling pathways.
- Primary focus of research has been on MDD, PTSD/Trauma, and Palliative Care/Anxiety/Existential Distress. Several have completed Phase III, or are in Phase III.
- Typically, the trials exclude history of psychosis, Bipolar Disorder, active substance use disorder, or recent use of psychotropic medications (e.g., antidepressants).
- The trial structure typically involves one or two doses, usually 25mg, mandatory preparation, monitoring throughout, and post-dosing (re-)integration psychotherapy. Dosing sessions are often recorded and/or have two people present.

16

Psilocybin- MDD

Yingwe H, Plavén-Sigra P, Ekman CJ, et al. Short-Term and Late-Term Effects of Psilocybin on Symptoms in Major Depression: A Randomized Clinical Trial. *JAMA Netw Open*. 2026;9(5):e2612589. doi:10.1001/jamanetworkopen.2026.12589

- RDBPC trial with 35 patients with moderate to severe recurrent MDD received 25mcg of psilocybin or placebo, plus support sessions over 17 days.
- Psilocybin showed significantly greater reduction in MADRS at day 8. Effects observed as early as day 2.
- Secondary outcomes: significant improvements at days 15 and 42, but not at 12 months. Remission rate at 6 weeks were 53% vs. 6% for PBO.
- AE's- headache and anxiety- mild/transient mostly. 2 participants had severe persistent anxiety requiring medical attention. No serious AE's.
- Niacin was an ineffective blind.

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Psilocybin- MDD

G.M. Goodwin, S.T. Aaronson, O. Alvarez, et al. Single-dose psilocybin for a treatment-resistant episode of major depression. *NEJM*, 387 (18) (2022), pp. 1637-1648, 10.1056/nejmoa2206443

- Phase 2 RDB trial for TRD in 233 adults; dosed with 1mg, 10mg, or 25mg and assessed over 12 weeks. 67% were on an ADTs and tapered off 2 weeks before. Psilocybin was administered in a calming environment with music and eyeshades, followed by two integration sessions.
- At 3 weeks, 25mg significantly reduced depression scores, mean change 12 points. 37% response vs 18% in PBO. 29% remission vs 8% PBO. 20% retained response at week 12.
- 77% with TEAEs: headache, nausea, dizziness.
- SAEs: hospitalization, SI, and self-injury; 3 cases of suicidal behavior after 3 weeks in subjects with hx of same.

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Psilocybin- PTSD

Armstrong, S.B., Levin, A.W., Sepeda, N.D. et al. Safety, feasibility, and preliminary clinical outcomes of psilocybin-assisted therapy for veterans with severe, treatment-resistant PTSD: an open-label pilot clinical trial. *Commun Med* 6, 411 (2026). <https://doi.org/10.1038/s43856-026-01767-4>

- Military veterans were recruited with treatment-resistant PTSD.
- 12 participants received 8 hrs of therapy followed by two psilocybin dosing sessions at 15 mg and 25 mg, spaced 2–3 weeks apart, of synthetic psilocybin, along with approximately 8 hours of post-psilocybin therapy. Follow-up occurred at 4 wks post-2nd dosing.
- Significant reduction in clinician-related PTSD symptoms, mean difference 27.5 points ($p < 0.0001$).
- 75% remission; 83% response.
- No SAE's; TEAE's included headache, anxiety, and dizziness. Suicidality did not change from baseline to the final preparation, or between final prep and 1-month post-session 2.

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Psilocybin- PTSD

Cainan, M., Blest-Hopley, G., Busch, C., Adams, M., Ruffell, S.G.D., Piper, T., Roseman, L., Kettner, H. and Carhart-Harris, R. (2025). Exploring the Therapeutic Effects of Psychedelics Administered to Military Veterans in Naturalistic Retreat Settings. *Brain Behav*, 15: e70660. <https://doi.org/10.1002/brb3.70660>

- Fifty-eight veterans attended psilocybin or ayahuasca retreats. These lasted 5 to 7 days in Jamaica or Peru and included guided preparation and integration sessions, and incorporated group support, rituals, and community-building elements.
- The greatest effect sizes occurred for depression and PTSD. 29% improvement on PHQ-9; PCL-5 26% improvement.
- PCL-5: Ayahuasca: 26.4%; Psilocybin 24.8%.
- Males had overall better outcomes, except for PTSD. Male: 24%; Female: 32%.
- Higher baseline scores on the PCL-5 and PHQ-9 correlated with greater outcome improvements.
- Mean Baseline: PHQ-9= 13.43; PCL-5= 39.95.
- Mean Endpoint: PhQ-9= 5.59; PCL-5= 19.14 ($p < 0.001$ for both).

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Psilocybin- AUD

Bogenschutz MP, Ross S, Bhatt S, et al. Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial. *JAMA Psychiatry*. 2022;79(10):963-962. [doi:10.1001/jamapsychiatry.2022.2096](https://doi.org/10.1001/jamapsychiatry.2022.2096)

- RDB trial with 93 participants with AUD received 2 medication sessions at weeks 4 and 8 with psilocybin (25-40 mg/70kg) or diphenhydramine. They received 12 sessions of psychotherapy (MET/CBT). Med sessions involved lying with eyeshades, listening to music, and were supervised for safety.
- PHDD (% Heavy Drinking Days) over 32 weeks: 9.7% HDD for psilocybin vs 23.6% for PBO. Also fewer average drinks per day.
- More intense mystical experiences correlated with better outcomes.
- No SAEs

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LSD

- Lysergide, or lysergic acid diethylamide (LSD), is a semisynthetic psychedelic drug in the ergoline family.
- LSD potently binds to human serotonin (5-hydroxytryptamine (5-HT)) 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, dopamine D₂, and α_2 adrenergic receptors and less potently to α_1 adrenergic, D₁, and D₃ receptors. LSD is a partial agonist at 5-HT_{2A} receptors.
- LSD more potently binds 5-HT_{2A} receptors than psilocybin, mescaline, and DMT.
- An oral pharmaceutical formulation of LSD is DT120 (lysergide D-tartrate).

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LSD- MDD

<https://ir.definiumtx.com/news-events/press-releases/detail/232/definium-therapeutics-announces-positive-topline-results-from-phase-3-emerge-study-of-dt120-orally-disintegrating-tablet-odt-in-major-depressive-disorder>. Accessed 09/11/26

- Top line results from the Emerge Phase 3 RDBPC trial with DT120 ODT 100mcg.
- At week 6, MADRS reduced 13.3 points vs PBO 5.2 ($p < 0.0001$).
- Rapid- at week 1, 14.2 point PBO-adjusted reduction ($p < 0.0001$).
- Durability- at week 12, PBO-adjusted reduction of 7.3 ($p < 0.0001$).
- Response rate at week 6: 35% vs 7%.
- Remission rate at week 6: 24% vs 3%.
- 99% of treatment-emergent adverse events mild to moderate in severity, transient, and predominantly occurring on the day of dosing.
- No increase in suicidality.

23

LSD- GAD

<https://ir.definiumtx.com/news-events/press-releases/detail/243/definium-therapeutics-announces-positive-topline-results-from-phase-3-voyage-study-of-dt120-odt-in-generalized-anxiety-disorder>. Accessed 09/11/26.

- Top line results from VOYAGE Phase 3 RDBPC trial with with DT120 ODT 100mcg.
- At week 12, HAM-A reduced 11.6 points vs PBO 6.2 ($p < 0.0001$).
- At week 1, HAM-A reduced 11.9 vs 4.2 ($p < 0.0001$).
- Response rate at week 6: 43% vs 16%.
- Remission rate at week 6: 14% vs 4%.
- Treatment-emergent adverse events mild to moderate in severity, transient, and predominantly occurring on the day of dosing.
- No increase in suicidality.

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MDMA

- 3,4-methylenedioxymethamphetamine
- Not classified as a classical psychedelic as it primarily acts as an entactogen rather than a classical serotonergic hallucinogen. It induces prosocial effects, such as increased trust and self-compassion, while preserving cognitive clarity and ego functioning.
- MOA/Theory- Neuroimaging research shows that MDMA reduces within-network connectivity in the DMN and sensorimotor networks operating via monoaminergic release.
- Recognized as a Breakthrough Therapy by the FDA in 2017. An agreed upon protocol was developed. In 2024, the FDA did not approve based on methodological concerns.
- Trauma-focused psychotherapies (TFPT) are the best-evidenced interventions for PTSD, and they are typically first line. But these are plagued with a high drop-out rates, 50% or higher, and the response rates are approx. 50% for those that do complete.

25

MDMA- PTSD

Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, Ot'alora G.M, Garas W, Paleos C, Gorman I, Nicholas C, Mithoefer M, Carlin S, Poulter B, Mithoefer A, Quevedo S, Wells G, Claire SS, van der Kolk B, Tzarfaty K, Anliaz R, Worthy R, Shannon S, Woolley JD, Marta C, Gelfand Y, Hapke E, Amar S, Wallach Y, Brown R, Hamilton S, Wang JZ, Coker A, Matthews R, de Boer A, Yazar-Klosinski B, Emerson A, Doblin R. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med*. 2021 Jun;27(6):1025-1033. doi: 10.1038/s41591-021-01336-3.

- MAPPS 1- Phase 3 RDBPC trial for mod to severe PTSD; 90 participants.
- MDMA-AT reduced CAPS-5 by 24.4 points vs PBO 13.9 ($p < 0.0001$). Effect size was 0.91.
- 67% of the MDMA group no longer met the criteria for PTSD vs PBO 32%.
- No SAEs.
- TEAEs included muscle tightness, nausea, decreased appetite, and hyperhidrosis.

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MDMA- PTSD

Mitchell, J.M., Ot'alora G., M., van der Kolk, B. et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nat Med* 29, 2473-2480 (2023). <https://doi.org/10.1038/s41591-023-02565-4>

- MAPPS 2-Phase 3 RDBPC trial for moderate to severe (73%) PTSD; 104 participants.
- Ethnorracially diverse- 33% identified as non-white.
- MDMA-AT reduced PTSD symptoms at 18 weeks- CAPS-5 decreased 23.7 points vs PBO 14.8 ($p < 0.001$).
- MDMA-AT resulted in 86.5% response rate and 71.2% no longer met PTSD criteria.
- No SAEs.
- TAEAs: muscle tightness, nausea, decreased appetite, and transient BP increase. Most participants had at least one TEAE.

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DMT

- N,N-dimethyltryptamine
- Found in ayahuasca, but ayahuasca has a long duration and contains monoamine oxidase inhibitors, making it impractical for clinical use.
- Trials use IV or inhaled DMT.
- The acute psychedelic experience lasts roughly 20 to 30 minutes; easier to integrate into clinical practice.

28

DMT- TRD

Erritzoe, D., Barba, T., Benway, T. *et al.* A short-acting psychedelic intervention for major depressive disorder: a phase IIa randomized placebo-controlled trial. *Nat Med* 32, 591–598 (2026). <https://doi.org/10.1038/s41591-025-04154-z>

- Phase 2a RDBPC trial; 34 participants received a single 21.5-mg dose of i.v. DMT or placebo infused over 10 min, along with supportive psychotherapy, followed by a 2-week assessment. There was an open label extension with a 2nd dose (for the PBO group, their 1st dose).
- DMT reduced MADRS scores. At 2 weeks, DMT reduced MADRS score by 11 points vs PBO 3.6. After three months, the mean reduction in MADRS was 11.8 points.
- No significant difference between one or two doses in sustained MADRS reduction.
- No SAEs.
- TEAEs: infusion site pain, nausea, and transient anxiety.

29

DMT- TRD

Falchi-Carvalho M, Pailhano-Fontes F, Wietner I, Barros H, Bolcont R, Laborde S, Ruschi B, Silva S, Montanini D, C Barbosa D, Teixeira E, Florence-Vilela R, Almeida R, K A de Macedo R, Arichelle F, J Pantrigo É, V Costa-Macedo J, da Cruz Nunes JA, de Araújo Costa Neto LA, Nunes Ferreira LP, Dantas Cordeiro L, da Costa Bezerra RB, Arcoverde E, Galvão-Coelho N, B Araújo D. Rapid and sustained antidepressant effects of vaporized N,N-dimethyltryptamine: a phase 2a clinical trial in treatment-resistant depression. *Neuropsychopharmacology*. 2025 May;50(5):895-903. doi: 10.1038/s41386-025-02091-6. Epub 2025 Apr 22. PMID: 40258990, PMCID: PMC12032144.

- An open label, phase 2a trial using vaporized DMT, 15mg 1st dose followed by 60mg 2nd dose in 14 participants.
- An average reduction of 21.14 points on the MADRS by day 7 ($p < 0.001$).
- The response rate was 85.71%, and the remission rate was 57.14% 7 days post-administration, lasting up to 3 months.
- Suicidal ideation significantly decreased, with no severe ideation the day after dosing.
- No SAEs.

30

Hallucinogen Use/Disorder

SAMHSA. (2026). *Key substance use and mental health indicators in the United States: Results from the 2025 National Survey on Drug Use and Health* (HHS Publication No. PEP26-07-010, NSDUH Series H-61). Center for Behavioral Health Statistics and Quality, SAMHSA.

- Criteria as delineated for Substance Use Disorder, except the criterion for withdrawal is not included. Likewise, no Withdrawal syndrome.
- Use in the past year:
 - The percentage increased among adults aged 26 or older, from 2.1% (or 4.7 million people) in 2021 to 2.9% (or 6.6 million people) in 2025.
 - The percentage decreased among young adults aged 18 to 25, from 7.4% in 2021 to 6.0%
 - Percentages showed no change from 2021 to 2025 for adolescents aged 12 to 17
- HUD:
 - 2009 estimated prevalence of Hallucinogen Dependence was 0.04%

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Regulatory Processes- FDA

- **Phase 1:** Initial trial in humans, to gather information on safety and dosage, several dozen patients.
- **Phase 2:** Controlled clinical study to evaluate safety and acquire data on effectiveness, one hundred to a few hundred patients.
- **Phase 3:** Randomized controlled trial to assess overall safety and effectiveness and risk-benefit profile, several hundred to several thousand subjects.
- FDA then conducts a review of the clinical trials, the manufacturing, quality, and labeling.
- To approve a drug, sponsor must show safety and effectiveness based on "adequate and well-controlled investigations"—requiring at least one randomized controlled trial.
- The sponsor must comply with postmarketing requirements, including adverse event reporting and annual reports; FDA may require and enforce a Risk Evaluation and Mitigation Strategy (REMS) to ensure safe use.

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FDA Guidance

U.S. Department of Health and Human Services
Food and Drug Administration Center for Drug
Evaluation and Research (CDER). July 2026.

- The 5-HT_{2B} receptor subtype has been linked to heart valvulopathy in humans; therefore, sponsors should assess functional activity at the 5-HT_{2B} receptor subtype. FDA recommends that sponsors exclude subjects with preexisting valvulopathy or pulmonary hypertension from multiple-dose studies of drugs with this mechanism until this risk can be better characterized.
- Potential interactions to consider:
 - Use of selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, or monoamine oxidase inhibitors for 3 weeks or more may reduce the subjective effects of psychedelic drugs.
 - Use of tricyclic antidepressants or lithium for 3 weeks or more may potentiate the subjective effects of psychedelic drugs, creating a potential psychiatric safety concern. Use of selective serotonin reuptake inhibitors, serotonin/norepinephrine reuptake inhibitors, or monoamine oxidase inhibitors for less than 3 weeks may also potentiate the subjective effects of psychedelic drugs.
 - Use of monoamine oxidase inhibitors in combination with MDMA or other amphetamine-based psychedelic drugs can produce a life-threatening hypertensive crisis.
- Abuse Potential Assessment:
 - Self-administration and conditioned place preference studies are not usually required for psychedelic drugs because they typically do not produce positive signals in those studies.
 - A human abuse potential study may not be scientifically necessary for certain psychedelic drugs to support the abuse potential assessment in an NDA when the subjective effects predictive of abuse are well-characterized from extensive clinical studies and robust epidemiological data exist to demonstrate that individuals are using the psychedelic drug for abuse purposes.
 - Sponsors should consider the potential need for a risk evaluation and mitigation strategy.
- "Well-controlled" clinical trials—Given concerns for functional unblinding, the Agency encourages the consideration of innovative approaches for control groups.

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FDA Guidance

- **Durability:**
 - Sponsors should evaluate with a double-blind design the effect of treatment at 12 weeks.
 - Sponsors should continue to follow subjects beyond the Week 12 endpoint to monitor for symptom recurrence or, potentially, the need for repeat dosing.
 - If data suggest that readministration on a regularly scheduled basis is warranted, the recommended interdose interval for maintenance of effect should be studied; it may be reasonable to conduct studies of specific maintenance treatment paradigms in the postmarketing period.
- **Accounting for Assisted (Psycho)Therapy:**
 - Many of the psychedelic drug development programs involve administration of the investigational product and engaging in psychological support or psychotherapy either while the subject is experiencing the acute effects of the drug or in a separate session. This additional variable both complicates the assessment of effectiveness and presents a challenge for any future product labeling.
- **Monitoring:** Subjects receiving active treatment with psychedelic drugs may remain in a vulnerable state for several hours or longer; the Agency expects safety monitoring to include the following:
 - Observation by two monitors for the duration of the treatment session.
 - A health care provider with graduate-level professional training and clinical experience in psychotherapy, licensed to practice independently, serving as the lead monitor.
 - An assistant monitor with a nursing or bachelor's degree and at least 1 year of clinical experience in a licensed mental health care setting.

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Regulatory Processes- State alignment with Federal Reg

- Just as the CSA would need to be modified, each state has its own regulations around controlled substances.
- **FL statute 893.05:**

(2) The Attorney General shall apply the provisions of this section to any substance not currently controlled under the provisions of s. 893.03. The Attorney General may by rule:

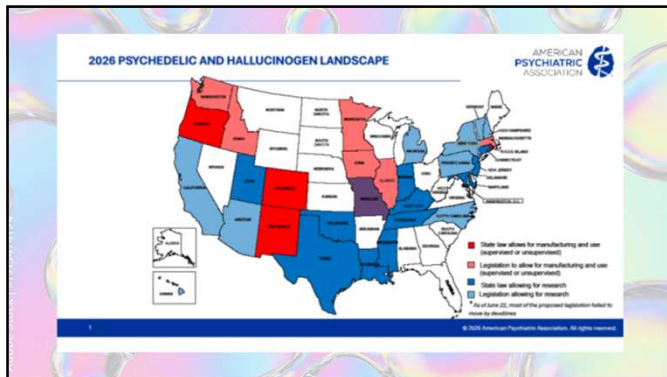
 - (a) Add a substance to a schedule established by s. 893.03, or transfer a substance between schedules, if he or she finds that it has a potential for abuse and he or she makes with respect to it the other findings appropriate for classification in the particular schedule under s. 893.03 in which it is to be placed.
 - (b) Remove a substance previously added to a schedule if he or she finds the substance does not meet the requirements for inclusion in that schedule.

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Regulatory Processes- State Decriminalization/Legalization

- Classic hallucinogens are on Schedule I (federal CSA, state drug schedules). Still technically a violation of federal reg even if decriminalized by a state.
- Decriminalization/legalization is initiated by a state legislature or state popular-vote referendum.
- Clinical trials are not required for decriminalization or legalization.
- In lieu of legalization, some states have undertaken "studies" that are not per se clinical or scientific, but in the form of task force that may look at the scientific literature.
- States may require some form of safety monitoring, but such efforts depend on state implementation of psychedelic-specific standards rather than FDA requirements.

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The Oregon Experience

Korthuis PT, Cook RR, Gregoire D, et al. Safety and Mental Health Outcomes of Oregon State-Regulated Psilocybin Services. *JAMA Netw Open.* 2026;9(8):e2630608. doi:10.1001/jamanetworkopen.2026.30608

- 346 participants from 24 of 26 psilocybin service centers were included.
- Mostly Caucasian; M=F; 19 participants (5.5%) identified as veterans, 76.6% completed college, and 29.0% had a household income above \$200 000.
- Mean psilocybin dose of 31.9mg.
- 1.2%, all psychedelic-naïve, experienced adverse behavioral reactions requiring medical attention; no medical SAEs.
- At 1 month, 92.2% felt they benefited, and 58.6% ranked the experience among the 10 most meaningful of their life.
- PHQ-9 depression scores declined from 9.3 at baseline to 4.2 at 1-month and 5.2 at 3-month follow-up.

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Summary and Musings

- The clinical trial data on reductions in scales, response, remission, and effect size are robust.
 - Still not the silver bullet that the public may think they are.
 - How will these treatments fit into the therapeutic options? Third-line, second-line, first-line?
- These treatments appear to be quite safe (reference the data on SAEs and TEAEs)
 - The trials excluded people with histories of psychosis, active/recent substance use disorders (except for the trials specifically targeting SUDs), etc., and had protocols including preparation, facilitation, and re-integration.
 - Like medical marijuana (and ketamine?), people may mistakenly think that the psychedelics can be used recreationally or to self-treat.
- The protocols are labor intensive compared to many of the currently available treatment options.
 - Models of care have to address scalability, coding, and reimbursement. Just because these may get FDA approval, third party payers still might deny coverage as they did for many years for TMS.
 - Training?
- Professional medical organizations will play a significant role in guiding appropriate use, assisting state legislatures develop appropriate regulations on use and risk mitigation, perhaps even providing guidance to third party payers (public and private).
 - This will include explaining why this is very different than recreational (or spiritual/cultural) use.
 - The evidence-base is rapidly growing and evolving. Professional education will be needed on an ongoing basis.

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