Psychedelics in Psychiatry: Hope or Hype?

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January 13, 2026

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Disclosures

- **Andrew Penn, MS, PMHNP:**
  - Advisory Board—Alkermes PLC, NACCME, Osmind, MindMed, Otsuka, Tactogen; Consultant—1440 Foundation, Alkermes PLC, Board of Psychedelic Medicine and Therapies California Institute of Integral Studies, Luciem, Fireside Project, Mind Medicine (MindMed) Inc, NACCME, Otsuka
  - Grant/Research Support—Filament; MAPS; Usona
  - Employee: UCSF, Salma Health, Kaiser Permanente (ended 2019)

  - As most psychedelic compounds remain in research and thus, do not have a FDA approved label, most of what I will discuss will be inherently off-label uses

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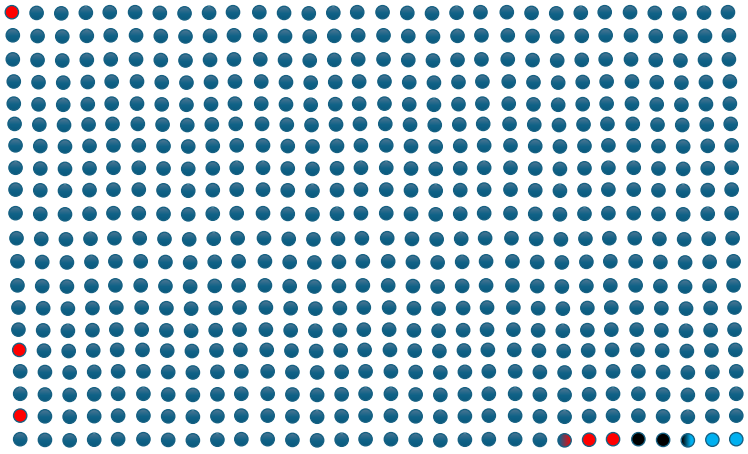
Learning Objectives

- Explain the emergence of psychedelic therapies from their historical roots to current investigations
- Discuss possible mechanisms of action for psychedelic therapies
- Describe appropriate patient selection and risk mitigation strategies
- Discuss what evidence still needs to be found to support the FDA approval of psychedelic therapies

3

A Brief (and incomplete) History of Psychedelics



Carhart Harris RL & Goodwin G (2017) Neuropsychopharmacology 42, 2105–2113. Penn A & Yehuda (2023) *Psychedelic Medicine.* Murareskeu B (2020) *The Immortality Key*, Macmillan Book Ru
Eleusis., North Atlantic, Berkeley, CA s

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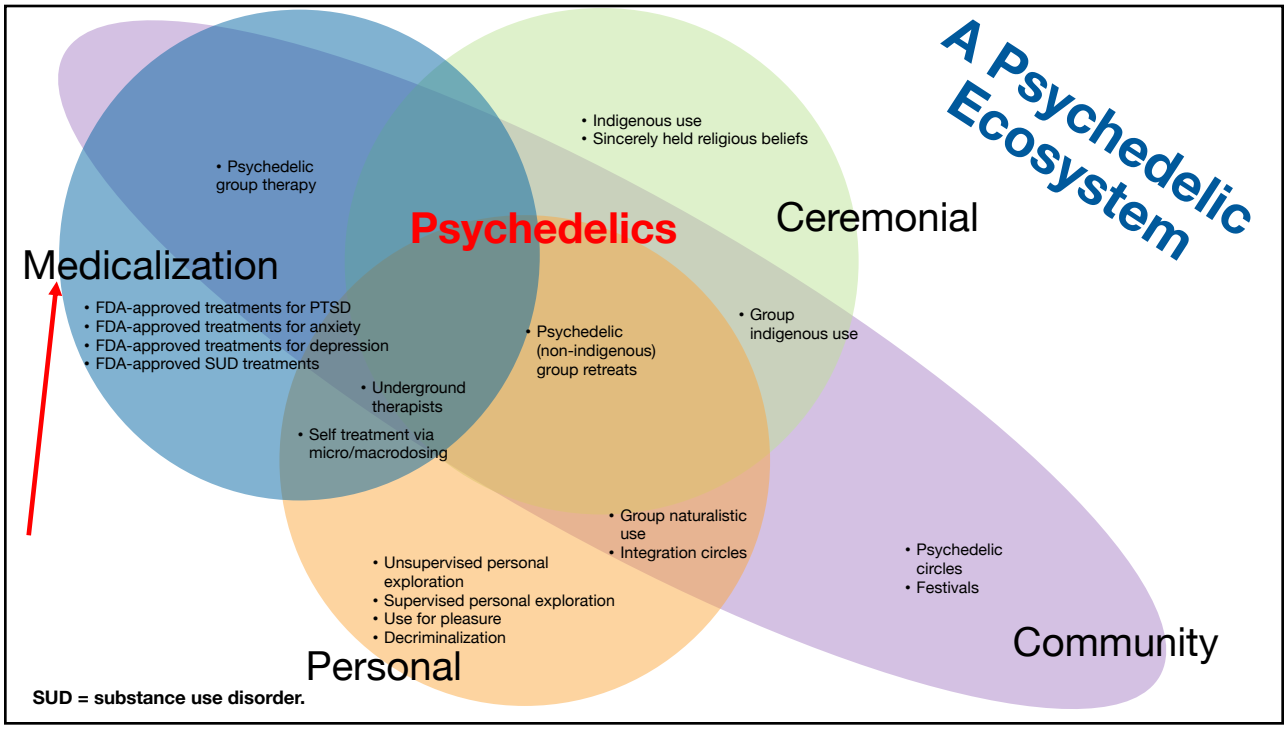

SUD = substance use disorder.

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5 Million People in the United States Might Benefit from Psilocybin for Depression

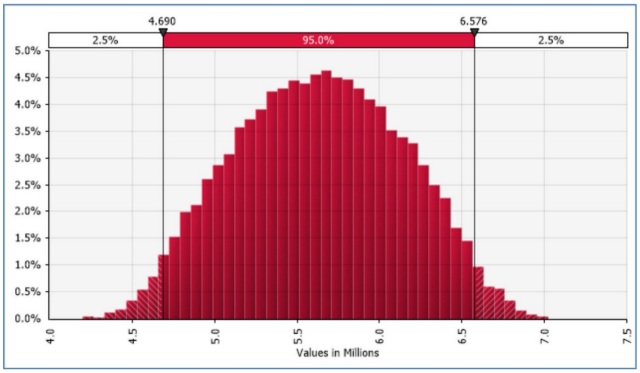

Figure 1. Patients being treated for MDD who are eligible for PSIL-AT. Multivariate sensitivity analyses, 20,0000 iterations.

PSIL-AT = psilocybin-assisted therapy; MDD = major depressive disorder.

Rab SF, et al. *Psychedelics*. 2024;1(2):26-30.

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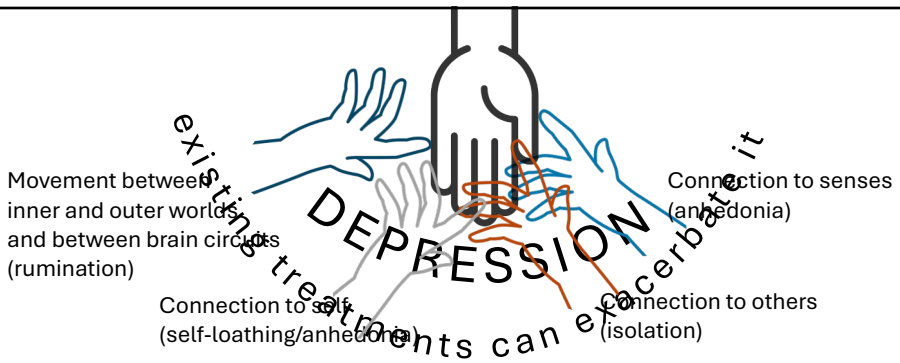


IS
DISCONNECTION

Watts R, et al. Patients' Accounts of Increased "Connectedness" and "Acceptance" After Psilocybin for Treatment-Resistant Depression. *Journal of Humanistic Psychology*. 2017;57(5):520-564.

7

Clinical Use: What Drugs Are We Talking About?

(These are the templates – increasingly, we are seeing novel compounds emerging from pharma)

Ketamine

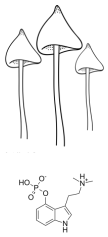
Already in Use

Esketamine

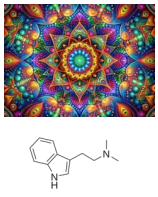
MDMA
(Midomafetamine)

Ibogaine

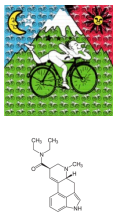
Psilocybin/psilocin



n,n –DMT
(deuterated and non deuterated forms)



LSD/MM-120



5meo-DMT

DMT = dimethyltryptamine

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How Might Psychedelics Work?

9

For what conditions?

10

11

How is Psychedelic Assisted Therapy (PAT) different than what we do now?

OR

Raison CL. Personal Communication. 2017.

12

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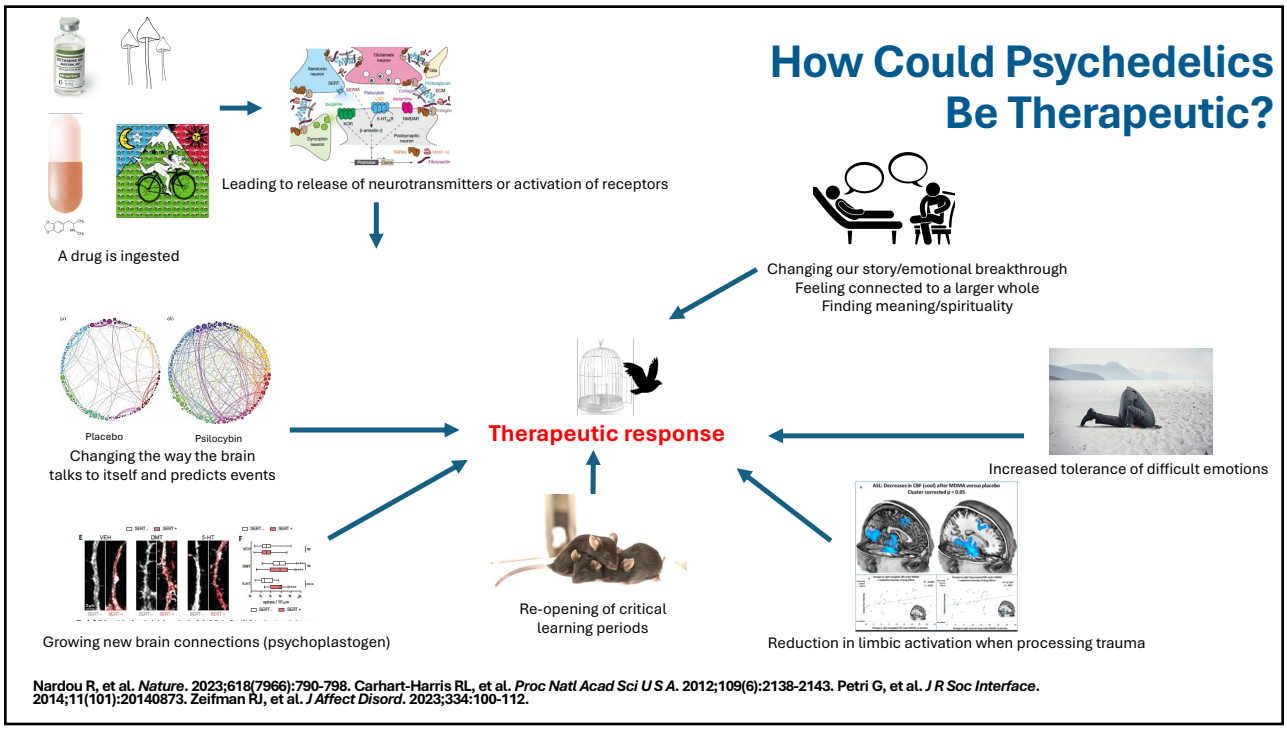

Nardou R, et al. *Nature*. 2023;618(7966):790-798. Carhart-Harris RL, et al. *Proc Natl Acad Sci U S A*. 2012;109(6):2138-2143. Petri G, et al. *J R Soc Interface*. 2014;11(101):20140873. Zeifman RJ, et al. *J Affect Disord*. 2023;334:100-112.

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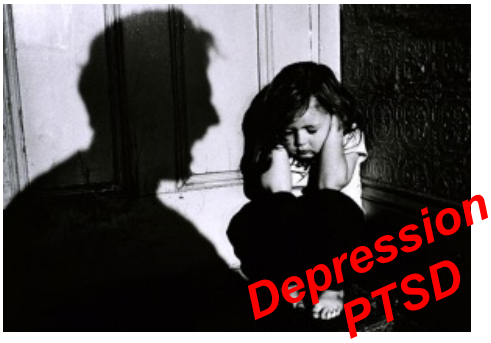
The Brain Evolved as a Prediction Machine

Adaptive learning:
- Be careful in forests where tigers live

Maladaptive learning:
- Never leave your cave; starve to death



Adaptive learning:
- People can hurt you;
- caution is sometimes warranted

Maladaptive learning:
- A negative face indicates forthcoming violence
- When people don't notice you they're upset with
- When something goes wrong, it's your fault
- It will never get better

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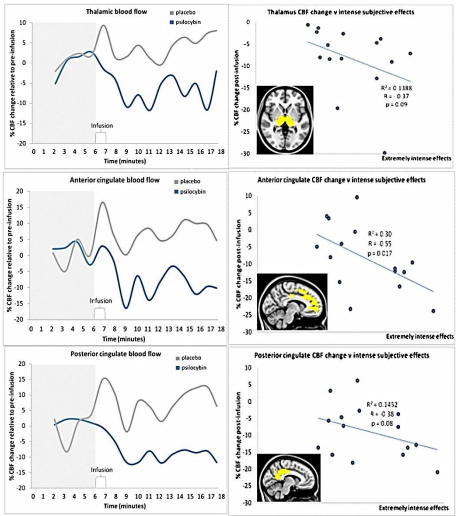
Psilocybin *Decreases* Activity in Key Connectivity Hubs

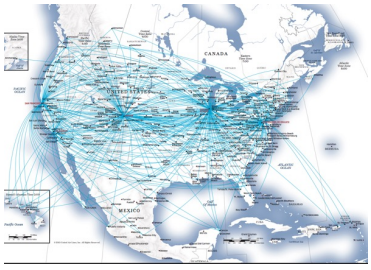
(proportionate to subjective effects)

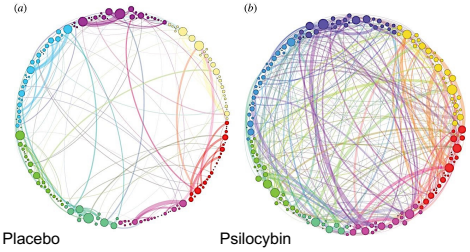


Thalamus

Anterior cingulate

Posterior cingulate





Carhart-Harris RL, et al. *Proc Natl Acad Sci U S A*. 2012;109(6):2138-2143. Petri G, et al. *J R Soc Interface*. 2014;11(101):20140873.

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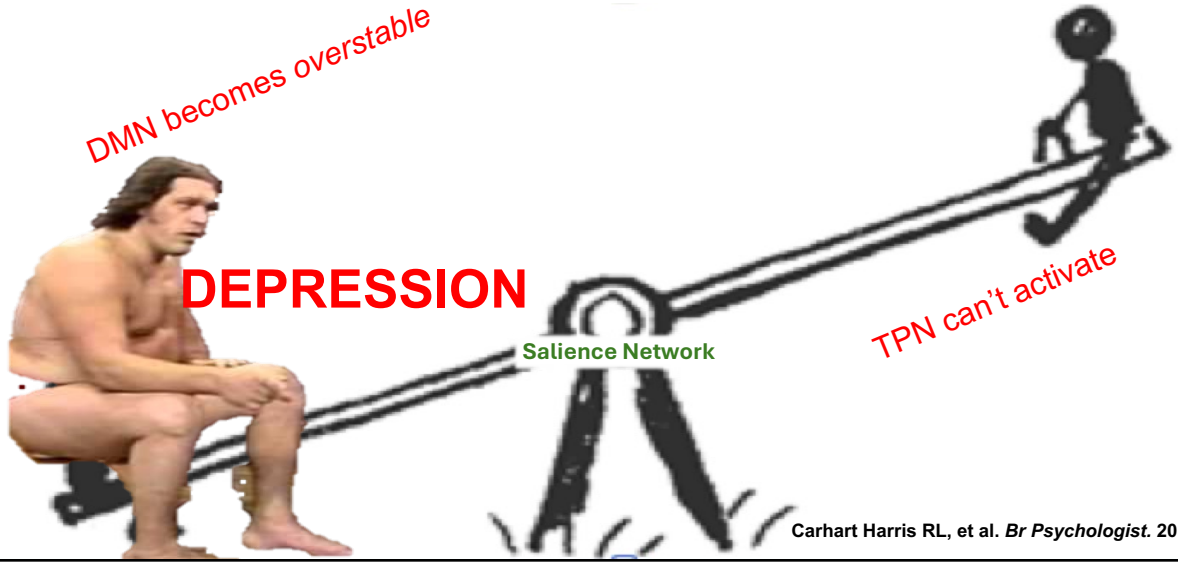
Default Mode Network
Introspective
Inward focused

Central Executive (task positive) Network
External activities
Executive

Normal Network Entropy



Carhart Harris RL, et al. *Br Psychologist.* 2014;27(9).

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The Cortex Loosens Its Grip

Relaxed Beliefs Under Psychedelics (REBUS)

- The brain tries to conserve energy by making predictions
- Early aversive experiences create overweighted "priors" (erroneous beliefs) that leads to incorrect assessments
- The depressed cortex limits information arising from lower (limbic) regions
- Under transient psychedelic "hot state," brain becomes less rigid, more prone to perturbation and more entropic/anarchic, allowing lower emotional experiences to arise
- Following this state, brain (especially the DMN) resets in a more supple, less rigid way

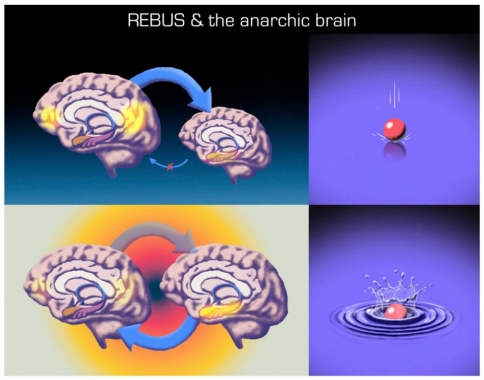

Fig. 2. These schematics depict: on the top row, brain organization in psychopathologies such as depression in which high-level priors (e.g., instantiated by the DMN) are overweighted (thick top-down arrow), causing a suppression of and insensitivity to bottom-up signaling (e.g., stemming from the limbic system). In this figure, we show compromised bottom-up signaling via a thin arrow with a red cross over its center. The graphic on the top right depicts a pathologically rigid or frozen system, insensitive to perturbation, represented in this figure as a heavy ball dropped on a solid surface having a minimal effect on the system, i.e., the ball lands with an uneventful thud. The bottom row depicts brain organization under a psychedelic. In this figure, the top-down arrow has been made translucent to reflect a deweighting or relaxation of high-level priors or beliefs (this component of the model is referred to by the acronym REBUS). The effect of this deweighting is to enable bottom-up information intrinsic to the system, to travel up the hierarchy with greater latitude and compass. We refer to this component of the model as the anarchic brain. That the two brains on the bottom row are on the same level and of the same size is intended to reflect a generalized decrease in hierarchical constraints under the psychedelic. The graphic on the bottom right represents a phenomenon known as critical slowing, i.e., systems at criticality display maximal sensitivity to perturbation. In this figure, one can see ripples appearing after a heavy ball is dropped into a liquid surface, reflecting how, in this particular system, and unlike its frozen counterpart above, there will be a slow recovery to the same perturbation. Illustrations by Pedro Oliveira, courtesy of Favo Studio.

Carhart-Harris RL & Friston K, et al. *Pharmacol Rev.* 2019;71:316–344.

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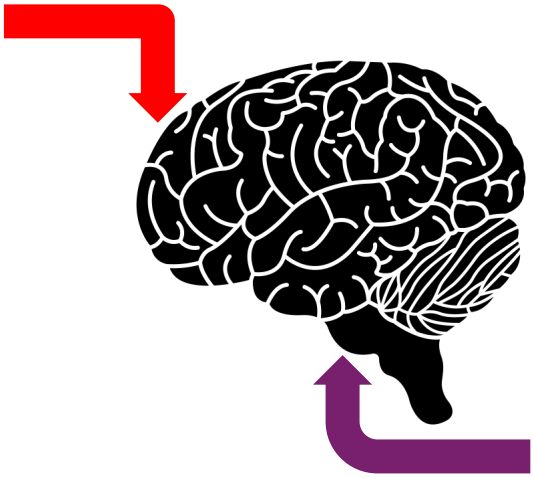
In Depression: Top-down Dominates Incoming, "Bottom-up" Information

Prediction: ***"They're going to leave if they really knew about me."***



New Experience: ***Feeling connected and cared for***

Carhart-Harris RL & Friston K, et al. *Pharmacol Rev*. 2019;71:316–344.

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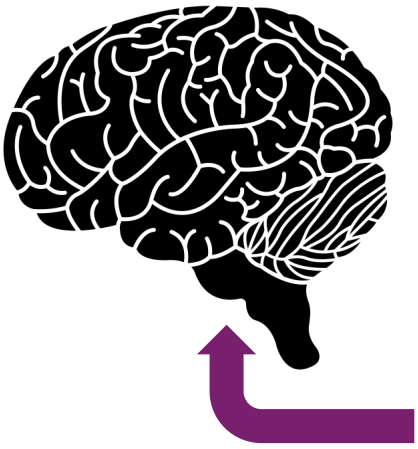
On Psychedelics: Top-down Inhibition Goes Off-line, Increased Sensitivity to New Information

New prediction: ***"Maybe I am loveable."***



New Experience:
Feeling connected and cared for

Carhart-Harris RL, et al. *Pharmacol Rev*. 2019;71:316–344.

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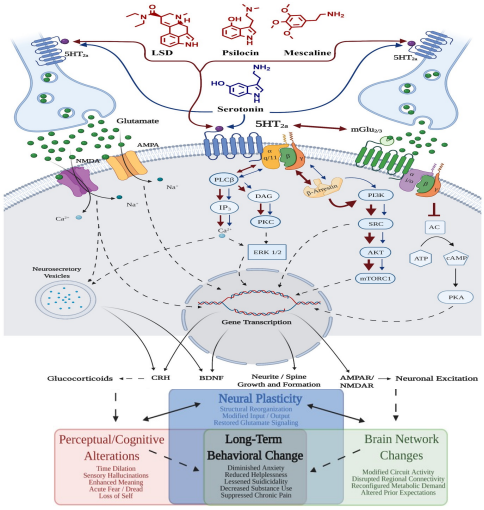
Psilocybin Causes Rapid Changes in the Cell that May Cause Dendritic Growth

- Classic Psychedelics are $5HT_{2A}$ agonists
- On presynaptic glutamatergic neurons, this causes GLU release
- Activating postsynaptic $5HT_{2A}$ receptors leads to changes inside the cell and growth by changing gene transcription (plasticity)
- Additionally, it appears that 5HT2A receptors *inside* the neuron are activated by classical psychedelics (intracellular receptors)



Banks MI, et al. (2021)Catalysts for change: the cellular neurobiology of psychedelics. *Molecular biology of the cell*. ;32(12):1135–1144.

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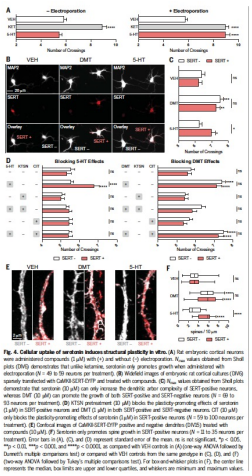
5HT2A receptor activity *inside* cells by DMT may be responsible for neuroplasticity

- 5HT2A receptors are expressed on the *outside* of neurons (GCPR's) and *inside* neurons (intracellular)
- Activation of intracellular 5HT2Ar's by DMT may initiate cascade of AMPA, TrKB, and mTOR signaling, resulting in neuroplasticity
- This neuroplastic event, when blocked before giving a psychedelic, diminishes the antidepressant effects in animal models.



Vargas, M. V., Dunlap, L. E., Dong, C., Carter, S. J., Tombari, R. J., Jami, S. A., Cameron, L. P., Patel, S. D., Hennessey, J. J., Saeger, H. N., McCorvy, J. D., Gray, J. A., Tian, L., & Olson, D. E. (2023). Psychedelics promote neuroplasticity through the activation of intracellular 5-HT2A receptors. *Science*, *379*(6633), 700–706. https://doi.org/10.1126/science.adf0435. 5HT2A= serotonin 2A. DMT= dimethyltryptamine. AMPA= α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid. TrKB= Tyrosine Kinase B. mTOR= mamilian target of rapamycin

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Could Psychedelics have a Common Convergent Pathway of Reopening Critical Periods for Learning and Development?

- A critical period is when an animal is optimally organized for new learning and development (plasticity)
  - E.g. vision, language acquisition, interpersonal skills
- Once closed, this kind of neural learning and plasticity is more difficult to occasion
- Some psychiatric conditions (e.g. autism, attachment disorders) *may be* related to challenges in relearning these social skills after the window closes

Article

Psychedelics reopen the social reward learning critical period

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Open access
Check for updates

Romain Nardou[1,2], Edward Sawyer[1,2], Young Jun Song[1,2], Makenzie Wilkinson[1,2], Yasmin Padovan-Hernandez[1], Júnia Lara de Deus[1,2], Noelle Wright[1,2], Carine Lama[1,2], Sehr Faltin[1,2], Loyal A. Goff[2,3,4], Genevieve L. Stein-O'Brien[1,2,5] & Gül Dölen[1,2,6,7,8]

Psychedelics are a broad class of drugs defined by their ability to induce an altered state of consciousness[1,2]. These drugs have been used for millennia in both spiritual and medicinal contexts, and a number of recent clinical successes have spurred a renewed interest in developing psychedelic therapies[3–9]. Nevertheless, a unifying mechanism that can account for these shared phenomenological and therapeutic properties remains unknown. Here we demonstrate in mice that the ability to reopen the social reward learning critical period is a shared property across psychedelic drugs. Notably, the time course of critical period reopening is proportional to the duration of acute subjective effects reported in humans. Furthermore, the ability to reinstate social reward learning in adulthood is paralleled by metaplastic restoration of oxytocin-mediated long-term depression in the nucleus accumbens. Finally, identification of differentially expressed genes in the 'open state' versus the 'closed state' provides evidence that reorganization of the extracellular matrix is a common downstream mechanism underlying psychedelic drug-mediated critical period reopening. Together these results have important implications for the implementation of psychedelics in clinical practice, as well as the design of novel compounds for the treatment of neuropsychiatric disease.

Nardou, R., Sawyer, E., Song, Y.J. *et al.* Psychedelics reopen the social reward learning critical period. *Nature* 618, 790–798 (23).

Nardou, R., Lewis, E.M., Rothhaas, R. *et al.* Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature* 569, 116–120 (2019). https://doi.org/10.1038/s41586-019-1075-9. Gariépy, J. F., Watson, K. K., Du, E., Xie, D. L., Erb, J., Amasino, D., & Platt, M. L. (2014). Social learning in humans and other animals. *Frontiers in neuroscience*, *8*, 58. https://doi.org/10.3389/fnins.2014.00058

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LSD, Ketamine, Ibogaine, and Psilocybin Activate Transcription Factors Responsible for Open Social Learning

(saline and cocaine do not)

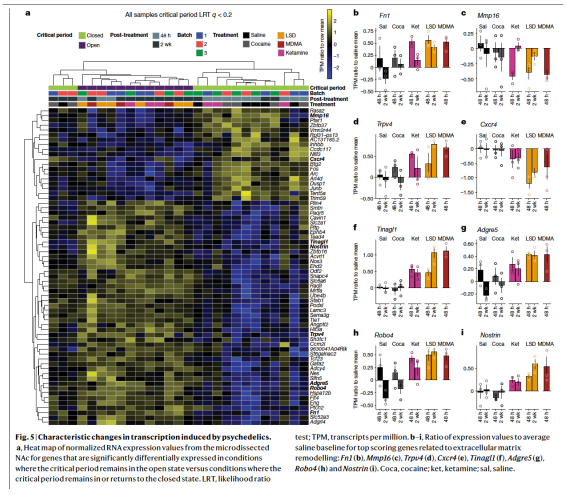
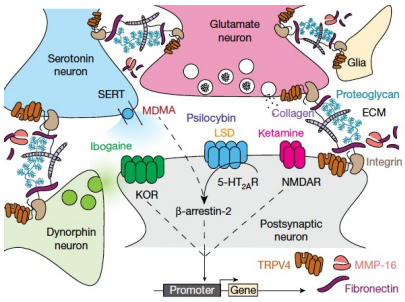


Fig. 5 | Characteristic changes in transcription induced by psychedelics. **a**, Heat map of normalized RNA expression values from the microdissected NAc for genes that are significantly differentially expressed in conditions where the critical period remains in the open state versus conditions where the critical period remains in or returns to the closed state. LRT, likelihood ratio test; TPM, transcripts per million. **b**–**i**, Ratio of expression values to average saline baseline for top scoring genes related to extracellular matrix remodelling: *Fn1* (**b**), *Mmp16* (**c**), *Trpv4* (**d**), *Cxcr4* (**e**), *Tinagl1* (**f**), *Adgre5* (**g**), *Robo4* (**h**) and *Nostrin* (**i**). Coca, cocaine; ket, ketamine; sal, saline.



Despite different MOA's, LSD/psilocybin (5HT2A), Ibogaine (KOR), and Ketamine (NMDA) all activate genes associated with an open social learning period

Nardou, R., Sawyer, E., Song, Y.J. *et al.* Psychedelics reopen the social reward learning critical period. *Nature* 618, 790–798 (2023).

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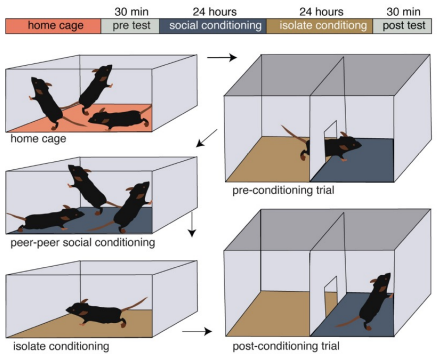
The duration of re-opened of the social learning period correlates to duration of drug action



Extended Data Fig. 1 | Social conditioned place preference assay. Time course (top) and protocol (bottom) for the social conditioned place preference (social CPP) assay used to measure the reward value of social interactions, where an increased amount of time spent in the bedding paired to the socially conditioned cue in the 'post' compared to 'pre' trial is interpreted as evidence for a learned association between the positive reward value of social interactions and a novel bedding cue (social reward learning).

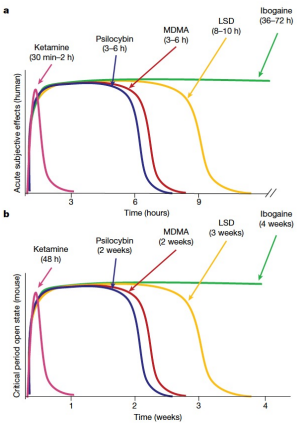


Fig. 3 | The durations of acute subjective effects in humans are proportional to the durations of the critical period open state in mice. a, Durations of the acute subjective effects of psychedelics in humans (data from refs. 15,16,20–22). **b**, Durations of the critical period open state induced by psychedelics in mice. Based on ref. 11 and Figs. 1 and 2 and Extended Data Fig. 5.

Nardou, R., Sawyer, E., Song, Y.J. *et al.* Psychedelics reopen the social reward learning critical period. *Nature* 618, 790–798 (2023).

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The Antidepressant Mechanism of Psilocybin may be from Reducing Experiential Avoidance (EA)

Person wants resolution

Psychedelic psychotherapy

Fear of and aversion to suffering/ Avoidance of emotion

Person feels resolution, peace, closure

Ego Dissolution and psychological insight predicts decreased EA.
Connectedness mediates this decrease in EA.

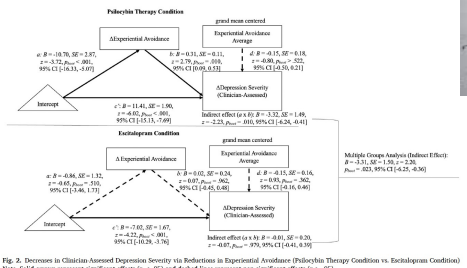
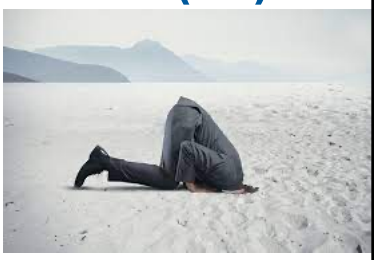
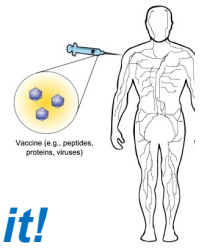


Fig. 2. Decreases in Clinician-Assessed Depression Severity via Reductions in Experiential Avoidance (Psilocybin Therapy Condition vs. Escitalopram Condition)
Note. Solid arrows represent significant effects ($p < .05$) and dashed lines represent non-significant effects ($p > .05$).





That was tough, but I did it!

Zeifman, R. J., Wagner, A. C., Monson, C. M., & Carhart-Harris, R. L. (2023). How does psilocybin therapy work? An exploration of experiential avoidance as a putative mechanism of change. *Journal of affective disorders, 334*, 100–112. https://doi.org/10.1016/j.jad.2023.04.105

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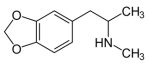
Midomafetamine – 3,4, methylenedioxymethamphetamine (MDMA)



Release of presynaptic **5-HT**

Stimulation of postsynaptic 5-HT$_{1A, 2A}$ receptors

Elevated mood
Prosocial
Decreased fear

Release of **oxytocin**

Prosocial
Increased trust
Decreased fear

Interpersonal trust

Release of **prolactin**

Mas M, et al. *J Pharmacol Exp Ther*. 1999;290(1):136-145. McGregor IS, et al. *Br J Pharmacol*. 2008;154(2):358-368.
Rudnick G, et al. *Proc Natl Acad Sci U S A*. 1992;89(5):1817-1821. Carhart-Harris RL, et al. *Biol Psychiatry*. 2015;78(8):554-562.

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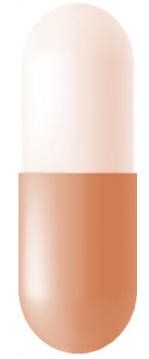
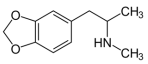
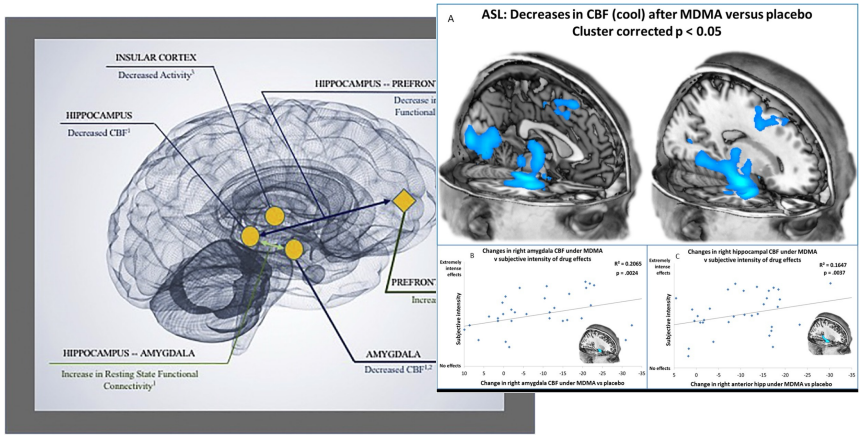
Putative mechanism of action of MDMA-AT:
Decreased activity at the R amygdala and hippocampus, increased activity at the prefrontal cortex







Feduccia AA, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;84(Pt A):221-228. CBF = cerebral blood flow.
Carhart-Harris RL, et al. *Biol Psychiatry*. 2015;78(8):554-562.

28

Does MDMA-AT make Trauma Therapy More Tolerable?

Flooded, overwhelmed, treatment is *intolerable*

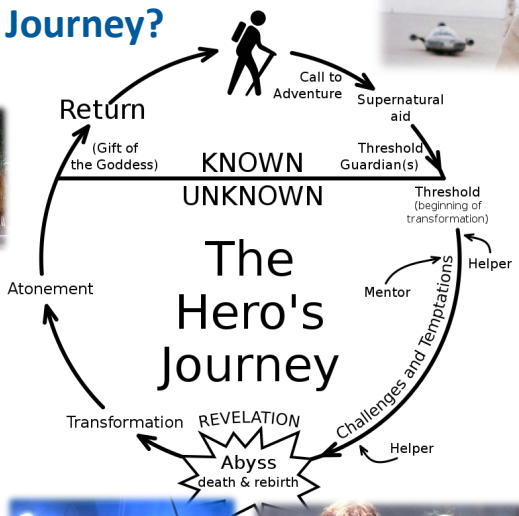
Optimal arousal zone?

Reluctant, emotional numbing, treatment is *avoided*

Siegel DJ. *The Developing Mind: Toward Neurobiology of Interpersonal Experience*. New York, NY: Guilford Press; 1999. Ogden P. *Trauma and the Body: A Sensorimotor Approach to Psychotherapy*. New York, NY: W.W. Norton; 2006.

29

Are Psychedelic Experiences a Kind of Hero's Journey?



Oritigo, K M. (2021). Beyond the Narrow Life: A Guide for Psychedelic Integration and Existential Exploration. Rogers, B. A., Chicas, H., Kelly, J. M., Kubin, E., Christian, M. S., Kachanoff, F. J., Berger, J., Puryear, C., McAdams, D. P., & Gray, K. (2023). Seeing your life story as a Hero's Journey increases meaning in life. Journal of Personality and Social Psychology, 125(4), 752–778.

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Changing our story
Feeling connected to a larger whole
Finding meaning/spirituality

- *"[…] It's almost like […] those movies where there's, like, vines, like, holding somebody back and, like, psilocybin is, like, you know, the machete that breaks through and, like* ***you're able to, like, kind of get that off and, like, be able to move again****." – Psilocybin self administration*

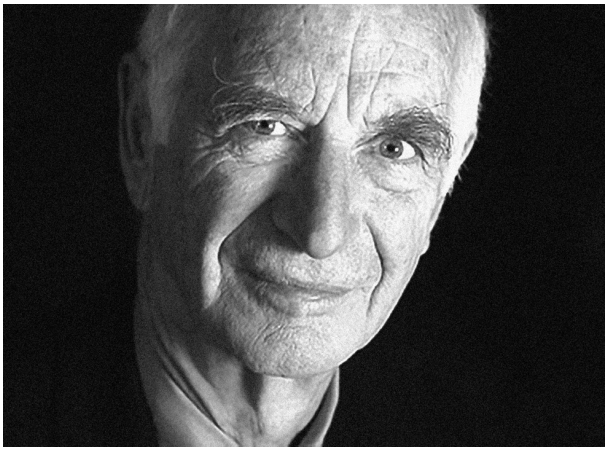
- *"We went right into my past, childhood, early adulthood, a big trauma I lived through. And then* ***it started to become way more clear why I had made all these connections and the puzzle of my anxiety became very clear****, like the origins of it." – MDMA for Life Threatening Illness Anxiety*

- ***I went through a sense of breaking through into a very warm feeling in my chest.*** *And that was quickly an entry into* ***the very cavernous, spiritual state****. And then it was just a series of traveling. It was a physical experience. It just was like I was passing through gateway after gateway. It had the sense of going down, like sort of feeling everything deeper, but it was all centered here. And then I would enter into different realms, and I decided to call them that. Very visual, very vivid. And it's like you could spend lifetimes there, it was incredibly beautiful." – MDMA for Life Threatening Illness Anxiety*

DellaCrosse, M., Pleet, M., Morton, E., Ashtari, A., Sakai, K., Woolley, J., & Michalak, E. (2022). "A sense of the bigger picture:" A qualitative analysis of follow-up interviews with people with bipolar disorder who self-reported psilocybin use. *PloS one*, *17*(12), e0279073. https://doi.org/10.1371/journal.pone.0279073. Barone, W., Mitsunaga-Whitten, M., Blaustein, L. O., Perl, P., Swank, M., & Swift, T. C. (2022). Facing death, returning to life: A qualitative analysis of MDMA-assisted therapy for anxiety associated with life-threatening illness. *Frontiers in psychiatry*, *13*, 944849. https://doi.org/10.3389/fpsyt.2022.944849

31

Does psychedelic therapy ask the patient to change their relationship with suffering?



"You know, people come to therapy really for a blessing. Not so much to fix what's broken, but to get what's broken blessed."

– James Hillman

But will the FDA or payors care about qualitative change?

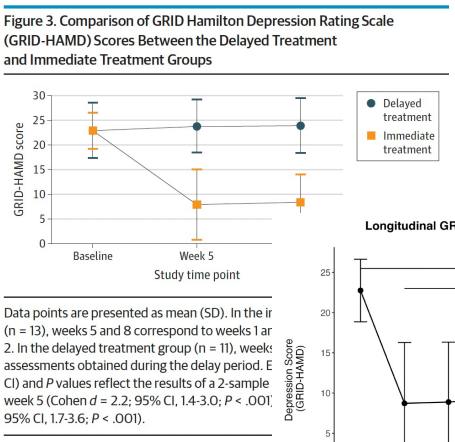
Hillman J (1996) The Soul's Code, Ballentine Books, New York, NY Hultgren J, et al. *Gen Hosp Psychiatry*. 2025;96:234-243.

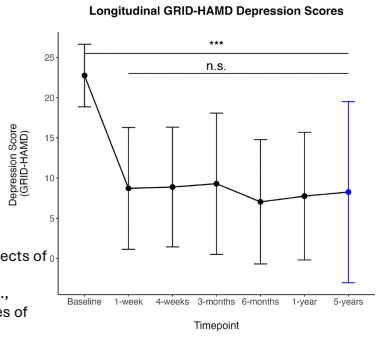
32

2020: First Phase 2 Psilocybin/MDD Study (2025 LTFU)

Alan Davis

- **Drug**: Psilocybin or Wait List control
- **Indication**: MDD
- **Size**: N=27
- **Sponsorship:** Investigator Initiated
- **Type:** Waitlist control, 2 doses (1 med, 1 high) with supportive therapy.
- **Key Findings**: Depression as measured by the GRID-HAMD showed significant drops (cohen's *d*=2.2 at 5 weeks, 2.6 at 8 weeks). In those who enrolled in LTFU, 67% were still in remission at 5 years.

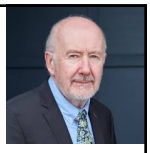




Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2021). Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA psychiatry*, *78*(5), 481–489. https://doi.org/10.1001/jamapsychiatry.2020.3285 Davis, A. K., DellaCrosse, M. A., Sepeda, N. D., Levin, A. W., Cosimano, M., Shaub, H., Washington, T., Gooch, P. M., Gilead, S., Gaughan, S. J., Armstrong, S. B., & Barrett, F. S. (2025). Five-year outcomes of psilocybin-assisted therapy for Major Depressive Disorder. *Journal of Psychedelic Studies* (published online ahead of print 2025). https://doi.org/10.1556/2054.2025.00461

33

2022: Second Psilocybin for TRD Ph2 trial



Guy Goodwin

- **Drug**: psilocybin
- **Indication**: TRD
- **Size**: N=233
- **Sponsorship:** Industry Initiated
- **Type:** DB RCT, single dose (25, 10, 1mg) psilocybin with "psychological support"
- **Key Findings:** Dose dependent antidepressant response lasting at least 12 weeks. First study to downplay psychotherapy component towards "support." SI in 23-36% of subjects, with one attempt. Sets the stage for compass phase 3

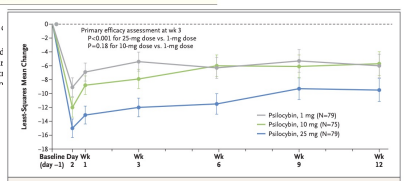
Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression

G.M. Goodwin, S.T. Aaronson, O. Alvarez, P.C. Arden, A. Baker, J.C. Bennett, C. Bird, R.E. Blom, C. Brennan, D. Brusch, L. Burke, K. Campbell-Coker, R. Carhart-Harris, J. Cattell, A. Daniel, C. DeBattista, B.W. Dunlop, K. Eisen, D. Feifel, M.K. Forbes, H.M. Haumann, D.J. Hellerstein, A.I. Hoppe, M.I. Husain, L.A. Jelen, J. Kamphuis, J. Kawasaki, J.R. Kelly, R.E. Key, R. Kishon, S. Knatz Peck, G. Knight, M.H.B. Koolen, M. Lean, R.W. Licht, J.L. Maples-Keller, J. Mars, L. Marwood, M.C. McElhiney, T.L. Miller, A. Mirow, S. Mistry, T. Mletzko-Crowe, L.N. Modlin, R.E. Nielsen, E.M. Nielson, S.R. Offerhaus, V. O'Keane, T. Pálenlček, D. Printz, M.C. Rademaker, A. van Reemst, F. Reinholdt, D. Repantis, J. Rucker, S. Rudow, S. Ruffell, A.J. Rush, R.A. Schoevers, M. Seynaeve, S. Shao, J.C. Soares, M. Somers, S.C. Stansfield, D. Sterling, A. Strockis, J. Tsai, L. Visser, M. Wahba, S. Williams, A.H. Young, P. Ywema, S. Zisook, and E. Malievskaia

ABSTRACT

BACKGROUND
Psilocybin is being studied for use in treatment-resistant

METHODS
In this phase 2 double-blind trial, we randomly assigned resistant depression to receive a single dose of a proprietar of psilocybin at a dose of 25 mg, 10 mg, or 1 mg (conti



Goodwin, G. M., Aaronson, S. T., Alvarez, O., Arden, P. C., Baker, A., Bennett, J. C., Bird, C., Blom, R. E., Brennan, C., Brusch, D., Burke, L., Campbell-Coker, K., Carhart-Harris, R., Cattell, J., Daniel, A., DeBattista, C., Dunlop, B. W., Eisen, K., Feifel, D., Forbes, M., ... Malievskaia, E. (2022). Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. *The New England journal of medicine*, *387*(18), 1637–1648. https://doi.org/10.1056/NEJMoa2206443

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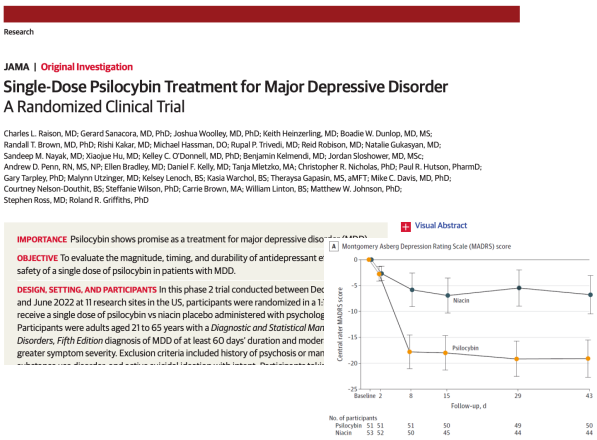
2022: Third Psilocybin for MDD Ph2 trial

Charles Raison

- **Drug**: psilocybin or niacin
- **Indication**: MDD
- **Size**: N=104
- **Sponsorship:** Industry Initiated
- **Type:** DB RCT, single dose (25mg) psilocybin or niacin placebo with "psychological support"
- **Key Findings:** significant drops on MADRS and improvement of functioning at 43 days in psilocybin group. No emergent SI. Sets the stage for Usona phase 3.



Research

JAMA | Original Investigation

Single-Dose Psilocybin Treatment for Major Depressive Disorder
A Randomized Clinical Trial

Charles L. Raison, MD; Gerard Sanacora, MD, PhD; Joshua Woolley, MD, PhD; Keith Heinzerling, MD; Boadie W. Dunlop, MD, MS; Randall T. Brown, MD, PhD; Rishi Kakar, MD; Michael Hassman, DO; Rupal P. Trivedi, MD; Reid Robison, MD; Natalie Gukasyan, MD; Sandeep M. Nayak, MD; Xiaojue Hu, MD; Kelley C. O'Donnell, MD, PhD; Benjamin Kelmendi, MD; Jordan Sloshower, MD, MSc; Andrew D. Penn, RN, MS, NP; Ellen Bradley, MD; Daniel F. Kelly, MD; Tanja Mletzko, MA; Christopher R. Nicholas, PhD; Paul R. Hutson, PharmD; Gary Tarpley, PhD; Malynn Utzinger, MD; Kelsey Lenoch, BS; Kasia Warchol, BS; Theraysa Gapasin, MS, aMFT; Mike C. Davis, MD, PhD; Courtney Nelson-Douthit, BS; Steffanie Wilson, PhD; Carrie Brown, MA; William Linton, BS; Matthew W. Johnson, PhD; Stephen Ross, MD; Roland R. Griffiths, PhD

IMPORTANCE Psilocybin shows promise as a treatment for major depressive diso

OBJECTIVE To evaluate the magnitude, timing, and durability of antidepressant e safety of a single dose of psilocybin in patients with MDD.

DESIGN, SETTING, AND PARTICIPANTS In this phase 2 trial conducted between Dec and June 2022 at 11 research sites in the US, participants were randomized in a 1: receive a single dose of psilocybin vs niacin placebo administered with psycholog Participants were adults aged 21 to 65 years with a *Diagnostic and Statistical Man Disorders, Fifth Edition* diagnosis of MDD of at least 60 days' duration and moder greater symptom severity. Exclusion criteria included history of psychosis or mar

Visual Abstract

A Montgomery Asberg Depression Rating Scale (MADRS) score

Change from MADRS score

Niacin

Psilocybin

Baseline 2 8 15 29 43

Follow-up, d

No. of participants

Psilocybin	51	51	51	50	49	50
Niacin	53	52	50	45	44	44

Raison, C. L., Sanacora, G., Woolley, J., Heinzerling, K., Dunlop, B. W., Brown, R. T., Kakar, R., Hassman, M., Trivedi, R. P., Robison, R., Gukasyan, N., Nayak, S. M., Hu, X., O'Donnell, K. C., Kelmendi, B., Sloshower, J., Penn, A. D., Bradley, E., Kelly, D. F., Mletzko, T., ... Griffiths, R. R. (2023). Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial. *JAMA*, *330*(9), 843–853. https://doi.org/10.1001/jama.2023.14530

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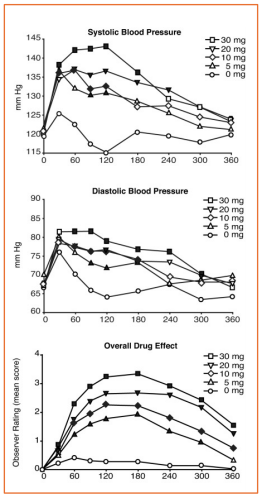
Psilocybin: In Research Settings, Side Effects Are Generally Manageable and Abate After Drug Effects End

• Transient hypertension and tachycardia	34%–76%
• Headaches	30%–50%
• Nausea	10%–30%
• Physical discomfort	20%
• Visual disturbance	44%
• Transient anxiety	25%–100%
• Transient thought disorder/paranoia	2%–75%

Compass trial reported 3 cases of SI in 25mg active drug group who did not respond to treatment

- With close monitoring and reassurance in a controlled setting, transient anxiety can be managed without anxiolytic medication or hospital admission
- *Personal or family Hx of psychosis is an exclusion*



Griffiths RR, et al. Psychopharmacology. 2011;218(4):649-665. Thomas K, et al. J Psychoactive Drugs. 2017;49(5):446-455. Goodwin, GM. N Engl J Med. 2022;387:1637-48. Raison CL et al. JAMA 2023; Epub

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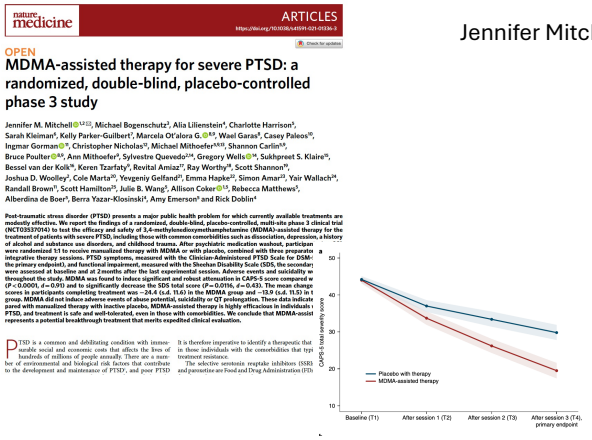
2021: First MDMA Ph 3 study in PTSD

Jennifer Mitchell

- **Drug**: MDMA or placebo
- **Indication**: Severe PTSD
- **Size**: N=90
- **Sponsorship:** Industry Initiated
- **Type:** DB RCT, MDMA + therapy vs Placebo + therapy
- **Key Findings**: significant decreases in CAPS-5 scores (*d*=0.91) and improvements in functioning in MDMA = therapy group. Some suicidality in both groups, 1 attempt in placebo group.



nature medicine ARTICLES

OPEN

MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study

Jennifer M. Mitchell, Michael Bogenschutz, Alia Lilienstein, Charlotte Harrison, Sarah Kleiman, Kelly Parker-Guilbert, Marcela Ot'alora G., Wael Garas, Casey Paleos, Ingmar Gorman, Christopher Nicholas, Michael Mithoefer, Shannon Carlin, Bruce Poulter, Ann Mithoefer, Sylvestre Quevedo, Gregory Wells, Sukhpreet S. Klaire, Bessel van der Kolk, Keren Tzarfaty, Revital Amiaz, Ray Worthy, Scott Shannon, Joshua D. Woolley, Cole Marta, Yevgeniy Gelfand, Emma Hapke, Simon Amar, Yair Wallach, Randall Brown, Scott Hamilton, Julie B. Wang, Allison Coker, Rebecca Matthews, Alberdina de Boer, Berra Yazar-Klosinski, Amy Emerson and Rick Doblin

Post-traumatic stress disorder (PTSD) presents a major public health problem for which currently available treatments are modestly effective. We report the findings of a randomized, double-blind, placebo-controlled, multi-site phase 3 clinical trial (NCT03537014) to test the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for the treatment of patients with severe PTSD, including those with common comorbidities such as dissociation, depression, a history of suicidal and substance use disorders, and childhood trauma. After 3 preparatory medication-free sessions, 90 participants were randomized 1:1 to receive manualized therapy with MDMA or with placebo, combined with three preparatory and integrative therapy sessions. PTSD symptoms, measured with the Clinician-Administered PTSD Scale for DSM-5 (the primary endpoint), and functional impairment, measured with the Sheehan Disability Scale (SDS, the secondary endpoint), were assessed at baseline and at 2 months after the last experimental session. Adverse events and suicidality were monitored throughout the study. MDMA was found to induce significant and robust attenuation in CAPS-5 score compared with placebo ($P < 0.0001$, $d = 0.91$) and to significantly decrease the SDS total score ($P = 0.016$, $d = 0.43$). The mean change in scores in participants completing treatment was −24.4 (s.d. 11.6) in the MDMA group and −13.9 (s.d. 11.5) in the placebo group. MDMA did not induce adverse events of abuse potential, suicidality or QT prolongation. These data indicate that, when paired with manualized therapy with inactive placebo, MDMA-assisted therapy is highly efficacious in individuals with severe PTSD, and treatment is safe and well-tolerated, even in those with comorbidities. We conclude that MDMA-assisted therapy represents a potential breakthrough treatment that merits expedited clinical evaluation.

PTSD is a common and debilitating condition with immeasurable social and economic costs that affects the lives of hundreds of millions of people annually. There are a number of environmental and biological risk factors that contribute to the development and maintenance of PTSD, and poor PTSD

It is therefore imperative to identify a therapeutic that in those individuals with the comorbidities that typ treatment resistance.

The selective serotonin reuptake inhibitors (SSRI) and paroxetine are Food and Drug Administration (FD

a

CAPS-5 total severity score

Placebo with therapy

MDMA-assisted therapy

Baseline (T1) After session 1 (T2) After session 2 (T3) After session 3 (T4), primary endpoint

Mitchell, J. M., 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., Klaire, S. S., van der Kolk, B., Tzarfaty, K., … Doblin, R. (2021). MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nature medicine*, *27*(6), 1025–1033. https://doi.org/10.1038/s41591-021-01336-3

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2023: Second MDMA Ph 3 study for PTSD

Jennifer Mitchell

- **Drug**: MDMA or placebo
- **Indication**: Moderate-Severe PTSD
- **Size**: N=104
- **Sponsorship:** Industry Initiated
- **Type:** DB RCT, MDMA + therapy vs Placebo + therapy
- **Key Findings**: significant decreases in CAPS-5 scores (*d*=0.7) and improvements in functioning in MDMA = therapy group. Some suicidality in both groups, no attempts. Final evidence for (ill-fated) NDA to the FDA.

nature medicine

Article https://doi.org/10.1038/s41591-023-02565-4

MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial

Received: 2 June 2023

Accepted: 24 August 2023

Published online: 14 September 2023

Check for updates

Jennifer M. Mitchell, Marcela Ot'alora G., Bessel van der Kolk, Scott Shannon, Michael Bogenschutz, Yevgeniy Gelfand, Casey Paleos, Christopher R. Nicholas, Sylvestre Quevedo, Scott Hamilton, Michael Mithoefer, Kelly Parker-Guilbert, Keren Tzarfaty, Alberdina de Boer, Rick Doblin, Collaborator Group*

This multi-site, randomized, double-blind study assessed the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA-AT) versus placebo, both with therapy, in participants with moderate to severe post-traumatic stress disorder. Clinician-Administered PTSD Scale for DSM-5 (primary endpoint) and Sheehan Disability Scale (SDS) total score (key secondary endpoint) were

a

CAPS-5

CAPS-5 total severity score (s.e.m.)

Placebo with therapy (n = 50)

MDMA-AT (n = 53)

P < 0.001, d = 0.7

Baseline After session 1 After session 2 After session 3

Mitchell, J. M., Ot'alora G, M., van der Kolk, B., Shannon, S., Bogenschutz, M., Gelfand, Y., Paleos, C., Nicholas, C. R., Quevedo, S., Balliett, B., Hamilton, S., Mithoefer, M., Kleiman, S., Parker-Guilbert, K., Tzarfaty, K., Harrison, C., de Boer, A., Doblin, R., Yazar-Klosinski, B., & MAPP2 Study Collaborator Group (2023). MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nature medicine*, *29*(10), 2473–2480. https://doi.org/10.1038/s41591-023-02565-4

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MDMA: In Research Settings, Side Effects Are Generally Manageable and Abate After Drug Effects End

Supplementary Data Table 3: Treatment Emergent Adverse Events Related to MDMA

Adverse Event (PT)	MDMA-assisted therapy (n=46)	Placebo with therapy (n=44)
Muscle Tightness	29 (63.0%)	5 (11.4%)
Decreased Appetite	24 (52.2%)	5 (11.4%)
Nausea	14 (30.4%)	5 (11.4%)
Hyperhidrosis	9 (19.6%)	1 (2.3%)
Feeling Cold	9 (19.6%)	3 (6.8%)
Restlessness	7 (15.2%)	0
Mydriasis	7 (15.2%)	0
Dizziness Postural	6 (13.0%)	2 (4.5%)
Bruxism	6 (13.0%)	1 (2.3%)
Nystagmus	6 (13.0%)	0
Blood Pressure Increased	5 (10.9%)	0
Feeling Jittery	5 (10.9%)	0
Non-Cardiac Chest Pain	5 (10.9%)	1 (2.3%)
Dry Mouth	5 (10.9%)	2 (4.5%)
Vision Blurred	4 (8.7%)	1 (2.3%)
Pollakiuria	4 (8.7%)	1 (2.3%)
Intrusive Thoughts	4 (8.7%)	0
Vomiting	4 (8.7%)	0
Stress	4 (8.7%)	0
Musculoskeletal Pain	4 (8.7%)	0
Pyrexia	3 (6.5%)	1 (2.3%)
Chills	3 (6.5%)	0
Substance Use (*cannabis)*	3 (6.5%)	0
Micturition urgency	3 (6.5%)	0
Muscle Twitching	3 (6.5%)	0
Somnolence	3 (6.5%)	0
Nervousness	3 (6.5%)	0

Muscle tightness, decreased appetite, nausea, sweating, feeling cold, restlessness most common

11.4% of placebo group reported some SI, 6.5% of MDMA group

Table 2 | Participants with treatment-emergent SAEs and AESIs

	MDMA ($n = 46$), n (%)	Placebo ($n = 44$), n (%)
SAEs	–	2 (4.5)
Suicide attempts	–	1 (2.3)
Suicidal ideation resulting in self-hospitalization	–	1 (2.3)
AESIs		
Suicidality (total)	3 (6.5)	5 (11.4)
Suicidal ideation	2 (4.3)	3 (6.8)
Intentional self-harm in the context of suicidal ideation	1 (2.2)	–
Suicidal behavior (suicide attempts and preparatory acts) and self-harm	–	1 (2.3)
Suicidal behavior (preparatory acts), self-harm and suicidal ideation	–	1 (2.3)
Cardiac events that could indicate QT prolongation (total)	–	1 (2.3)
Irregular heartbeats and palpitations	–	1 (2.3)
Abuse potential for MDMA (total)	–	–

The number of participants experiencing one or more SAEs or AESIs relating to suicidality, cardiovascular symptoms that could indicate QT prolongation, and abuse potential following the first experimental session.

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

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2025: Ph 2 LSD for GAD

Reid Robison

- **Drug**: MM120 (LSD)
- **Indication**: GAD
- **Size**: N=198
- **Sponsorship:** Industry Initiated
- **Type:** DB RCT, LSD (200, 100, 50, 25mcg) or placebo
- **Key Findings:** significant dose—dependent reduction in anxiety measurements. Dose stratification counters functional unblinding argument.

JAMA | Preliminary Communication

Single Treatment With MM120 (Lysergide) in Generalized Anxiety Disorder
A Randomized Clinical Trial

Reid Robison, MD; Robert Barrow, MS; Craig Conant, BA; Eric Foster, PhD; Jamie M. Freedman, BS; Paula L. Jacobsen, PhD; Jamileh Jemison, MD, MS; Sarah M. Karas, PsyD; Daniel R. Karlin, MD, MA; Todd M. Solomon, PhD; Miri Halperin Wernli, PhD; Maurizio Fava, MD

IMPORTANCE Effective and well-tolerated pharmacotherapies for generalized anxiety disorder (GAD), which is one of the most common psychiatric disorders, are needed.

OBJECTIVE To determine the dose-response relationship of MM120 (lysergide D-tartrate) in adults with moderate to severe GAD.

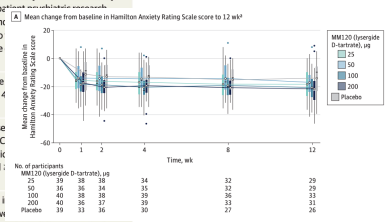
DESIGN, SETTINGS, AND PARTICIPANTS This phase 2b, multicenter, randomized, double-blind, placebo-controlled study enrolled 198 adults aged 18 to 74 years with a primary GAD diagnosis who presented with moderate to severe symptoms (defined by a Hamilton Anxiety Rating Scale [HAM-A] score ≥20) and was conducted at 22 outpatient psychiatric research sites in the US from August 2022 to August 2023. The anxiety and assessments were conducted by independent central raters who protocol, treatment allocation, and study visit date. The last date 27, 2023.

INTERVENTIONS Participants were randomized to receive a single treatment dose with 25 µg (n = 39), 50 µg (n = 40), 100 µg (n = 4 MM120 or placebo (n = 39).

MAIN OUTCOME AND MEASURES The primary outcome was a dose assessed using the multiple comparison procedure modeling (MC in HAM-A score at 4 weeks (score range, 0-56; higher scores indic indicates no or minimal anxiety; 8-14, mild; 15-23, moderate; and clinically important difference was 2.5 points.

RESULTS Of the 198 participants randomized, 194 were included i (mean age, 41.3 [SD, 13.6] years; 56.7% were female; and 3.6% w

Editorial
Supplemental content



Robison, R., Barrow, R., Conant, C., Foster, E., Freedman, J. M., Jacobsen, P. L., Jemison, J., Karas, S. M., Karlin, D. R., Solomon, T. M., Halperin Wernli, M., & Fava, M. (2025). Single Treatment With MM120 (Lysergide) in Generalized Anxiety Disorder: A Randomized Clinical Trial. *JAMA*, e2513481. Advance online publication. https://doi.org/10.1001/jama.2025.13481

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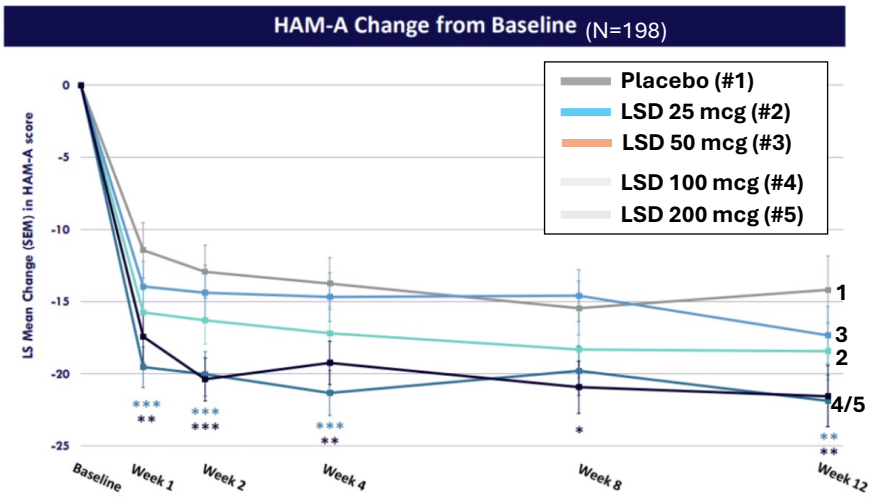
Phase 3: MindMed (MM-120): LSD for GAD

Two take-homes: LSD may help GAD. Unblinding may not be the reason why.



Guess of Treatment

Placebo: 33% thought active LSD; only 50% correctly guessed placebo

LSD 25 mcg: 87.5% correctly guessed LSD

LSD 50 mcg: 90% correctly guessed LSD

LSD 100 and 200 mcg: 100% correctly guessed LSD

Take-home point: Unblinding about the same between LSD groups, yet significant difference in clinical effect: *unlikely therapeutic benefit derives exclusively from unblinding*.

GAD = generalized anxiety disorder; HAM-A = Hamilton Anxiety Rating Scale.

Psychedelic Alpha [www.psychadelicalpha.com]. Last updated March 7, 2024. Accessed February 2025. https://psychedelicalpha.com/news/fda-hands-mindmeds-lsd-candidate-breakthrough-therapy-designation-in-generalised-anxiety-disorder-company-provides-12-week-data-and-fleshes-out-phase-3-program-plans. Business Wire [www.businesswire.com]. Last updated January 30, 2025. Accessed February 2025. https://www.businesswire.com/news/home/20250127889062/en/MindMed-Announces-First-Patient-Dosed-in-Panorama-the-Second-Pivotal-Phase-3-Study-of-MM120-in-Generalized-Anxiety-Disorder.

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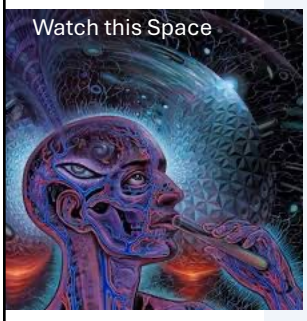

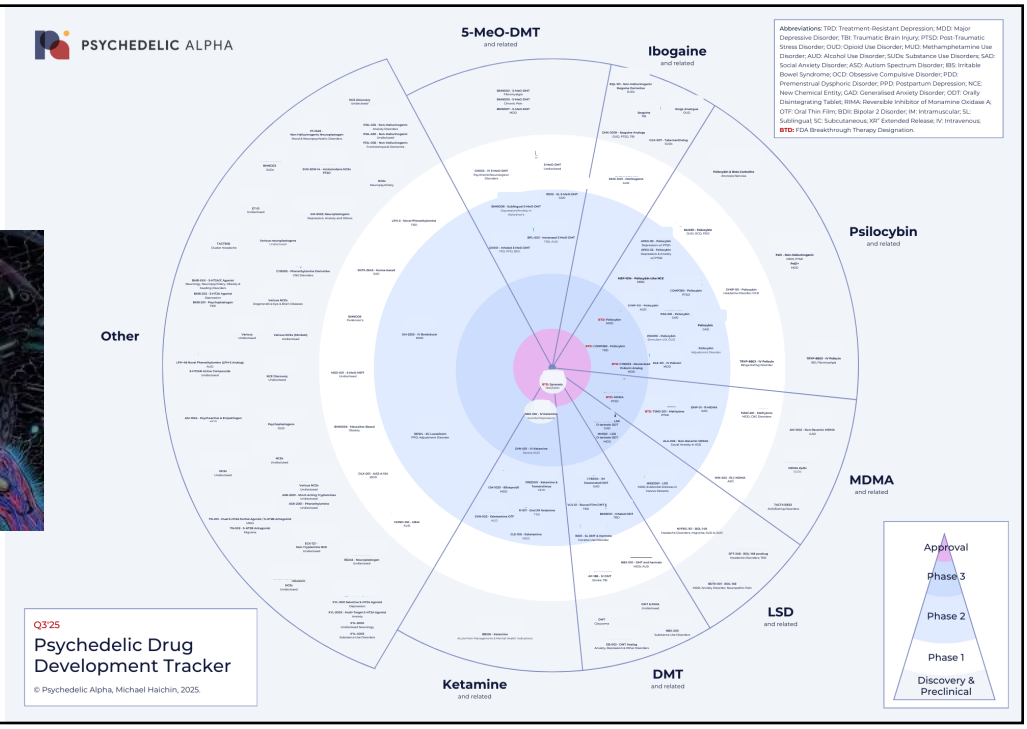

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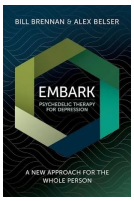
What Kind, and How Much Therapy, Is Needed with PAT?

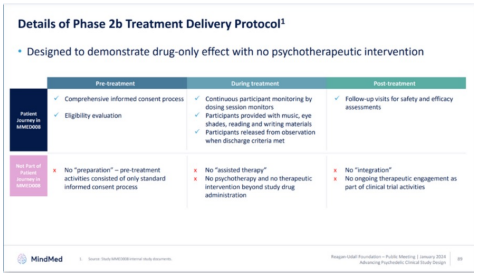
What kind of therapy should be delivered with PAT?



EBTs like CPT, exposure, CBT?
Manualized Psychedelic Therapies like EMBARK?

What is the MEC (minimal effective concentration) of therapy for PAT?

Take-home 3: LSD (MM-120) for GAD with Minimal Therapy Delivered Considerable Efficacy



EBT = evidence-based therapy; CPT = cognitive processing therapy; CBT = cognitive-behavioral therapy; MEC = minimal effective concentration.

Penn A, Yehuda R. *Psychedelic Med (New Rochelle)*. 2023;1(4):198-209. Business Wire. December 14, 2023. Accessed September 2025. https://www.businesswire.com/news/home/20231214537387/en/MindMed-Announces-Positive-Topline-Results-from-Phase-2b-Trial-of-MM-120-in-Generalized-Anxiety-Disorder Psychedelic Alpha. Accessed September 2025. https://psychedelicalpha.com/news/mindmeds-total-elimination-of-psychotherapy-in-lsd-study-stokes-debate-around-its-role-in-psychedelic-therapies. Cristea IA, Cuijpers P, Halvorsen JØ. *JAMA Psychiatry*. 2024;81(11):1053-1054.

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Two Elephants in the Room asking Big Questions

Is psychotherapy essential?
(what is the minimum dose?)

Is "the trip" essential?
(can you get the salutary Effects without the subjective Intoxication effects?)

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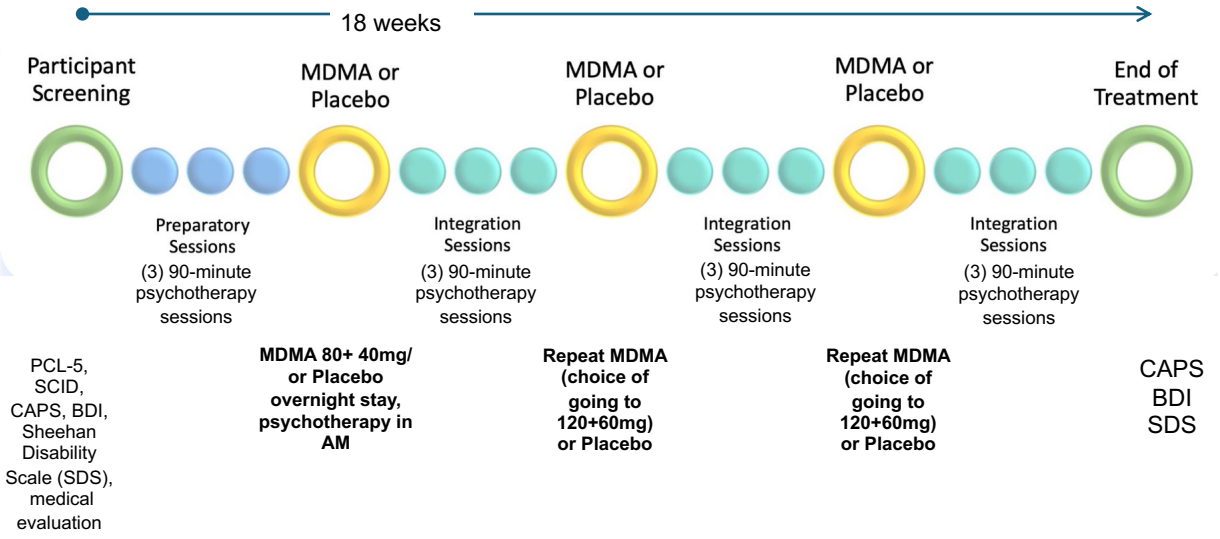
What is the MDMA Therapy Protocol?

12 non-MDMA + 3 MDMA or Placebo Therapy sessions



Mitchell JM, et al. *Nat Med*. 2021;27(6):1025-1033.

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The Shrinking Dose of Therapy

1 block = 1 hour of therapist labor

MAPS	48 hours	2 Clinicians	=96 hours				
		USONA	24 hours	2 clinicians	=48 hours		
						MindMed	10 hours
						1 clinician	= 10 hours

Where is the MEC of therapy in PAT?

Delix – take home

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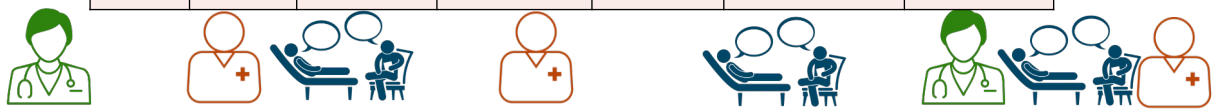
A Proposed Model for *Medical* PAT*

Role	Referring provider	Screening Clinician+	Preparation Therapy+	Dosing+	Integration Therapy+	Aftercare
Appropriate Clinicians	Any licensed medical or mental health professional	MD/DO PMHNP Psych-PA	PsyD/PhD MFT LCSW PMHNP Psychiatrist Psych-PA LPCC Chaplain The patient's own therapist	RN LPN Trainee clinician (from any of the fields on this table)	PsyD/PhD MFT LCSW PMHNP Psychiatrist Psych-PA LPCC Chaplain The patient's own therapist	Referring provider Screening clinician Therapist Dosing RN/LPN



Medical/Psychiatric Screening
1 hour

Treatment/ med ordered

Preparation
2-4 hours

Patient meets w/ nurse and therapist

Medicine Dosing
7-9 hours

Nurse with medical backup

Integration
2-4 hours

Warm handoff to therapist from nurse

Treatment Team
1 hour

Review treatment, plan for next steps

*Not decrim/ceremonial/religious freedom + all clinicians need to be PAT trained.
Penn A [www.substack.com]. Last updated April 13, 2024. Accessed February 2025. https://andrewpenn.substack.com/p/playing-to-our-strengths-in-pat.

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Should We Start Matching Level of Care to Level of Complexity and Acuity?

"Self-help" (no supervision or peer support)

Less supervision → **More supervision**

- No psychiatric comorbidity
- History of secure attachment
- Open to new experiences
- Psychedelic experienced
- In therapy

- New to psychedelics
- Apprehension about psychedelics
- Fear of losing control
- Anxious attachment
- Not already in therapy

- Complex PTSD
- Avoidant attachment

(correlates with challenging exp.)

- Borderline PD
- History of SI
- Any history of psychosis
- Any history of bipolarity

PD = personality disorder; SI = self-injury.

Stauffer CS, et al. *ACS Pharmacol Transl Sci*. 2020;4(2):526-532.

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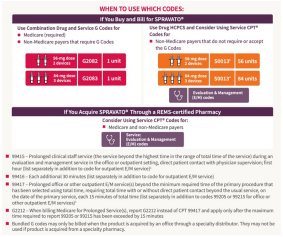
PAT is the art of the possible

Who is going to pay for this? | **What model already exists?** | **What is going to appeal to payors?**



2 hours/ Existing REMS/ Existing CPT codes

Future Short Acting Drug Candidates:

Subjectively Psychedelic
BPL003 (5MEO-DMT) –AtaiBeckley – 2 hrs
CYB003 (Deuterated DMT) – Cybin – 2-3 hours
Bretsilocin (5HT2A agonist/monoamine releaser) – Abbvie -2 hours
RE104 (4-HO-DiPT) – Reunion (PPD -3-4 hours

Subjectively nonpsychedelic
DLX-001 (isotryptamine neuroplastogen) – Delix – takehome
DLX-159 (tryptamine neuroplastogen) - Delix – takehome
Others under development

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