**TBI-BH ECHO**

Traumatic Brain Injury – Behavioral Health ECHO

UW Medicine | Psychiatry and Behavioral Sciences

# Psychedelics and TBI

## *A Rapid Review*

Nathan Sackett, MD, MS
Assistant Professor and Director
Center for Novel Therapeutics in Addiction Psychiatry
February 21st, 2025

UW Medicine
UW SCHOOL OF MEDICINE

Project ECHO

**TBI-BH ECHO**

# Speaker disclosures

Nathan Sackett, MD has no Conflicts of Interest

The following series planners have no conflicts of interest:

✓ Jennifer Erickson DO
✓ Jess Fann MD
✓ Cherry Junn MD
✓ Chuck Bombardier PhD
✓ Cara Towle MSN RN MA
✓ David Minor
✓ Amanda Kersey PhD
✓ Lauren Miles

# Objective

*"Doctor, I have a friend who has been using psychedelics after his TBI, do you think they could help me?"*

# Outline

I. Background
   a) Psychedelic Taxonomy
   b) TBI and Psychiatric comorbidities

II. Clinical Evidence
   a) Comorbidities
   b) TBI

III. MOA

IV. Limitations and Safety

# Case Presentation

**I. Background**

a) Psychedelic Taxonomy

b) TBI + Psychiatric Comorbidies

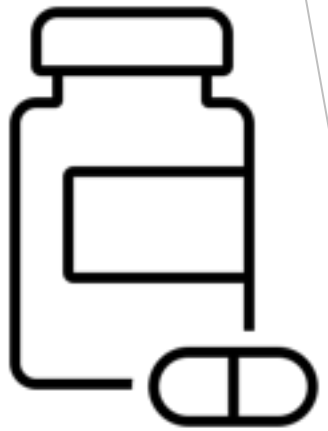
II. Clinical Evidence

a) Comorbidities

b) TBI

III. MOA

IV. Limitations and Safety



TBI-BH ECHO

**Receptor**

**5-HT2a:** LSD, Psilocybin, 5-MeO-DMT
**Mixed:** MDMA,MDA, Iboga
**NMDA:** Ketamine, DXM, NO

**Structure**

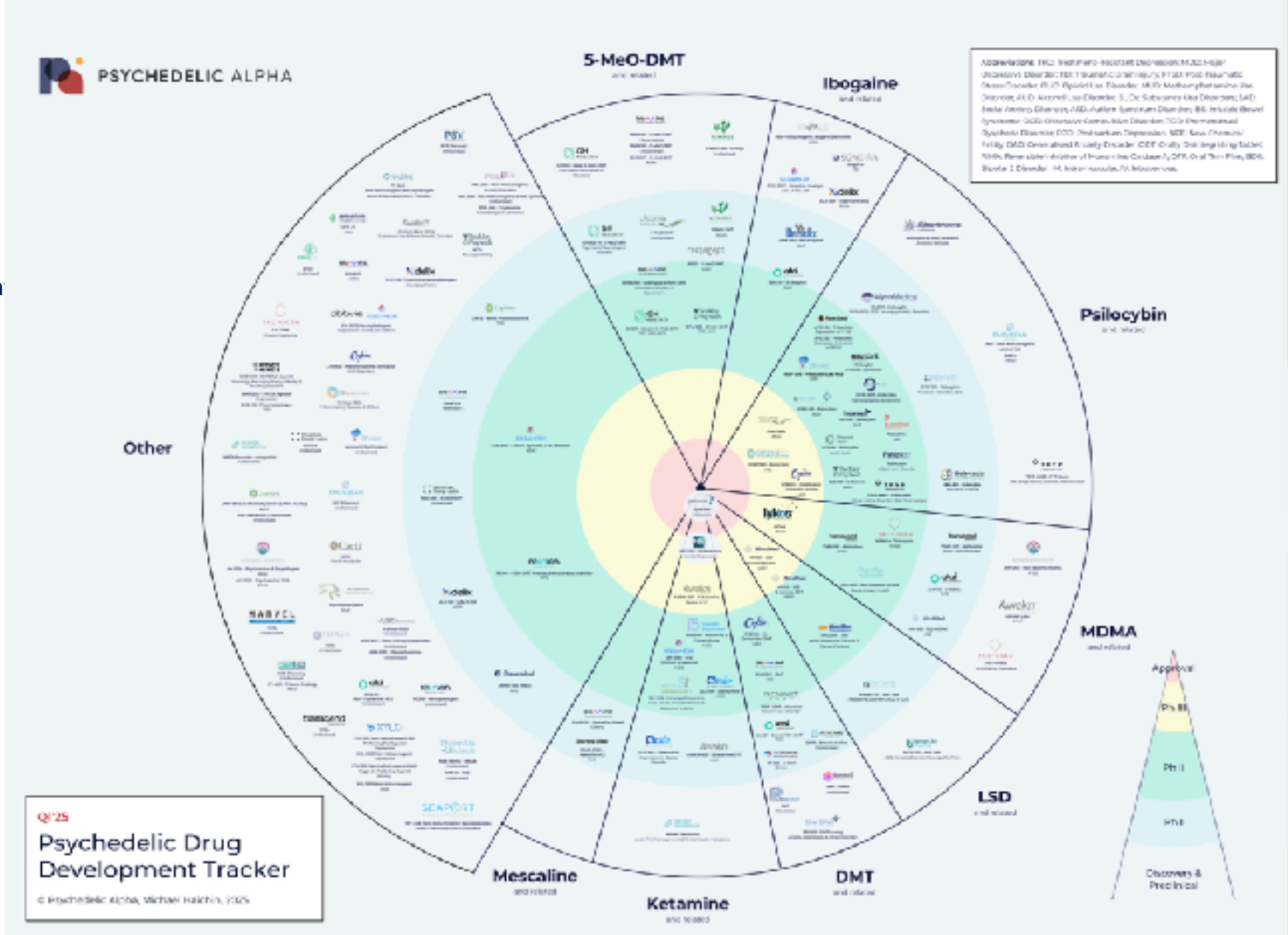
**Indolamines**
- **Tryptamines**: Psilocybin, DMT
- **Ergolines:** LSD, LSA

**Phenethylamines:** Mescaline, MDMA

**Descriptive**

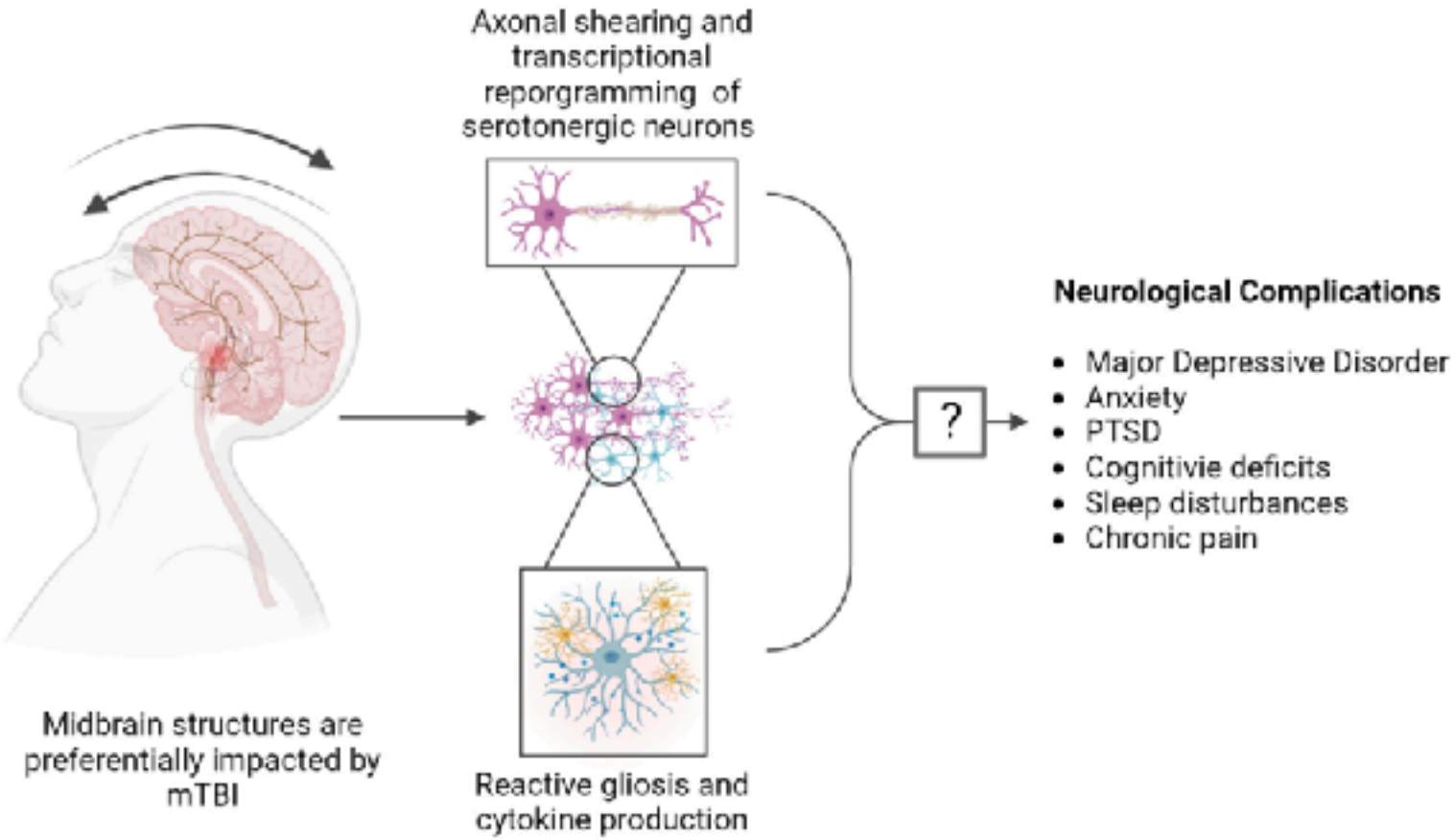
**Classic Psychedelics**: LSD, Psilocybin
**Empathogens:** MDMA
**Dissociative:** Ketamine

I. Background
  a) Psychedelic Taxonom
  b) TBI + Psychiatric Comorbidities
II. Clinical Evidence
  a) Comorbidities
  b) TBI
III. MOA
IV. Limitations and Safety

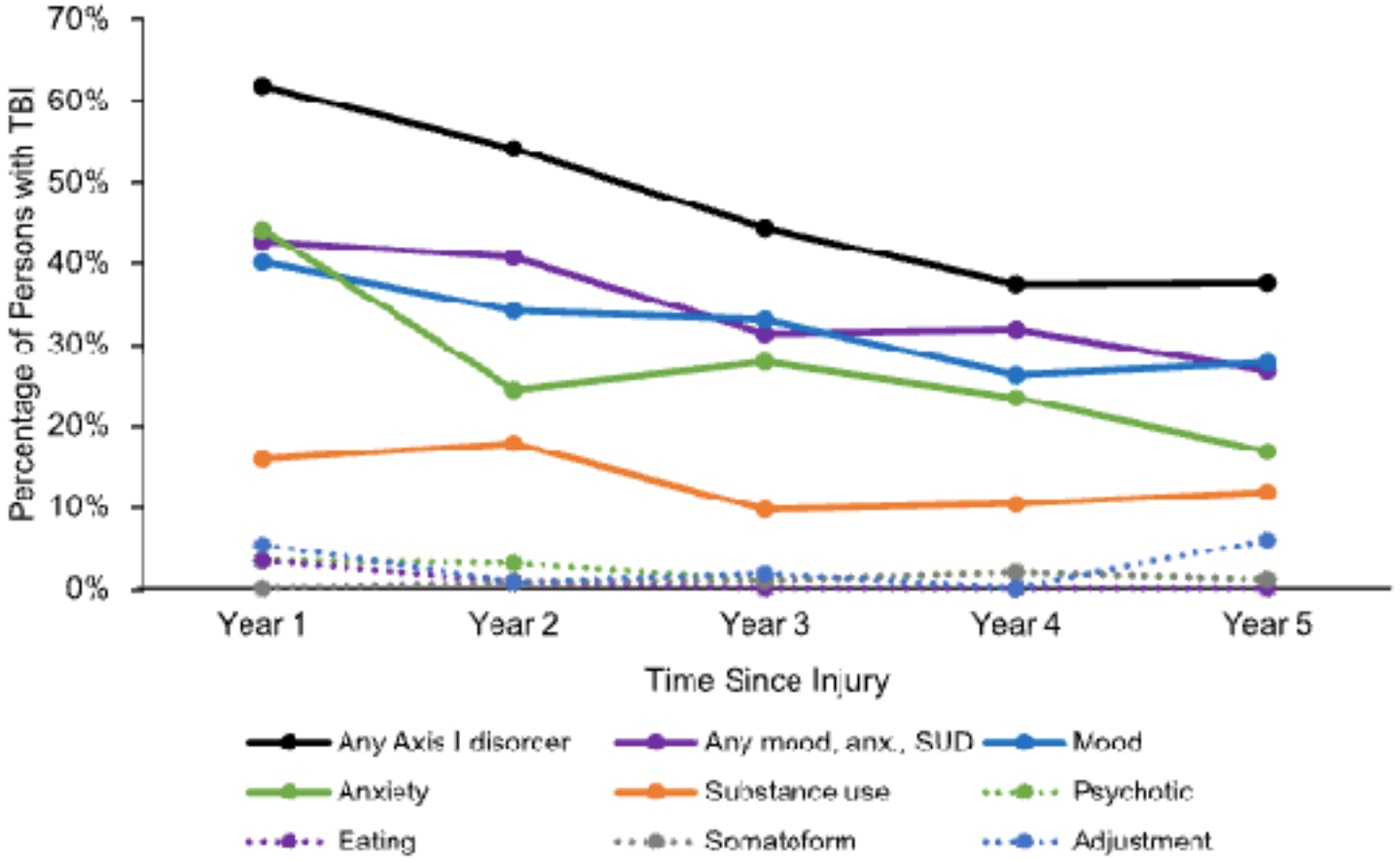



TBI-BH ECHO

## Traumatic Brain Injury Catalyzes Neurological Pathologies




O'Connell, C. J., Brown, R. S., Peach, T. M., Traubert, O. D., Schwierling, H. C., Notorgiacomo, G. A., & Robson, M. J. (2024). Strain in the midbrain: impact of traumatic brain injury on the central serotonin system. *Brain Sciences*, *14*(1). doi: 10.3390/brainsci14010051




Howlett, J. R., Nelson, L. D., & Stein, M. B. (2022). Mental health consequences of traumatic brain injury. *Biological Psychiatry*, *91*, 413-420. https://doi.org/10.1016/j.biopsych.2021.09.024

# Stages of Psychedelic Therapy



## Preparation

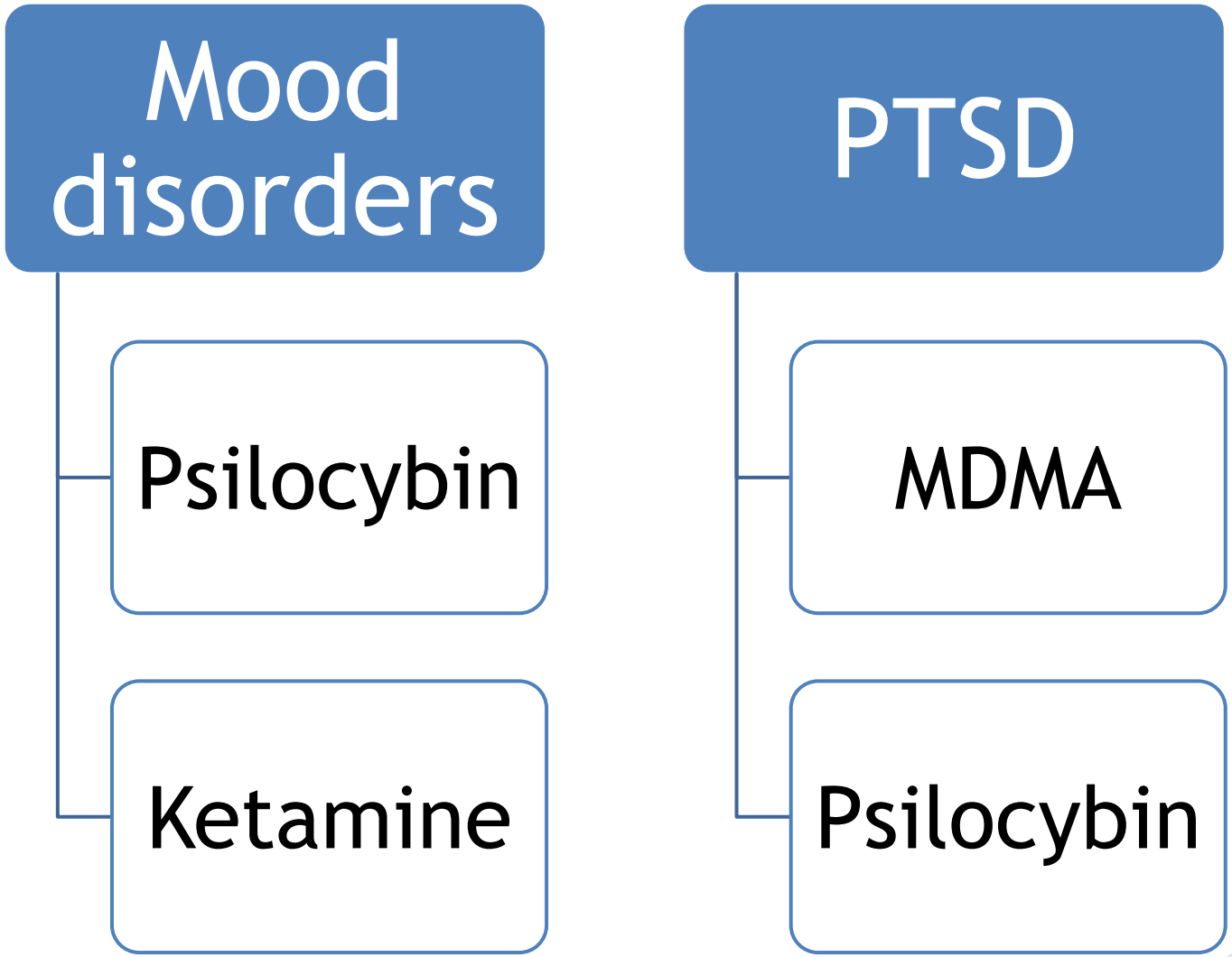
The participant meets with the study clinician(s) to build rapport, discuss what to expect during the dosing session, and set intentions for their experience.

## Dosing

After receiving the drug, the participant is monitored by clinician(s) in a comfortable environment. The participant typically listens to music with eyeshades on.

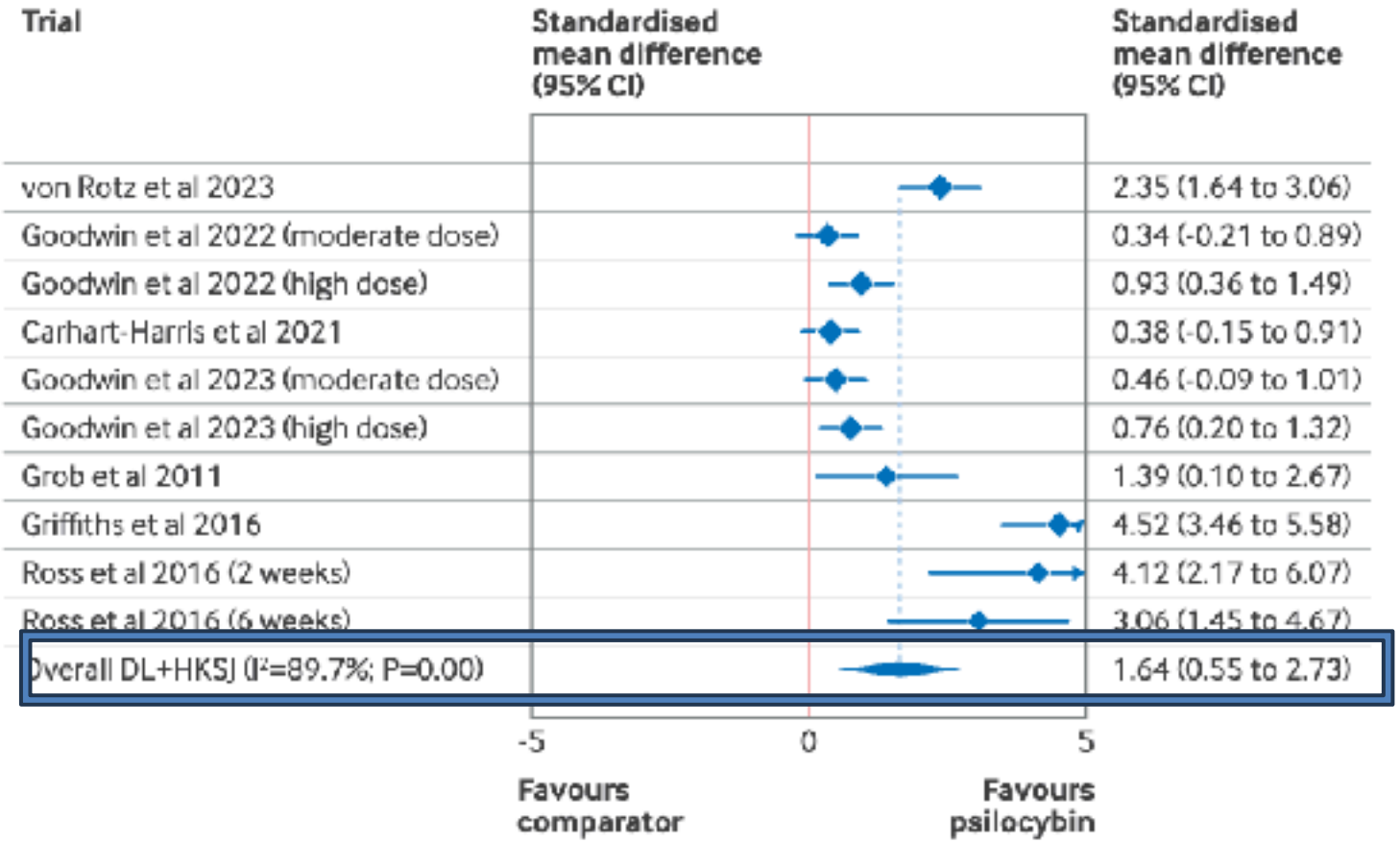
## Integration

In the weeks following dosing, the participant meets with the clinician(s) to make meaning of their experience and incorporate any insights into their life going forward.



# Psilocybin for Mood Disorders






TBI-BH ECHO


Metaxa, A.-M., & Clarke, M. (2024). Efficacy of psilocybin for treating symptoms of depression: systematic review and meta-analysis. *BMJ (Clinical Research Ed.)*, *385*, e078084. doi: 10.1136/bmj-2023-078084

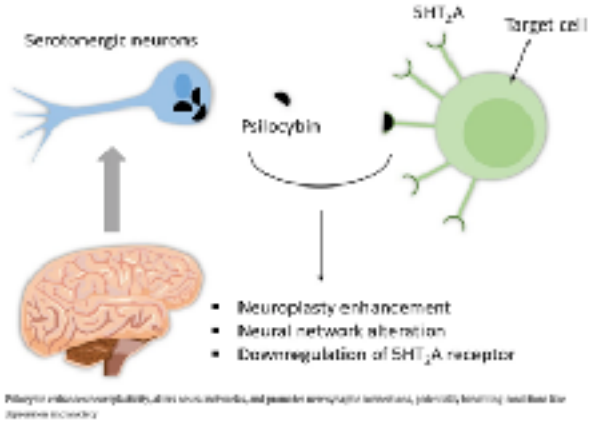
# Psilocybin: 30 Seconds

ACS Chemical Neuroscience
Review
pubs.acs.org/chemneuro

## DARK Classics in Chemical Neuroscience: Psilocybin

Haden A. Geiger,[†] Madeline G. Wurst,[†] and R. Nathan Daniels*[,†,‡]

[†]Department of Pharmaceutical Sciences, Lipscomb University College of Pharmacy and Health Sciences, Nashville, Tennessee 37204, United States
[‡]Department of Pharmacology, Vanderbilt University Medical Center, Nashville, Tennessee 37232-6600, United States


TBI-BH ECHO

# Ketamine for Mood Disorders



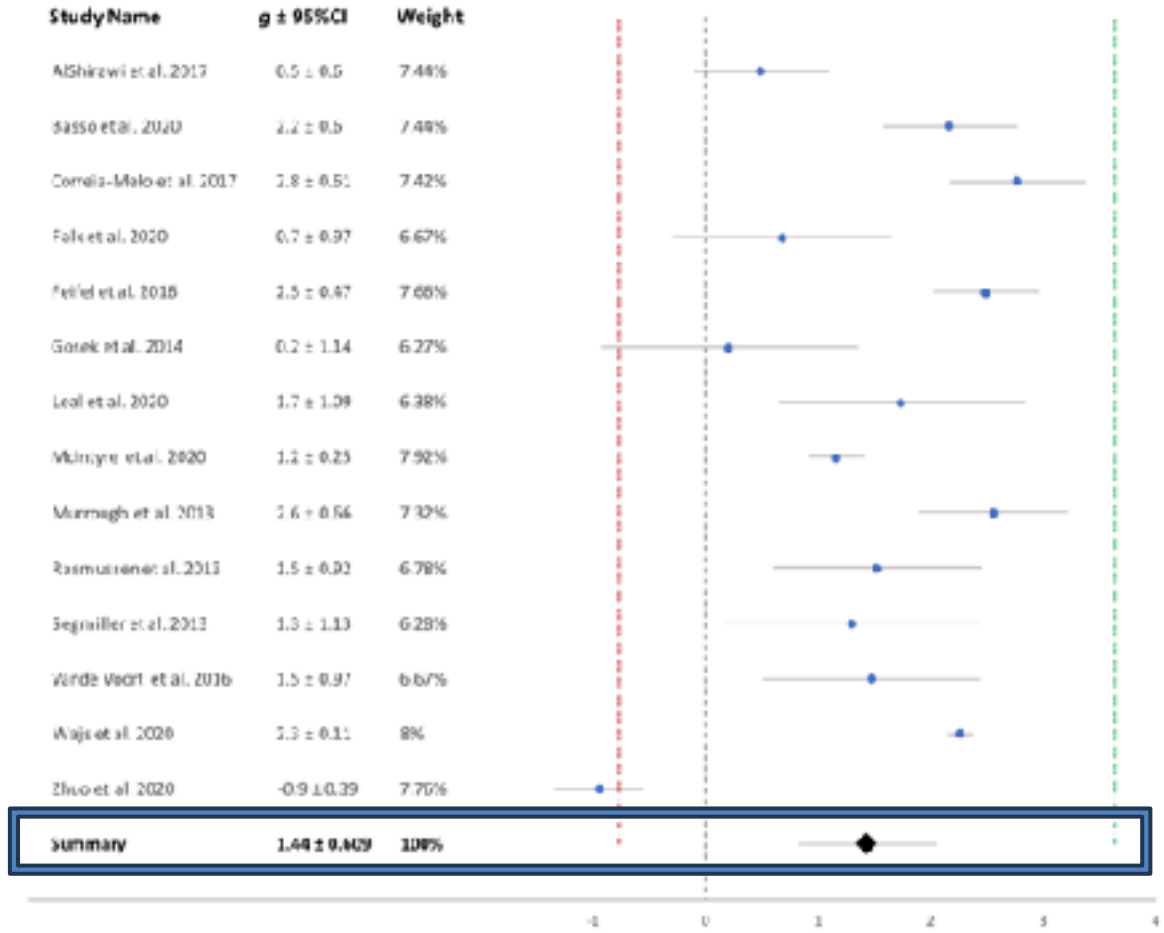
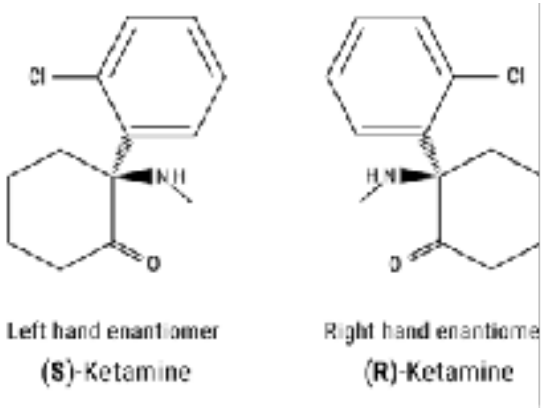



**Fig. 2.** Forest plot depicting the distribution of standardized symptomatologic improvement scores (Hedges' *g*), wherein the **red** and **green** dashed lines represent the **lower** and **upper** limits of the **95% prediction interval** computed by adding and subtracting 2*σ* to and from the **point estimate (black diamond)** ($p < 0.0001$), which represents $\mathbf{k} = 14$ **studies** and **pooled** $\mathbf{n} = 1079$.


Alnefeesi, Y., Chen-Li, D., Krane, E., Jawad, M. Y., Rodrigues, N. B., Ceban, F., … Rosenblat, J. D. (2022). Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis. *Journal of Psychiatric Research*, *151*, 693–709. doi: 10.1016/j.jpsychires.2022.04.037


TBI-BH ECHO

# Ketamine: 30 Seconds




Left hand enantiomer
(S)-Ketamine

Right hand enantiome
(R)-Ketamine

Review

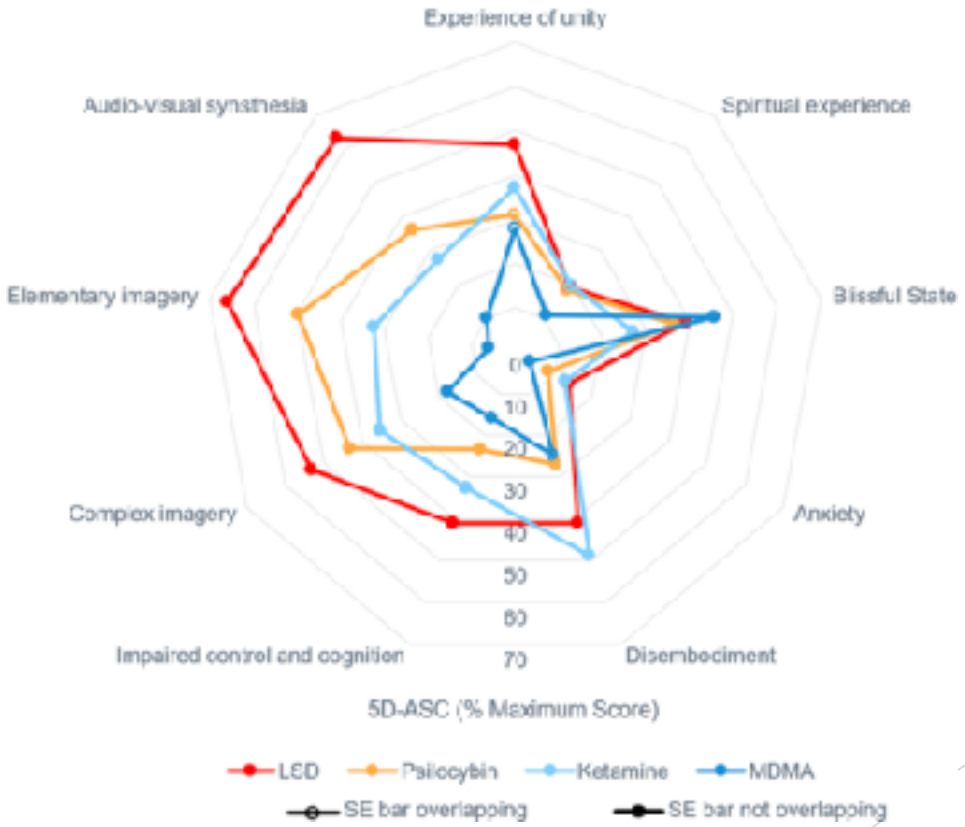
## Ketamine: A tale of two enantiomers

Luke A Jelen[1,2], Allan H Young[1,2] and James M Stone[1,2]

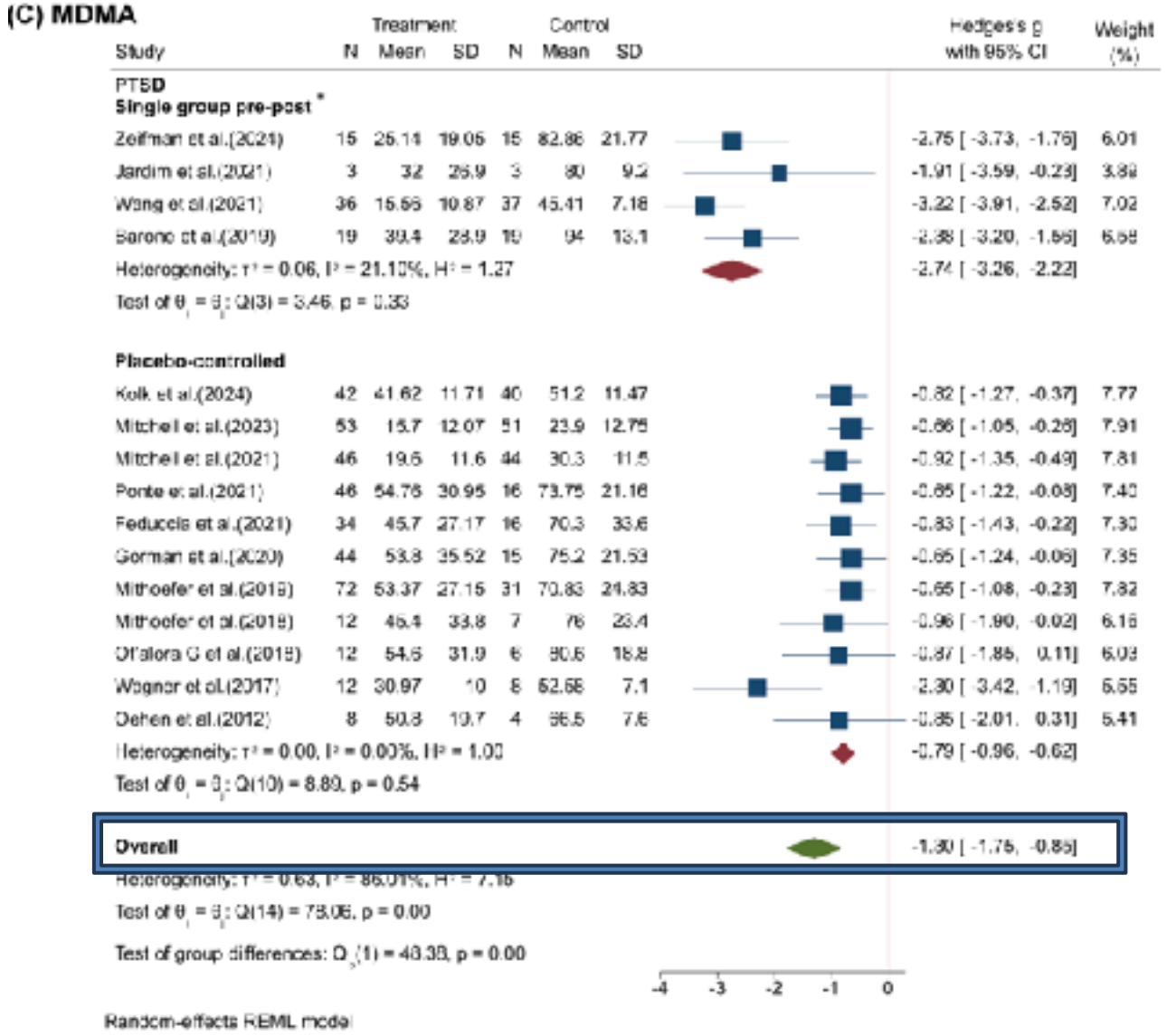
Psychopharm

Journal of Psychopharmacology
2021, Vol. 35(2) 109–123

Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0269881120959644
journals.sagepub.com/home/jop




TBI-BH ECHO




Yao, Y., Guo, D., Lu, T.-S., Liu, F.-L., Huang, S.-H., Diao, M.-Q., … Han, Y. (2024). Efficacy and safety of psychedelics for the treatment of mental disorders: A systematic review and meta-analysis. *Psychiatry Research*, *335*, 115886. doi: 10.1016/j.psychres.2024.115886

Original Article

CHRONIC STRESS

# Psychedelic Treatment for Trauma-Related Psychological and Cognitive Impairment Among US Special Operations Forces Veterans

Alan K. Davis[1,2], Lynnette A. Averill[3,4], Nathan D. Sepeda[2], Joseph P. Barsuglia[5], and Timothy Amoroso[3,4]

**Table 2.** Comparison of retrospective ratings (means and standard deviations) of mental health symptoms, suicidal ideation, and psychological flexibility in the 30-days before and 30-days after the clinical psychedelic treatment program.

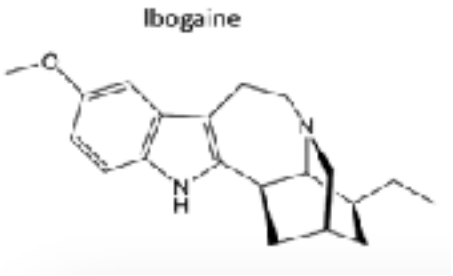
| Variable (N)[a,b] | Before treatment M (SD) | After treatment M (SD) | Change score M (SD) | t-test | Effect size (Cohen's d)[c] |
|---|---|---|---|---|---|
| PTSD symptoms (38) | 46.2 (18.8) | 12.0 (11.6) | −34.2 (19.3) | 10.90*** | −3.6 |
| Depression symptoms (51) | 4.1 (1.7) | 0.9 (1.1) | −3.2 (1.8) | 13.00*** | −3.7 |
| Anxiety symptoms (51) | 4.0 (2.1) | 1.1 (1.3) | −2.9 (1.9) | 10.85*** | −3.1 |
| Cognitive impairment (51) | 2.4 (1.2) | 1.0 (0.6) | −1.5 (1.0) | 10.03*** | −2.8 |
| Suicidal ideation (41) | 2.7 (2.8) | 0.4 (1.0) | −2.3 (2.5) | 5.94*** | −1.9 |
| Psychological flexibility[d] (51) | 3.3 (1.7) | 1.0 (0.8) | 2.3 (1.6) | 10.27*** | 2.9 |

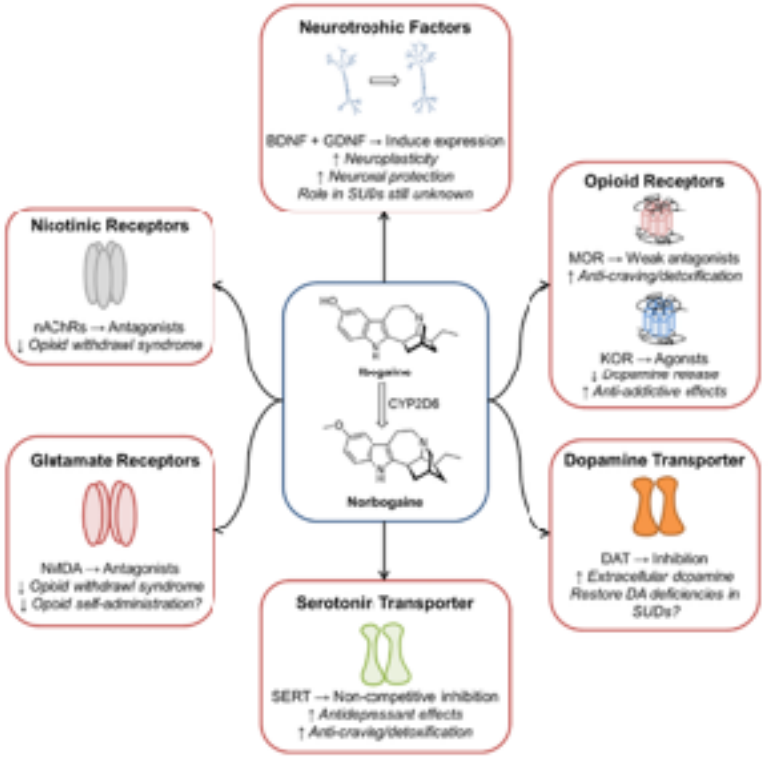
Davis, A. K., Averill, L. A., Sepeda, N. D., Barsuglia, J. P., & Amoroso, T. (2020). Psychedelic Treatment for Trauma-Related Psychological and Cognitive Impairment Among US Special Operations Forces Veterans. *Chronic Stress (Thousand Oaks, Calif.)*, *4*, 2470547020939564. doi: 10.1177/2470547020939564

# Ibogaine: 30 Seconds



Tabernanthe iboga




TBI-BH ECHO

The American Journal of Drug and Alcohol Abuse
Encompassing All Addictive Disorders

## Open-label study of consecutive ibogaine and 5-MeO-DMT assisted-therapy for trauma-exposed male Special Operations Forces Veterans: prospective data from a clinical program in Mexico

Alan Noel Davis, Yilong Xin, Nathan Sepeda & Lynnette A. Averill

| **Supplemental Table S2.** Head injury table *(N=86)* | | |
|---|---|---|
| | | **%** |
| **Head injury(s) (head impacted or shaken) during DEPLOYMENT(S)** | | |
| | No | 14 |
| | Yes | 86 |
| **Head injury cause** | | |
| | Fragment | 2.7 |
| | Bullet | 1.4 |
| | Vehicular | 47.3 |
| | Fall | 55.4 |
| | Blast | 85.1 |

Davis, A. K., Xin, Y., Sepeda, N., & Averill, L. A. (2023). Open-label study of consecutive ibogaine and 5-MeO-DMT assisted-therapy for trauma-exposed male Special Operations Forces Veterans: prospective data from a clinical program in Mexico. *The American Journal of Drug and Alcohol Abuse*, *49*(5), 587-596.

nature medicine

Article

https://doi.org/10.1038/s41591-023-02705-w

# Magnesium–ibogaine therapy in veterans with traumatic brain injuries

Received: 8 May 2023

Accepted: 10 November 2023

Published online: 5 January 2024

Check for updates

Kirsten N. Cherian[1,8], Jackob N. Keynan[1,8], Lauren Anker[1], Afik Faerman[1], Randi E. Brown[1], Ahmed Shamma[1], Or Keynan[1], John P. Coetzee[1,3], Jean-Marie Batail[1], Angela Phillips[1], Nicholas J. Bassano[1], Gregory L. Sahlem[1], Jose Inzunza[4], Trevor Millar[4], Jonathan Dickinson[4], C. E. Rolle[1], Jennifer Keller[1], Maheen Adamson[5,6], Ian H. Kratter[1,7] & Nolan R. Williams[1,2]

**Table 2 | Baseline and follow-up statistics of WHODAS-2.0**

| | Baseline and follow-up statistics | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Post-MISTIC | Baseline versus post-MISTIC | | | 1 month | Baseline versus 1 month | | |
| | | | $F^*$ | $P_{FDR}$ | $d$ | | $F^*$ | $P_{FDR}$ | $d$ |
| WHODAS-2.0 total | 30.2±14.7 | 19.9±16.3 | 20.38 | <0.001 | 0.74 | 5.1±8.1 | 85.85 | <0.001 | 2.20 |
| CAPS-5 | 31.7±12.5 | 3.9±4.8 | 206.14 | <0.001 | 2.30 | 4.8±7.9 | 191.77 | <0.001 | 2.54 |
| MADRS | 25.8±8.7 | 2.8±3.3 | 249.72 | <0.001 | 2.65 | 3.8±6.0 | 229.28 | <0.001 | 2.80 |
| HAM-A | 20.8±8.5 | 3.6±3.4 | 164.24 | <0.001 | 2.06 | 3.9±4.6 | 164.24 | <0.001 | 2.13 |
| | Percentage reporting SI | Percentage reporting SI | $X^2$ | $P_{FDR}$ | | Percentage | $X^2$ | $P_{FDR}$ | |

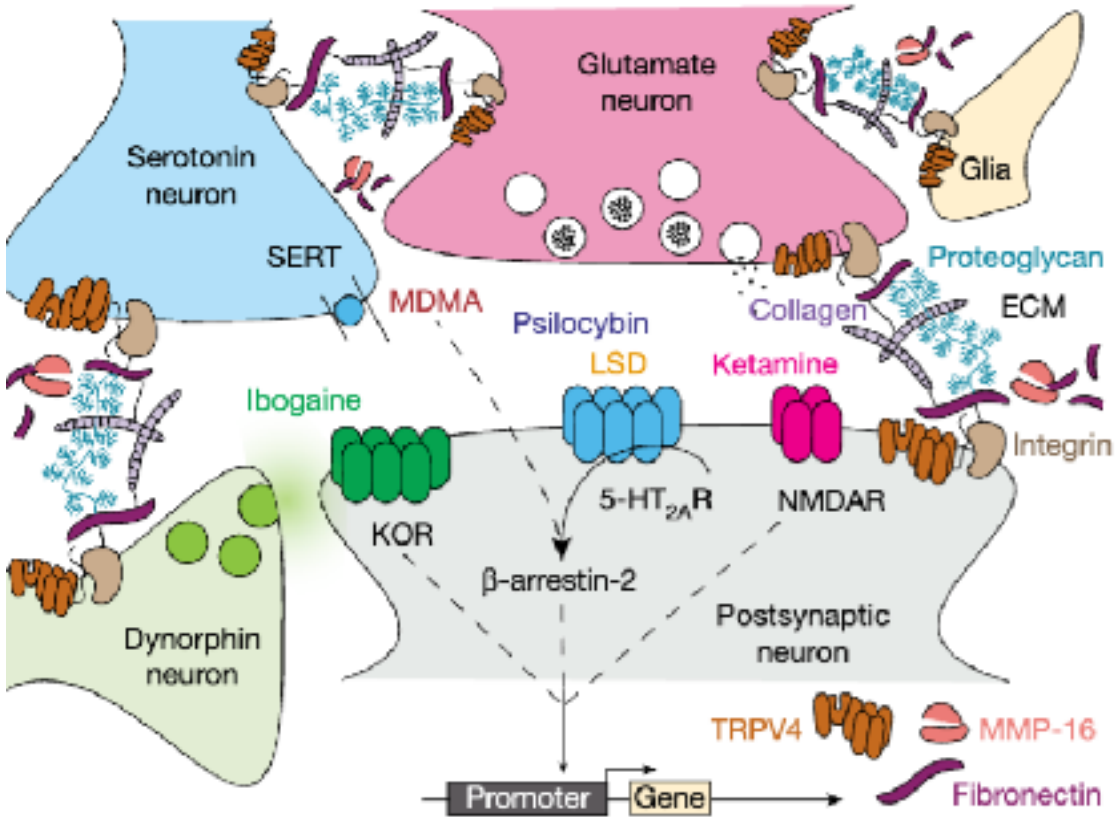
Cherian, K. N., Keynan, J. N., Anker, L., Faerman, A., Brown, R. E., Shamma, A., ... & Williams, N. R. (2024). Magnesium-ibogaine therapy in veterans with traumatic brain injuries. *Nature Medicine*, *30*(2), 373-381.

I. Background
  a) Psychedelic Taxonomy
  b) TBI + Psychiatric Comorbidities

II. Clinical Evidence
  a) Comorbidities
  b) TBI

**III. MOA: Pharmacologic**

IV. Limitations and Safety




Pharmacologic → Molecular → Structural → Behavioral

TBI-BH ECHO

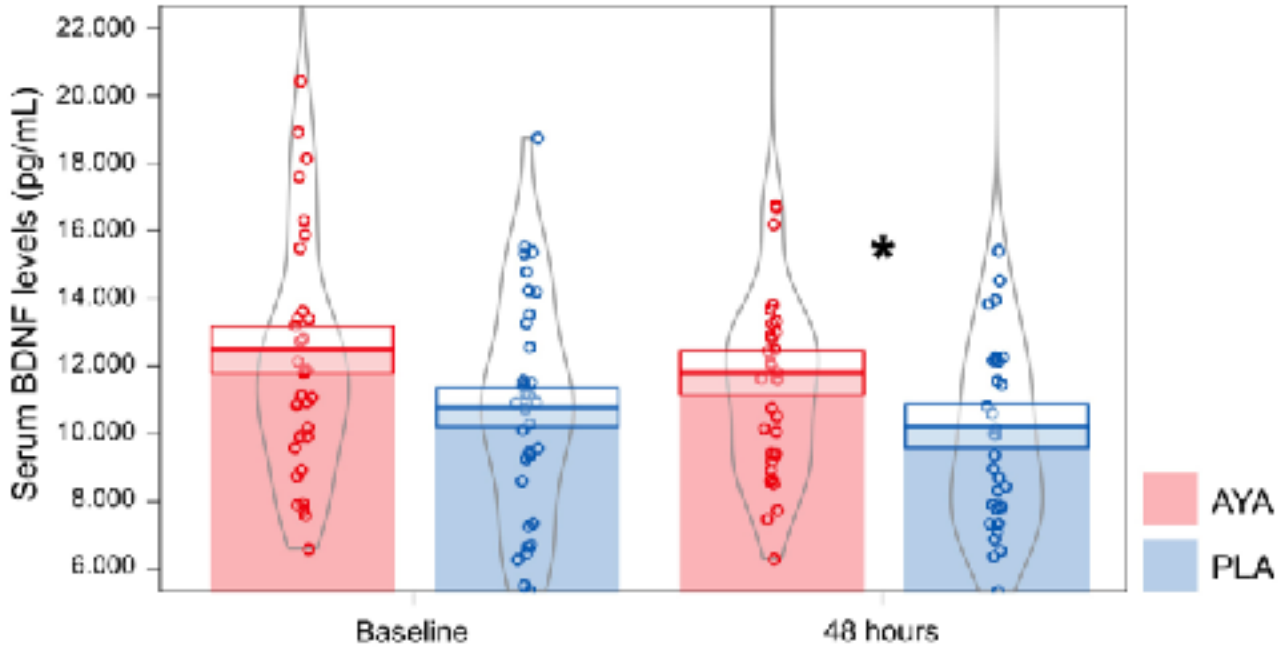
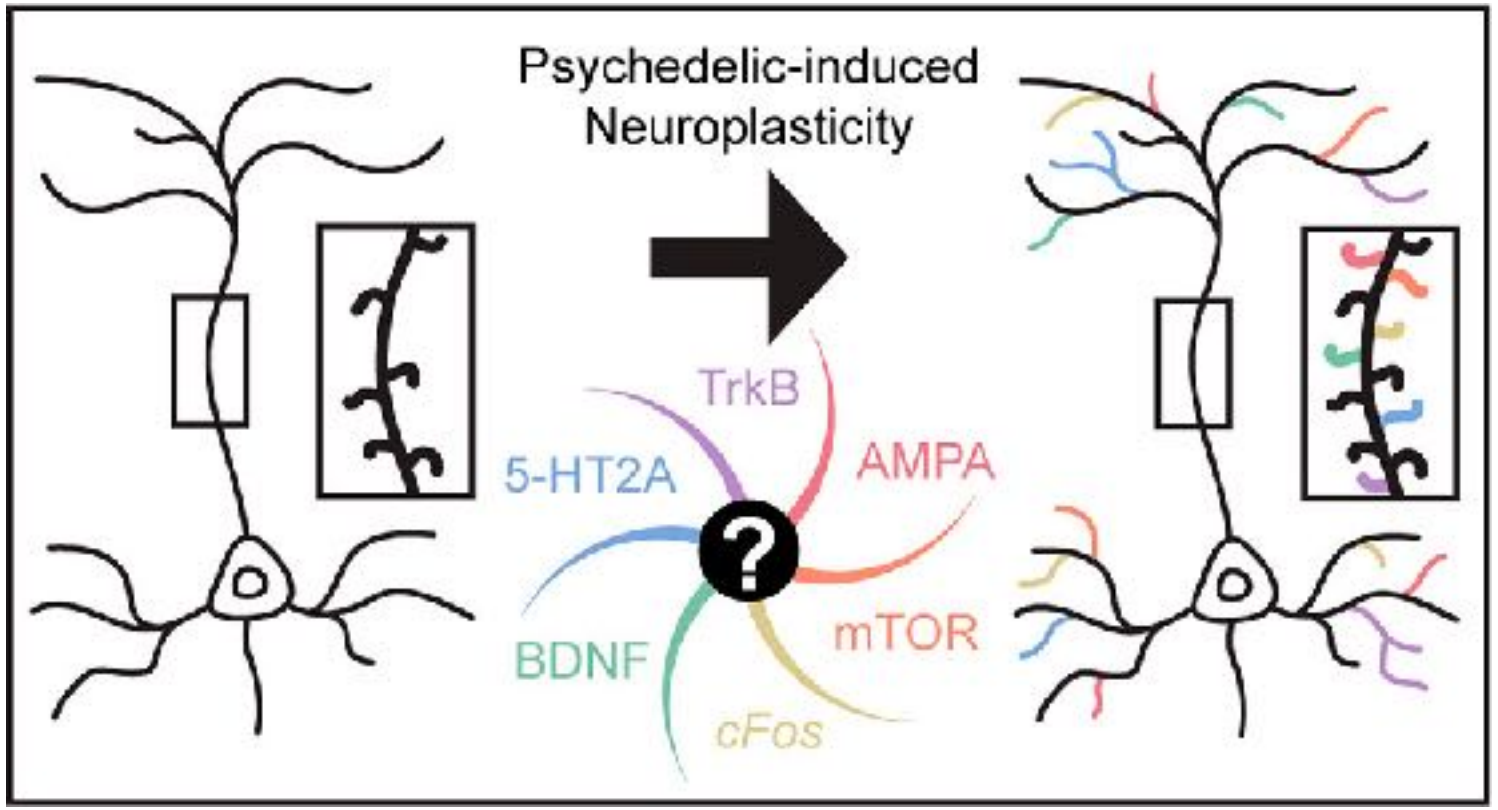


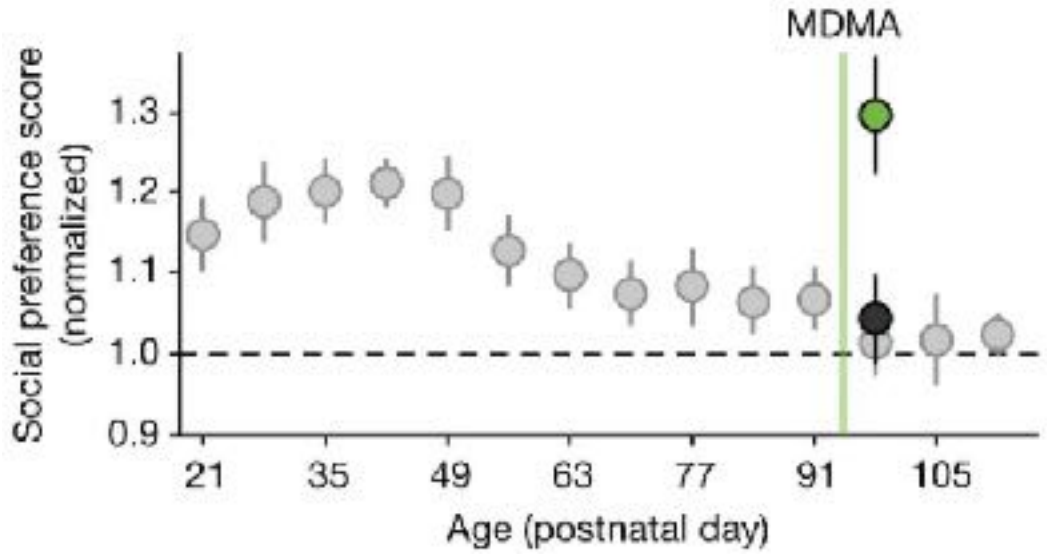

**Table S2. Mean values and statistics for the acute effects of LSD alone, LSD + ketanserin, and placebo.**

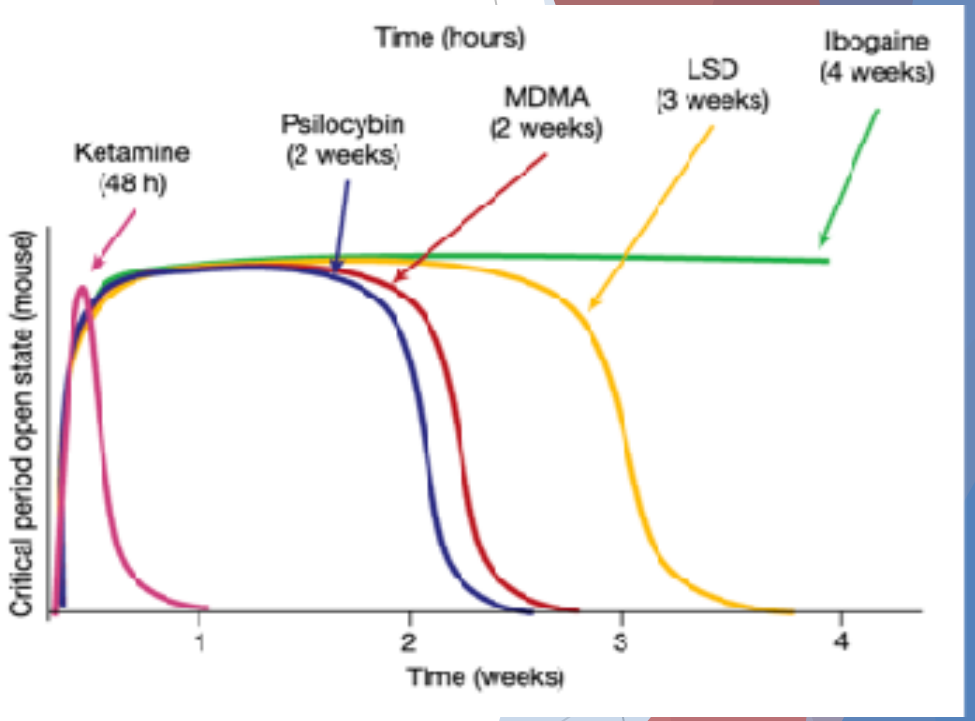
| | | Placebo (mean ± SEM) | LSD 25 µg (mean ± SEM) | LSD 50 µg (mean ± SEM) | LSD 100 µg (mean ± SEM) | LSD 200 µg (mean ± SEM) | LSD 200 µg + Ketanserin (mean ± SEM) |
|---|---|---|---|---|---|---|---|
| BDNF (pg/mL) | $C_{max}$ | 2953 ± 484 | 3800 ± 617 | 3561 ± 464 | 3848 ± 723 | 5685 ± 693 | 4372 ± 880 |

*P<0.05, **P<0.01, ***P<0.001; NS, not significant; $E_{max}$, maximal effect; $\Delta E_{max}$, maximal difference from baseline; $C_{max}$, maximal concentration

de Almeida, R. N., Galvão, A. C. de M., da Silva, F. S., Silva, E. A. D. S., Palhano-Fontes, F., Maia-de-Oliveira, J. P., … Galvão-Coelho, N. L. (2019). Modulation of Serum Brain-Derived Neurotrophic Factor by a Single Dose of Ayahuasca: Observation From a Randomized Controlled Trial. *Frontiers in Psychology*, *10*, 1234. doi: 10.3389/fpsyg.2019.01234
Holze, F., Vizeli, P., Ley, L., Müller, F., Dolder, P., Stocker, M., … Liechti, M. E. (2021). Acute dose-dependent effects of lysergic acid diethylamide in a double-blind placebo-controlled study in healthy subjects. *Neuropsychopharmacology*, *46*(3), 537–544. doi: 10.1038/s41386-020-00883-6






Nardou, R., Lewis, E. M., Rothhaas, R., Xu, R., Yang, A., Boyden, E., & Dölen, G. (2019). Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature*, *569*(7754), 116–120.
Nardou, R., Sawyer, E., Song, Y. J., Wilkinson, M., Padovan-Hernandez, Y., de Deus, J. L., Wright, N., et al. (2023). Psychedelics reopen the social reward learning critical period. *Nature*, *618*(7966), 790–798

## Limitations

- *TBI is heterogenous injury; hard to study*
- Limited studies
  - 9 phase 2 studies of psilocybin for mood;
  - 79 studies of Ketamine for mood;
  - 12 studies of MDMA for PTSD;
  - 3 cohort studies of ibogaine and 5-MeO-DMT for TBI

## Safety

- **More questions than answers**
- **Psilocybin, MDMA, Ketamine, Ibogaine (Cardiac)- generally safe;**
  - **Ibogaine require medical oversight**
  - **Unclear long-term effects**
  - **Expectancy bias is hard to manage**

*“Doctor, I have a friend who has been using psychedelics after his TBI, do you think they could help me?”*

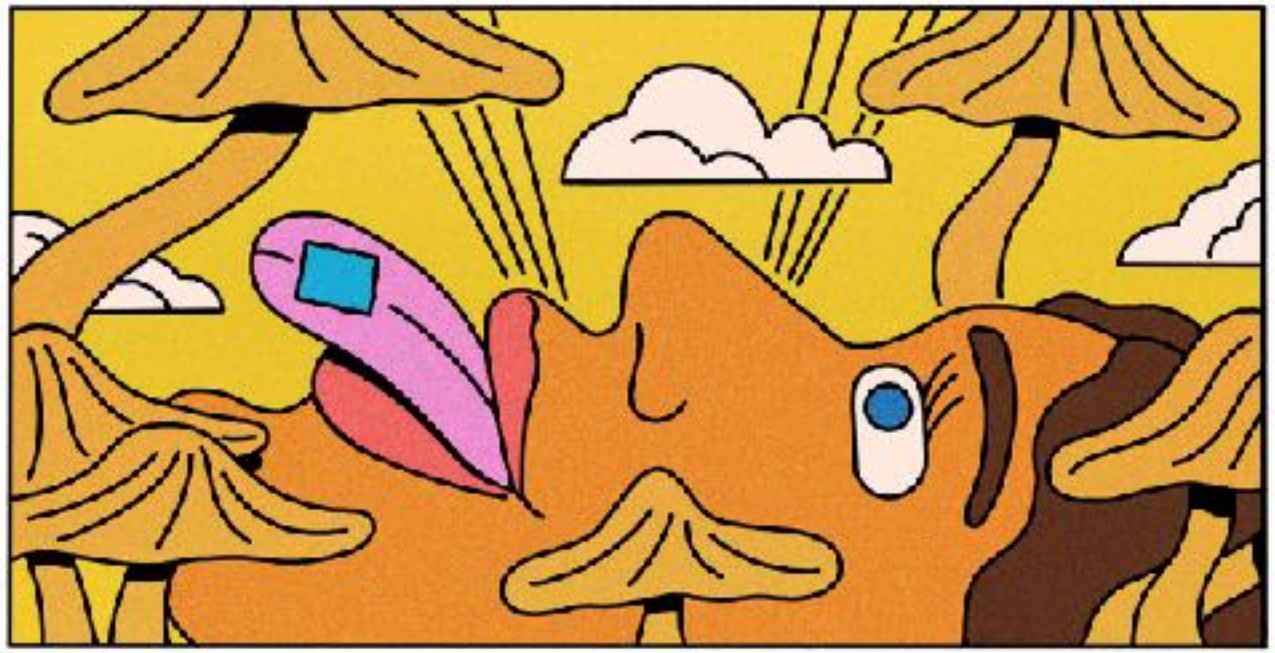
DX: Mood disorder due to TBI, PTSD, AUD-in SR, MUD- in SR and OUD – in SR.

*Engaged with therapist;*
*Did prep/integration at OPC*;
*Tried Psilocybin - assisted Psychotherapy* in community
- Counselled on options; OR vs clinical trial vs retreat vs underground
*Mood symptoms improved; PHQ - 9 23(pre) -> 3(post)*
*Was able to engage in groups*
*Cravings went away*
*Motivation to engage in care increased*
*Functionally, got a job, moved out of parents' house.*

# *Questions?*

*nathan9@uw.edu*

*Ntap.psychiatry.uw.edu*



TBI-BH ECHO

## Citations:


Kelmendi, B., Kaye, A. P., Pittenger, C., & Kwan, A. C. (2022). Psychedelics. *Current Biology*, *32*, R63–R67. https://doi.org/10.1016/j.cub.2021.12.009

https://psychedelicalpha.com/news/q125-psychedelic-drug-development-pipeline-bullseye-chart

O'Connell, C. J., Brown, R. S., Peach, T. M., Traubert, O. D., Schwierling, H. C., Notorgiacomo, G. A., & Robson, M. J. (2024). Strain in the midbrain: impact of traumatic brain injury on the central serotonin system. *Brain Sciences*, *14*(1). doi: 10.3390/brainsci14010051

Howlett, J. R., Nelson, L. D., & Stein, M. B. (2022). Mental health consequences of traumatic brain injury. *Biological Psychiatry*, *91*, 413–420. https://doi.org/10.1016/j.biopsych.2021.09.024

Wallace, S. S., Barak, G., Truong, G., & Parker, M. W. (2022). Hierarchy of evidence within the medical literature. *Hospital Pediatrics*, *12*, 745–750. https://doi.org/10.1542/hpeds.2022-006690

Metaxa, A.-M., & Clarke, M. (2024). Efficacy of psilocybin for treating symptoms of depression: systematic review and meta-analysis. *BMJ (Clinical Research Ed.)*, *385*, e078084. doi: 10.1136/bmj-2023-078084

Alnefeesi, Y., Chen-Li, D., Krane, E., Jawad, M. Y., Rodrigues, N. B., Ceban, F., … Rosenblat, J. D. (2022). Real-world effectiveness of ketamine in treatment-resistant depression: A systematic review & meta-analysis. *Journal of Psychiatric Research*, *151*, 693–709. doi: 10.1016/j.jpsychires.2022.04.037

Yao, Y., Guo, D., Lu, T.-S., Liu, F.-L., Huang, S.-H., Diao, M.-Q., … Han, Y. (2024). Efficacy and safety of psychedelics for the treatment of mental disorders: A systematic review and meta-analysis. *Psychiatry Research*, *335*, 115886. doi: 10.1016/j.psychres.2024.115886

Davis, A. K., Averill, L. A., Sepeda, N. D., Barsuglia, J. P., & Amoroso, T. (2020). Psychedelic Treatment for Trauma-Related Psychological and Cognitive Impairment Among US Special Operations Forces Veterans. *Chronic Stress (Thousand Oaks, Calif.)*, *4*, 2470547020939564. doi: 10.1177/2470547020939564

Davis, A. K., Xin, Y., Sepeda, N., & Averill, L. A. (2023). Open-label study of consecutive ibogaine and 5-MeO-DMT assisted-therapy for trauma-exposed male Special Operations Forces Veterans: prospective data from a clinical program in Mexico. *The American Journal of Drug and Alcohol Abuse*, *49*(5), 587-596.

Calder, A. E., & Hasler, G. (2023). Towards an understanding of psychedelic-induced neuroplasticity. *Neuropsychopharmacology*, *48*(1), 104–112. doi: 10.1038/s41386-022-01389-z

Moliner, R., Girych, M., Brunello, C. A., Kovaleva, V., Biojone, C., Enkavi, G., … Castrén, E. (2023). Psychedelics promote plasticity by directly binding to BDNF receptor TrkB. *Nature Neuroscience*, *26*(6), 1032–1041. doi: 10.1038/s41593-023-01316-5

Cherian, K. N., Keynan, J. N., Anker, L., Faerman, A., Brown, R. E., Shamma, A., ... & Williams, N. R. (2024). Magnesium-ibogaine therapy in veterans with traumatic brain injuries. *Nature Medicine*, *30*(2), 373-381.\

de Almeida, R. N., Galvão, A. C. de M., da Silva, F. S., Silva, E. A. D. S., Palhano-Fontes, F., Maia-de-Oliveira, J. P., … Galvão-Coelho, N. L. (2019). Modulation of Serum Brain-Derived Neurotrophic Factor by a Single Dose of Ayahuasca: Observation From a Randomized Controlled Trial. *Frontiers in Psychology*, *10*, 1234. doi: 10.3389/fpsyg.2019.01234

Holze, F., Vizeli, P., Ley, L., Müller, F., Dolder, P., Stocker, M., … Liechti, M. E. (2021). Acute dose-dependent effects of lysergic acid diethylamide in a double-blind placebo-controlled study in healthy subjects. *Neuropsychopharmacology*, *46*(3), 537–544. doi: 10.1038/s41386-020-00883-6

Olson, D. E. (2022). Biochemical Mechanisms Underlying Psychedelic-Induced Neuroplasticity. *Biochemistry*, *61*(3), 127–136. doi: 10.1021/acs.biochem.1c00812

Nardou, R., Lewis, E. M., Rothhaas, R., Xu, R., Yang, A., Boyden, E., & Dölen, G. (2019). Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature*, *569*(7754), 116–120.

Nardou, R., Sawyer, E., Song, Y. J., Wilkinson, M., Padovan-Hernandez, Y., de Deus, J. L., Wright, N., et al. (2023). Psychedelics reopen the social reward learning critical period. *Nature*, *618*(7966), 790–798


TBI-BH ECHO