Psychedelic-Assisted Therapy & the DoD

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Agenda

I. Political & Legal Landscape
II. Three Core Principles
III. Access

Personal Background

- Background with Psychedelic-Assisted Therapy (PAT)
  - Certified in PAT with MDMA (2019) and Psilocybin (2020)
  - Experienced in delivering PAT while in fellowship at Yale
- PAT-related Activities
  - Deputy Psychiatry Consultant, Novel & Emerging Therapeutics – Army OTSG
  - Consultant – VA, DARPA, & other DoD entities
  - Leading several projects in partnership with VA, FDA, and others

I. Political & Legal Landscape

	2021	2022	2023	2024
Federal	White House "strongly supports expanding the research of Schedule I substances to help advance evidence-based public policy."			Projected FDA Approval of MDMA-AT for PTSD (Aug) DEA to deschedule MDMA (90 days after FDA approval)
VA		3x VA clinical trials first to administer MDMA-AT to Veterans VA State of the Art Conference convened a team of teams to discuss clinical implementation and research across VA		VA releases RFA to begin funding VA studies of MDMA- and psilocybin-assisted therapy
DoD	DARPA - Funds UNC consortium to study "non-psychedelic psychedelics" (non-clinical)	NDAA 2022 - PAT amendment does NOT pass House or Senate	NDAA 2023 - 2x PAT amendments pass House but NOT Senate	NDAA 2024 - PAT amendment (Sec 723) signed into law Defense Appropriations Act 2024 - $10M appropriated for DoD PAT clinical trial program

NDAA 2024, Sec 723

SEC. 723. PROGRAM OF THE DEPARTMENT OF DEFENSE TO STUDY TREATMENT OF CERTAIN CONDITIONS USING CERTAIN PSYCHEDELIC SUBSTANCES.

(a) ESTABLISHMENT.—Not later than 180 days after the date of enactment of this Act, the Secretary of Defense shall establish a process to fund eligible entities to conduct research on the treatment of eligible members of the Armed Forces with a covered condition using covered psychedelic substances. Not later than 180 days after the date of the enactment of this Act, the Secretary shall designate a lead administrator to carry out the program under this section.

(b) ELIGIBLE ENTITIES.—The Secretary may enter into a partnership and award funding under this section to any of the following:

(1) A department or agency of the Federal Government or a State government.

(2) An academic institution.

(c) PARTICIPATION IN CLINICAL TRIALS.—The Secretary may authorize any member of the Armed Forces serving on active duty who is diagnosed with a covered condition to participate in a clinical trial that is conducted using funding awarded under this section and is authorized pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), without regard to—

(1) whether the clinical trial involves a substance included in the schedule under section 202 of the Controlled Substances Act (21 U.S.C. 812); or

(2) section 912a of title 10, United States Code (article 112a of the Uniform Code of Military Justice).

(d) REPORT REQUIRED.—Not later than one year after the date of the enactment of this Act, and annually thereafter for three years, the Secretary shall submit to the Committees on Armed Services of the House of Representatives and the Senate a report on funding awarded under this section, including the following:

(1) Identification of clinics designated to host activities under the program.

(2) A description of entities to whom the Secretary has awarded such funding.

(3) The number of members of the Armed Forces serving on active duty who participated in a clinical trial described in subsection (c), the covered conditions of such members treated, and whether such members returned to full duty.

(4) Information on the findings of such clinical trials.

(e) DEFINITIONS.—In this section:

(1) The term "covered condition" means any of the following:

(A) Post-traumatic stress.

(B) Traumatic brain injury.

(2) The term "covered psychedelic substances" means any of the following:

(A) 3,4-Methylenedioxy-methamphetamine (commonly known as "MDMA").

(B) Psilocybin.

(C) Ibogaine.

(D) 5-Methoxy-N,N-dimethyltryptamine (commonly known as "5-MeO-DMT").

(E) Qualified plant-based alternative therapies.

(3) The term "Secretary" means the Secretary of Defense.

(4) The term "State" has the meaning given such term in section 901 of title 32, United States Code.

Defense Appropriations Act 2024

	Budget Request	Final Bill
RESEARCH AND DEVELOPMENT		
Program increase - DoD wide psychedelic medical clinical trials		10,000

DoD Legal Considerations

- No serious legal barriers (verified by MRDC JAG legal review)
  - Can conduct Schedule I research in DoD (AR 40-7).
  - Schedule I substance administered in the context of an FDA- and **command-approved** participation in a clinical trial or treatment setting **is a legal prescription**. Would not be "wrongful" (UCMJ 112a), "illegal," or "improper" for Active Duty (AR 635-200) or National Guard/Reserve (AR 135-178).
  - Participation in a civilian clinical trial must not be supported by DoD resources (can be on leave or PTDY) unless the clinical trial is approved through proper DoD channels (AR 40-7).
  - Schedule I substances legally administered in an appropriate setting would not affect security clearance (AR 380-67).
  - UAs not a concern **if adhere to regulations** (AR 600-85).

(Wolfgang & Hoge 2023)

II. Three Core Principles

Principle 1 – Key Distinction Between: Illicit Drugs vs. Pharmaceutical-Grade Medications

	Illicit Drugs (Ecstasy, Molly, etc.)	Pharmaceutical-Grade Medications (MDMA, etc.)
Adulterated	Often	Never
Dose	Unknown & Varied	Known & Precise
Setting	Uncontrolled	Controlled & Safe
Medical Screening	None	Extensive
Medical Monitoring	None	Close Monitoring

Principle 2 – Paradigm Shift: Chronic Medications → Medication-Assisted Therapy

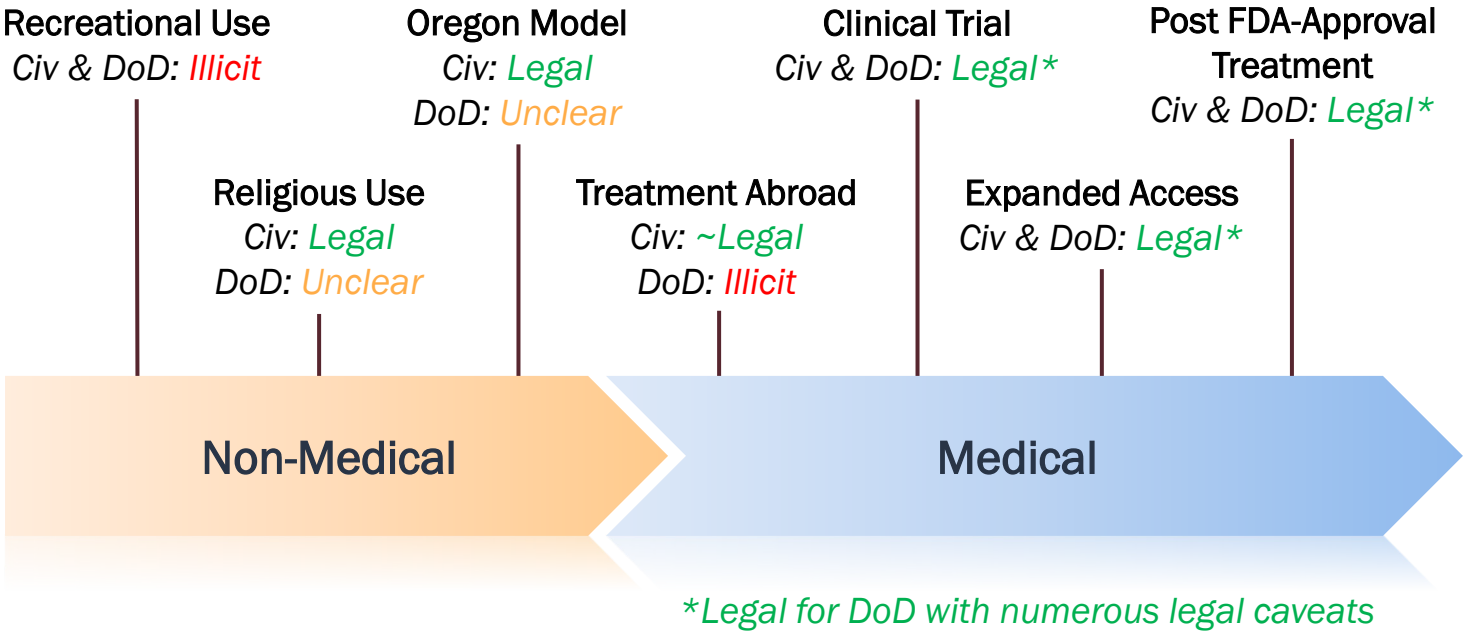
- Classic Paradigm: Chronic Medications
  - Cause of BH conditions is rooted in a neurobiological imbalance
  - Medications must be administered chronically to offset imbalance
- Emerging Paradigm: Medication-Assisted Therapy
  - Cause of BH conditions is rooted in cognitions, emotions, & behaviors
  - *Therapy* – not medication – is the *most important* aspect of treatment
  - The role of medications (psychedelics, stellate ganglion block, etc.) is to *enhance the therapy*
  - Medication taken infrequently (1-3 times total) and only in a supervised medical setting (analogous to surgical anesthesia)

Principle 3 – Psychedelic-Assisted Therapy ≈ Anesthesia-Assisted Procedure

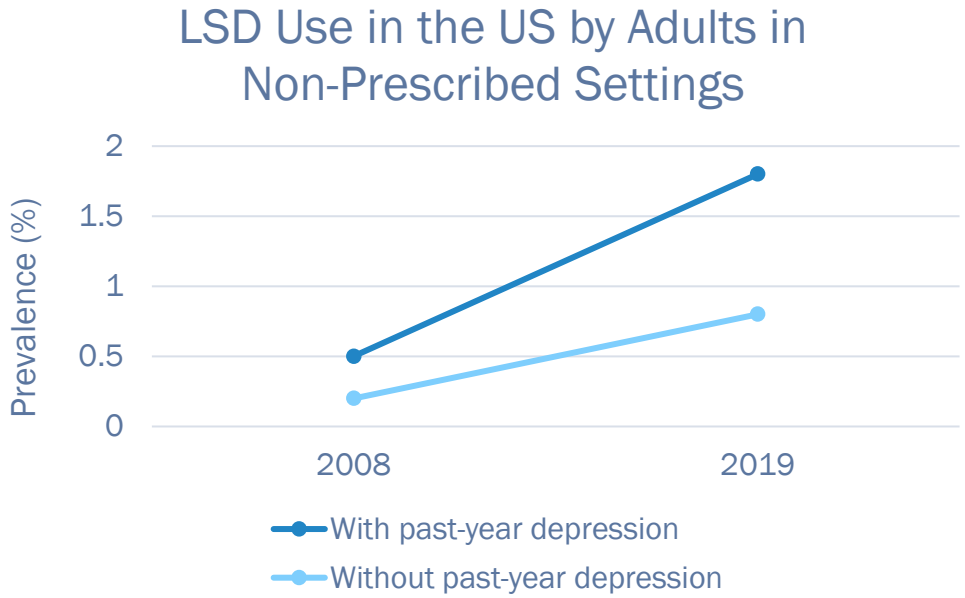
- MDMA/Ketamine/Psychedelics ≈ Anesthesia. Therapy ≈ Procedure.
  - *Anesthesia w/o Procedure* = temporary analgesia w/o addressing underlying issue
  - *Procedure w/o Anesthesia* = adequate for certain cases; for more severe & complex cases, may be insufficient, too painful, unreliable, lower enrollment, higher dropout
  - ***Anesthesia + Procedure*** = able to address deeper underlying issue, higher efficacy, lower dropout
- PAT as a **last-line treatment**: Orthopedic procedure for MSK injury ≈ PAT for BH condition
  - MSK: NSAID & Physical Therapy (1st line) → Orthopedic Surgery (Last line)
  - BH: Antidepressants & Psychotherapy (1st line) → PAT (Last line)
- No one goes home with anesthesia/psychedelic → Medication **only given in controlled medical setting**
- Resource-intensive & higher cost → Requires additional logistical/structural support
- Instead of SMs being medically discharged → Fix underlying impairment & **potential for SMs to RTD**

III. Access

Spectrum of Medical & Non-Medical Psychedelic Use

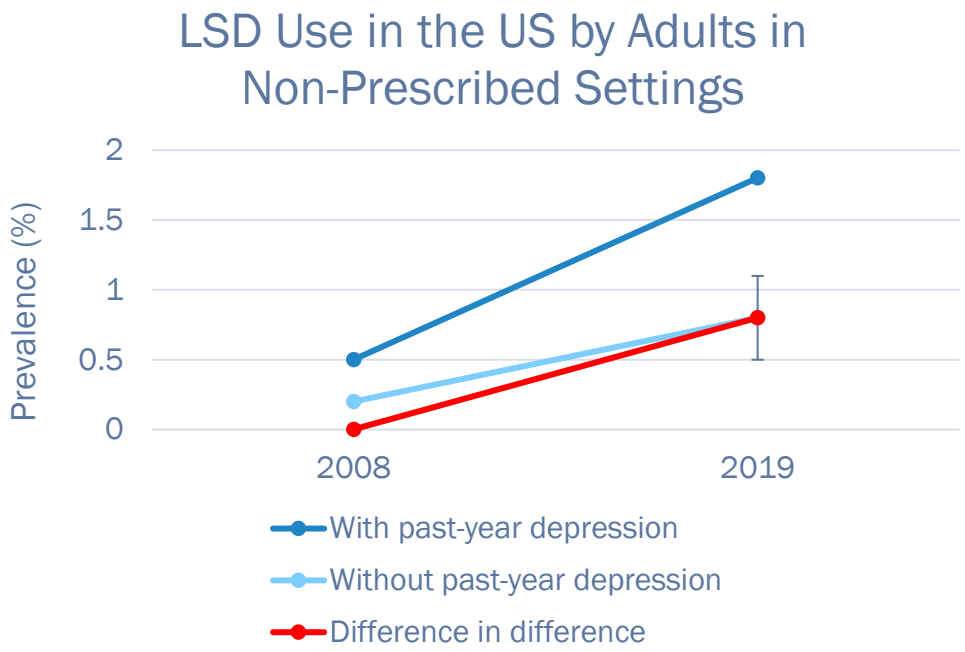


Non-Medical Use Increasing in Depressed Adults



(Walsh et al., JAMA Psych 2023)

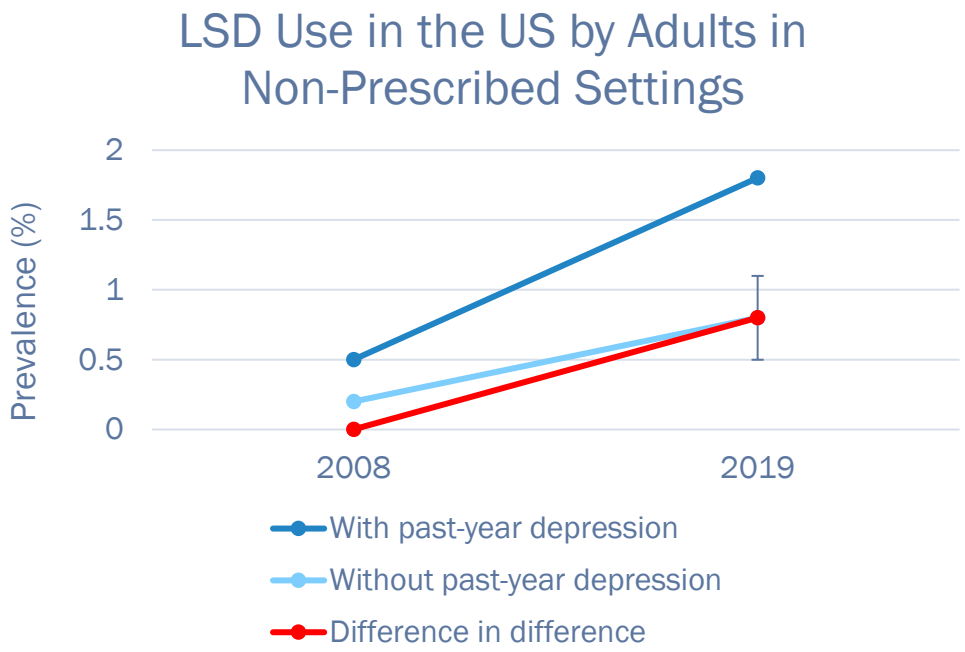
Non-Medical Use Increasing in Depressed Adults



- Solution?
  - Gut reaction:
    - ✓ ↓ access to legal PAT

(Walsh et al., JAMA Psych 2023)

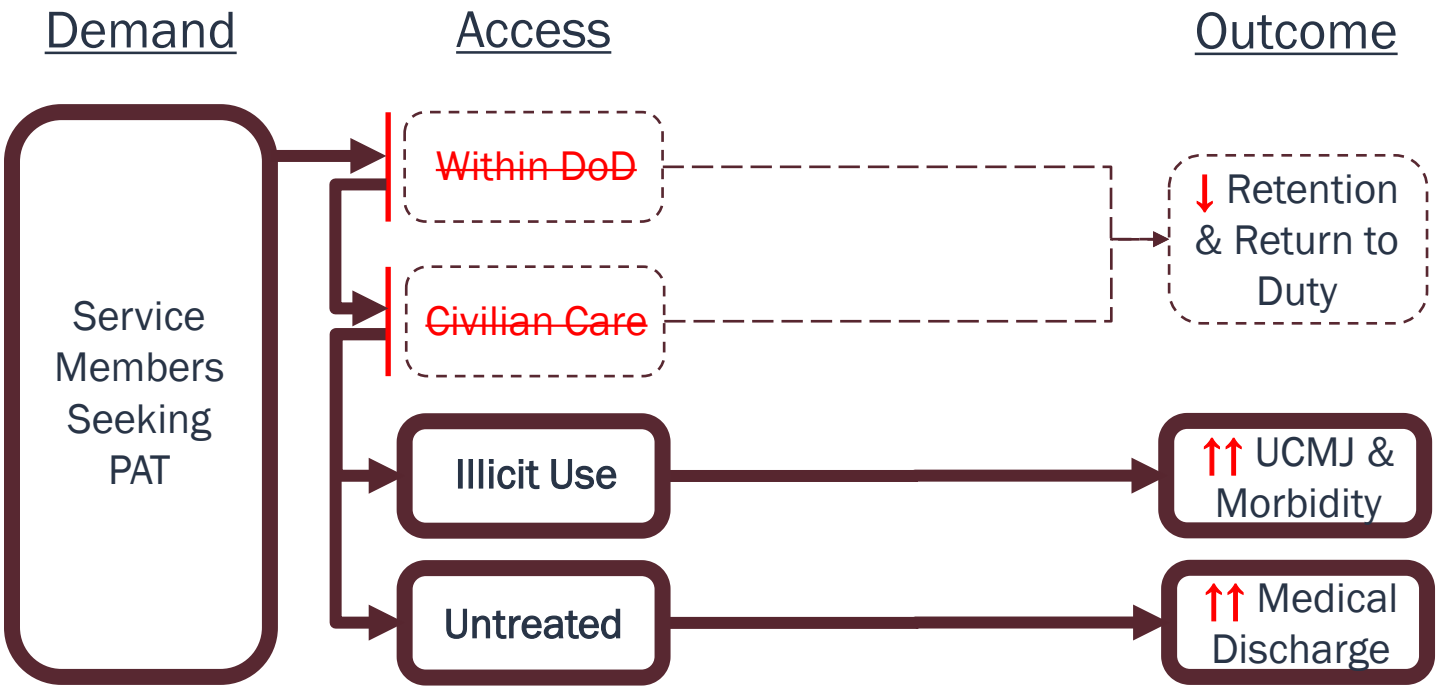
Non-Medical Use Increasing in Depressed Adults



- Solution?
  - ~~Gut reaction:~~
    - ~~✓ ↓ access to legal PAT~~
  - Evidence-based response:
    - ✓ ↑ screening, education, & prevention
  - ***And*** (not *instead of*)
    - ✓ ↑ (not ↓) access to legal, FDA-approved, medically controlled settings

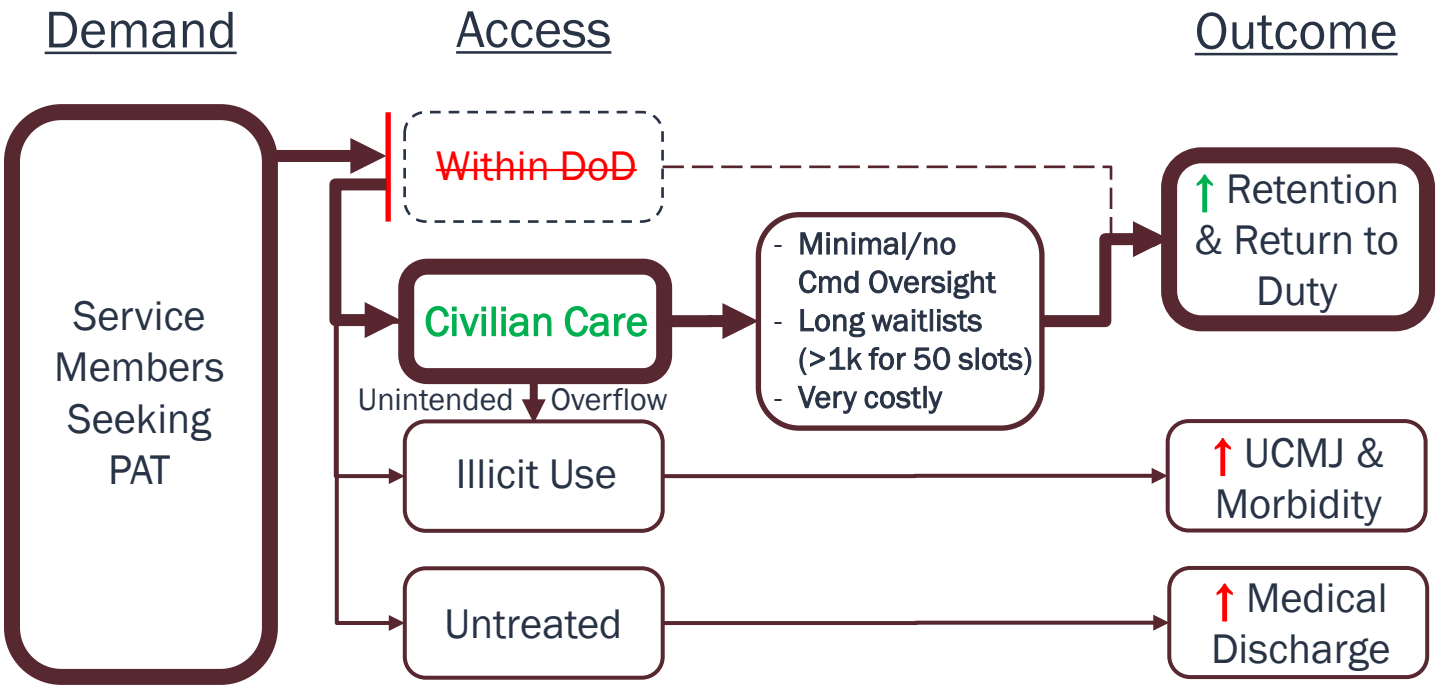
(Walsh et al., JAMA Psych 2023)

Framing the Problem:
Scenario 1 – No DoD & Civilian Access



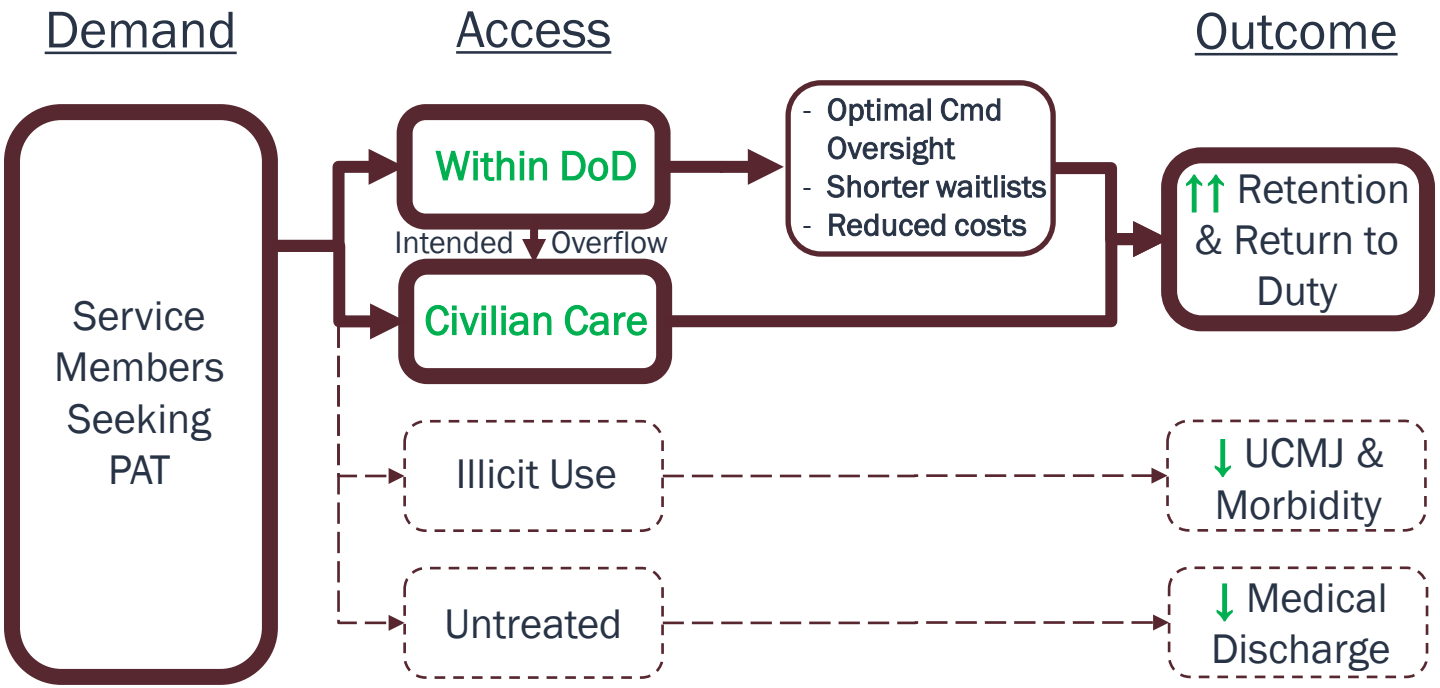
(Wolfgang, in prep.)

Framing the Problem:
Scenario 2 – No DoD & Only Civilian Access



(Wolfgang, in prep.)

Framing the Problem: Scenario 3 – DoD & Civilian Access



(Wolfgang, in prep.)

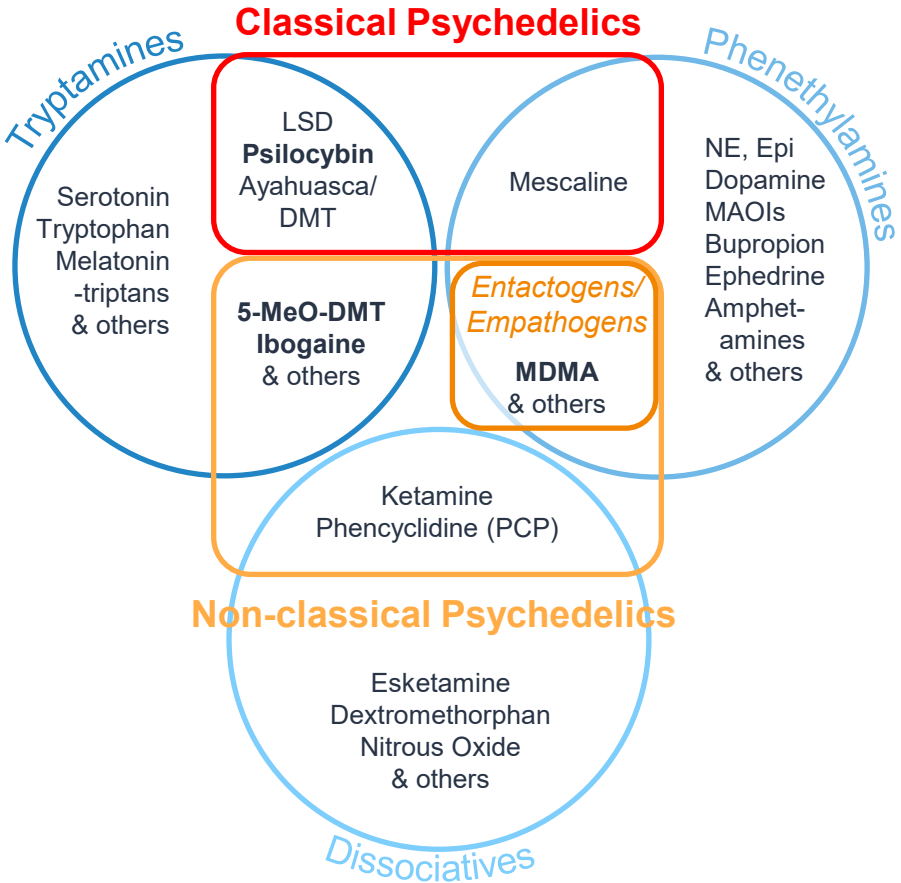
IV. Summary & Conclusion

Summary & Conclusion

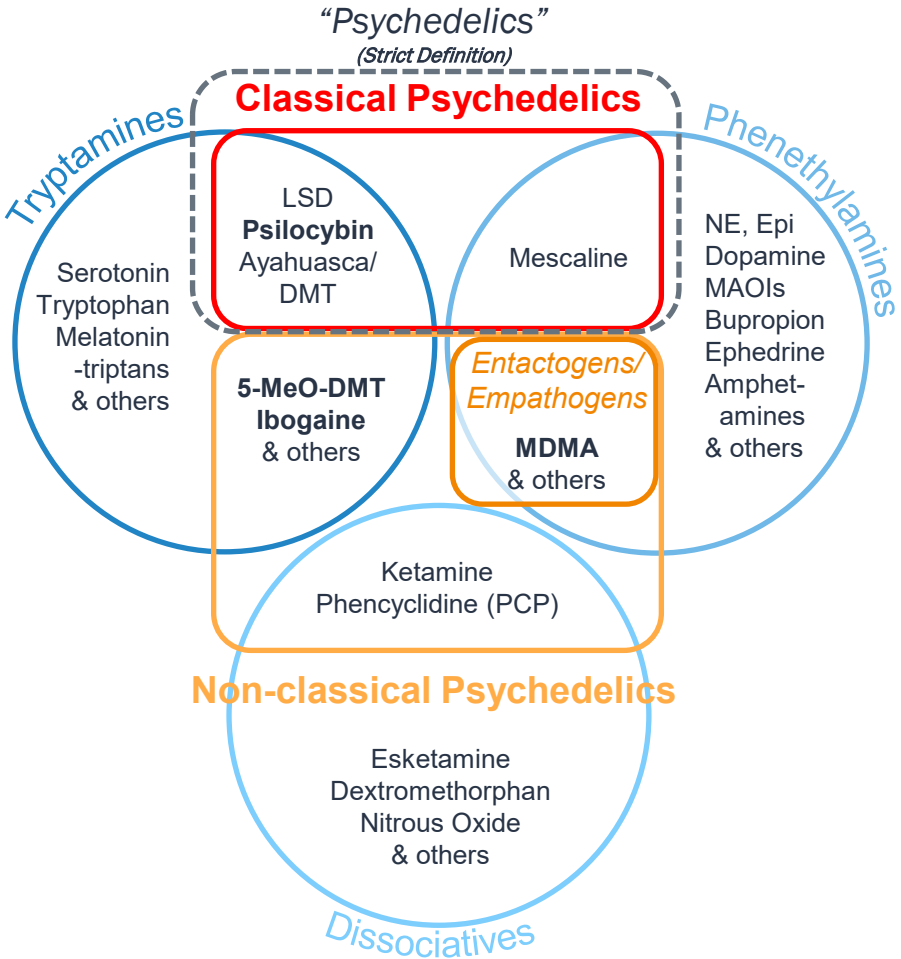
- MDMA-AT anticipated to be FDA-approved Aug 2024
- Psilocybin anticipated ~2027; all others 2030+
- VA moving full steam ahead with a “team of teams” across system to prepare for clinical implementation and conduct more research
- DoD clinical trial(s) authorized & appropriated to begin
- Will we be prepared?

Back-up Slides

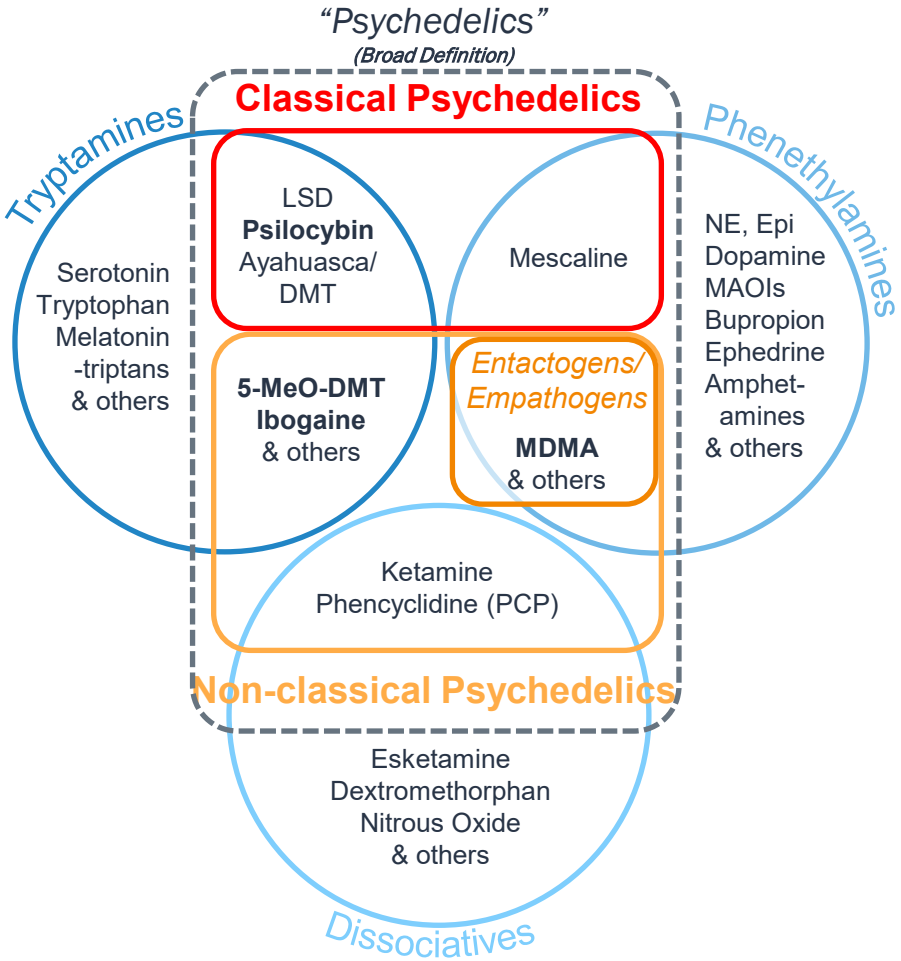
III. Overview of Psychedelics & Psychedelic-Assisted Therapy



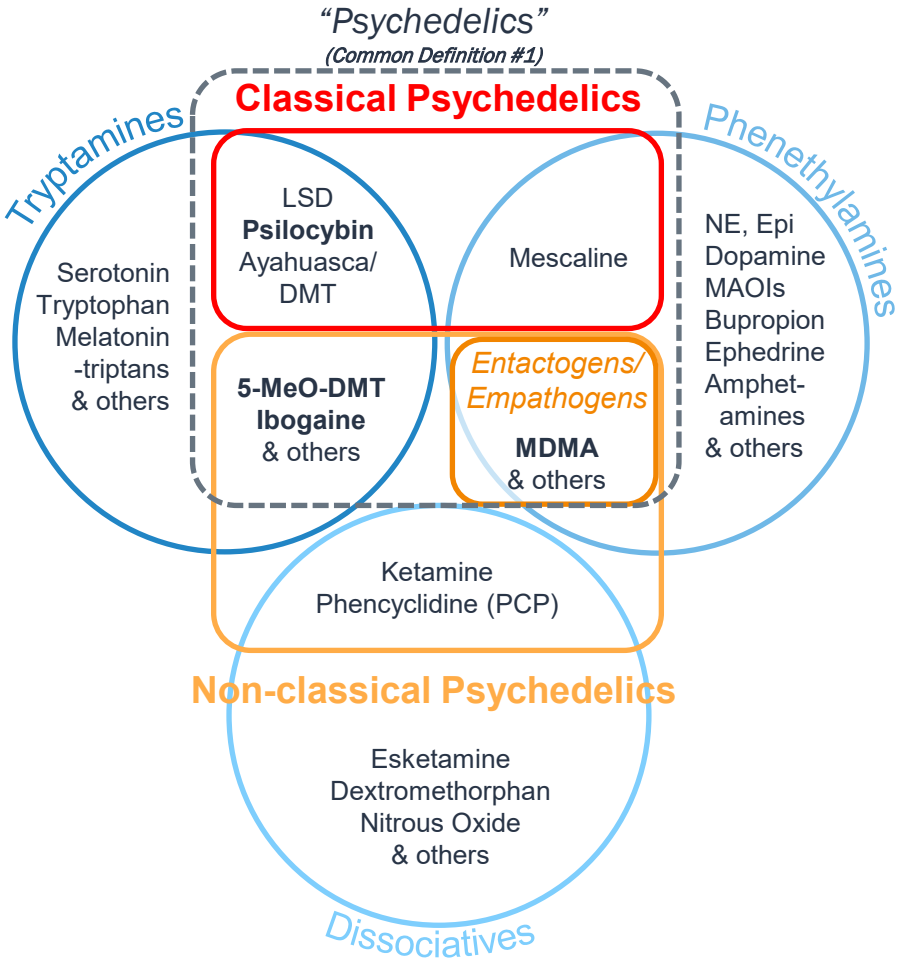
(Wolfgang & Hoge 2023)



(Wolfgang & Hoge 2023)



(Wolfgang & Hoge 2023)



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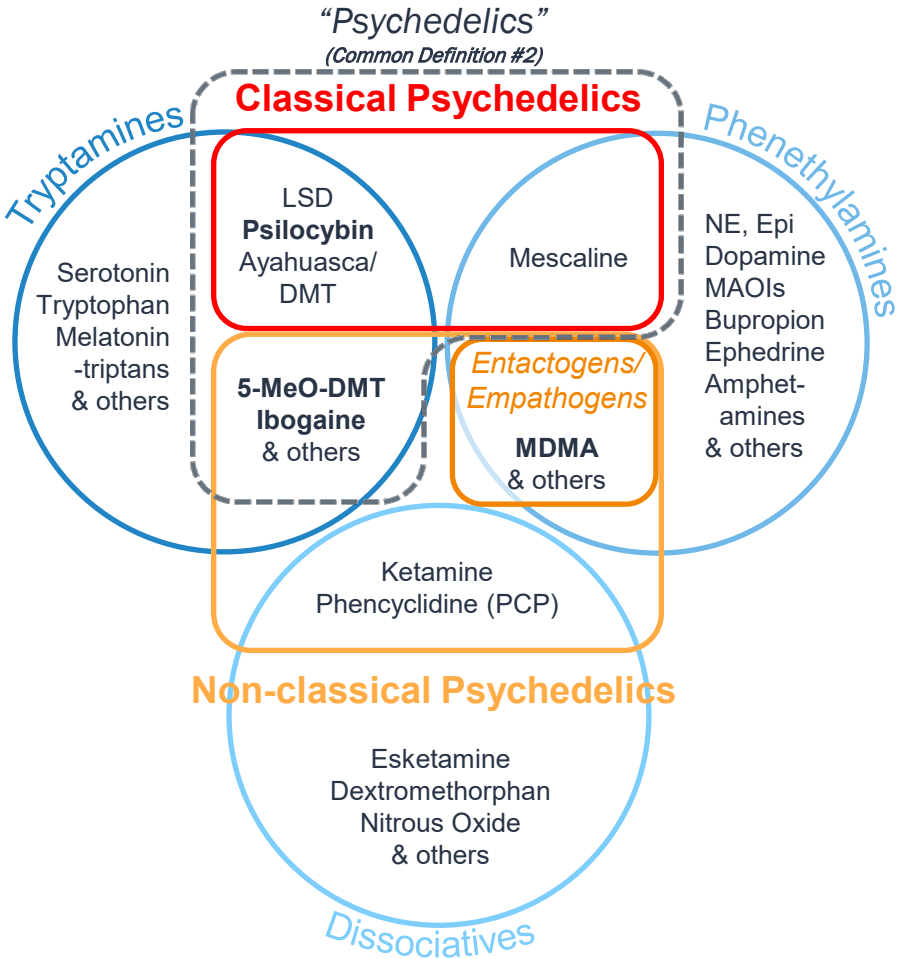

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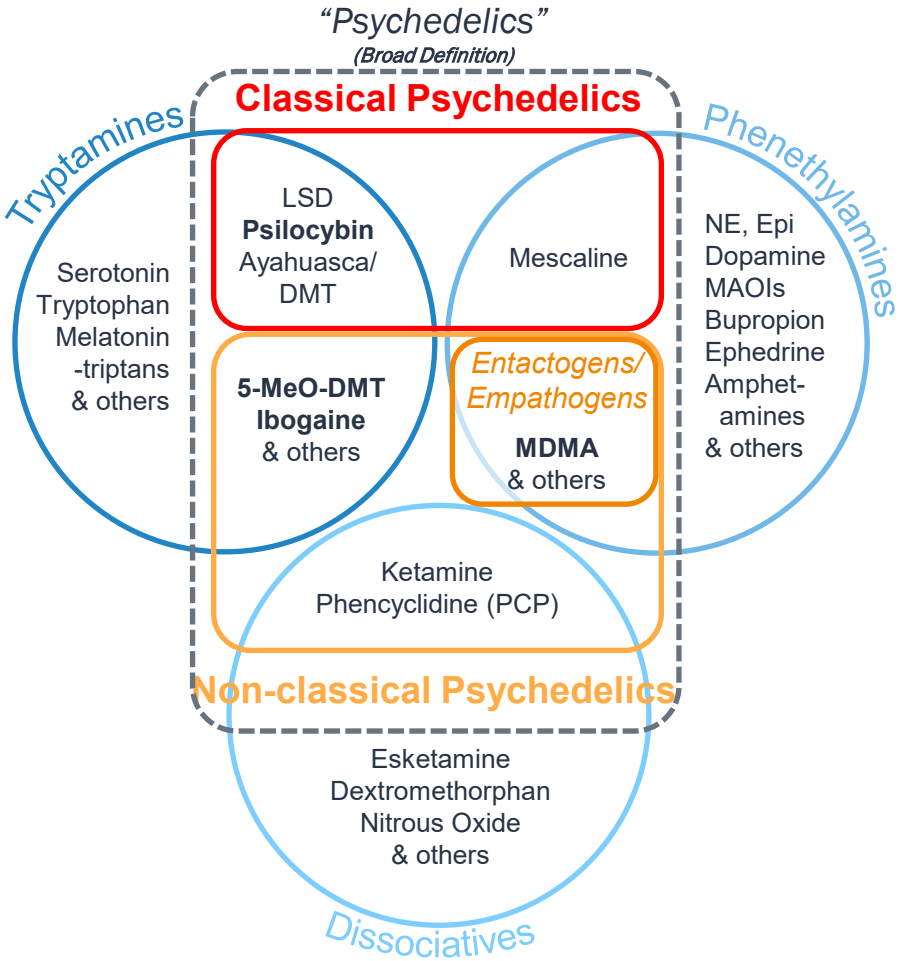
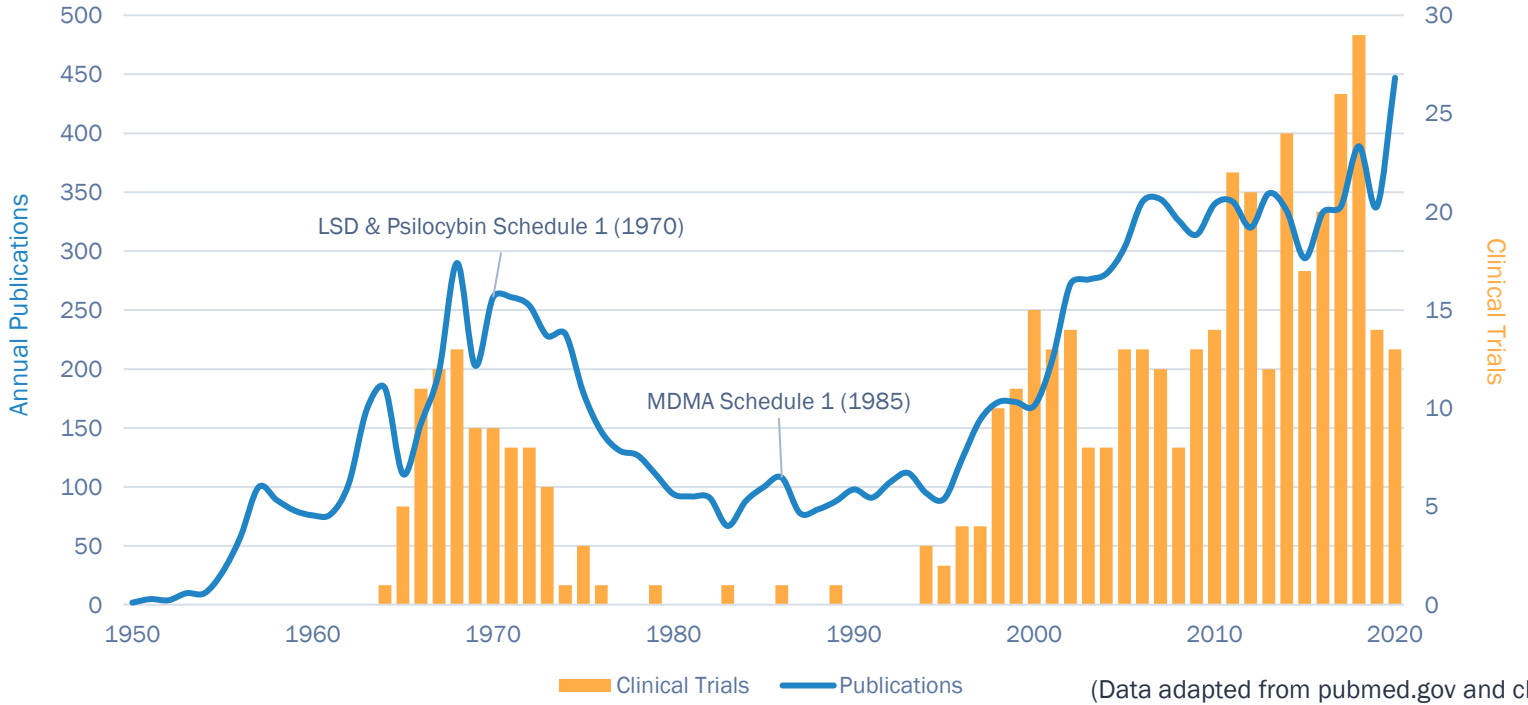
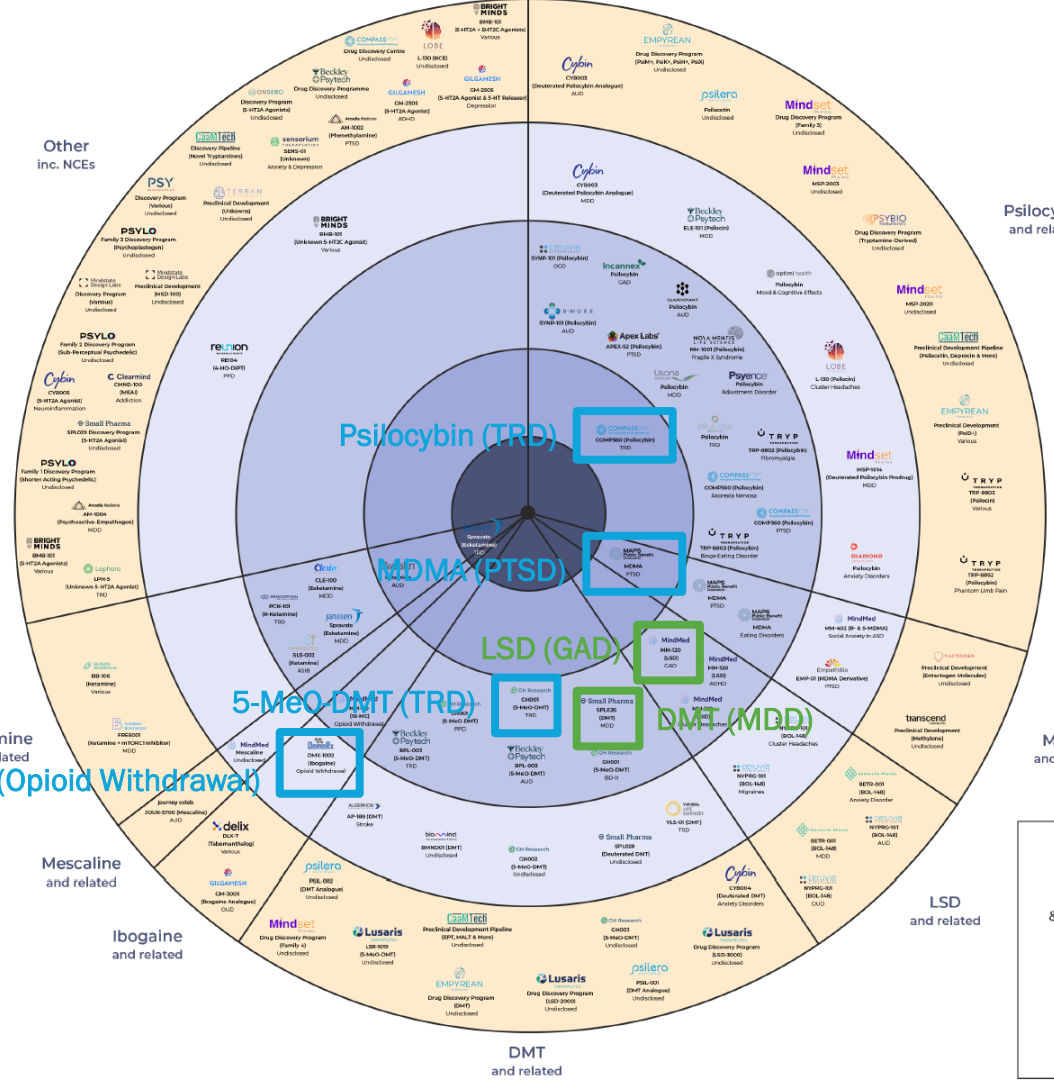


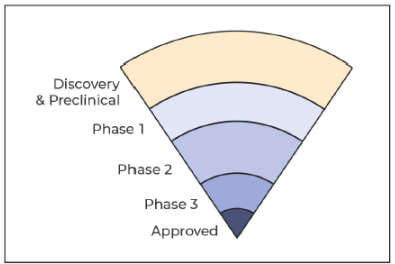
(Wolfgang & Hoge 2023)

Studies of MDMA, Psilocybin, & LSD



(Data adapted from pubmed.gov and clinicaltrials.gov)


Psilocybin (TRD)
MDMA (PTSD)
LSD (GAD)
5-MeO-DMT (TRD)
DMT (MDD)
Ibogaine (Opioid Withdrawal)
Psilocybin and related
MDMA and related
LSD and related
DMT and related
Ibogaine and related
Mescaline and related
Ketamine and related
Other inc. NCEs


Discovery & Preclinical
Phase 1
Phase 2
Phase 3
Approved

(A)

Overview of Published RCT Evidence

Medication	PTSD RCT Data	Depress-ion RCT Data	Suicida-lity RCT Data	Pain RCT Data	TBI RCT Data	Projected FDA Approval (Indication)	Note
Ketamine	✓	✓	✓	✓✓	-	1970 (Analgesia)	VA/DoD CPGs recommend ketamine for both depression (2022) AND suicidality (2019)
Esketamine	-	✓✓	✓✓	✓	-	2019 (Depression)	Primarily used for depression
MDMA	✓✓	✓✓	-	✓	-	2024 (PTSD)	Strongest evidence for PTSD
Psilocybin	-	✓	✓	✓	-	~2027 (Depression)	Positive depression and headache RCTs
LSD	-	-	-	✓	-	~2030 (Anxiety)	Primarily anxiety (modern RCTs) and alcohol use disorder (1960s)
DMT (Ayahuasca)	-	✓	-	-	-	~2030+ (Unknown)	IV form being studied for depression
5-MeO-DMT	-	-	-	-	-	~2030+ (Unknown)	Undergoing Phase 1/2 studies
Ibogaine	-	-	-	-	-	~2030+ (Unknown)	Promising PTSD/TBI data in observational studies
Cannabinoids (Various)	✓	-	-	✓	-	1985 (Nausea, Vom.) 2018 (Seizures)	PTSD and pain data is overall equivocal, but strongest evidence is null for both

✓/✓✓ = Strongest Phase **2/3** RCT Data Positive ✓/✓✓ = Strongest Phase **2/3** RCT Data Null - = No RCT Data

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Esketamine	-	✓✓	✓✓	✓	-	2019 (Depression)	Primarily used for depression
MDMA	✓✓	✓✓	-	✓	-	**2024 (PTSD)**	**Strongest evidence for PTSD**
Psilocybin	-	✓	✓	✓	-	**~2027 (Depression)**	**Positive depression and headache RCTs**
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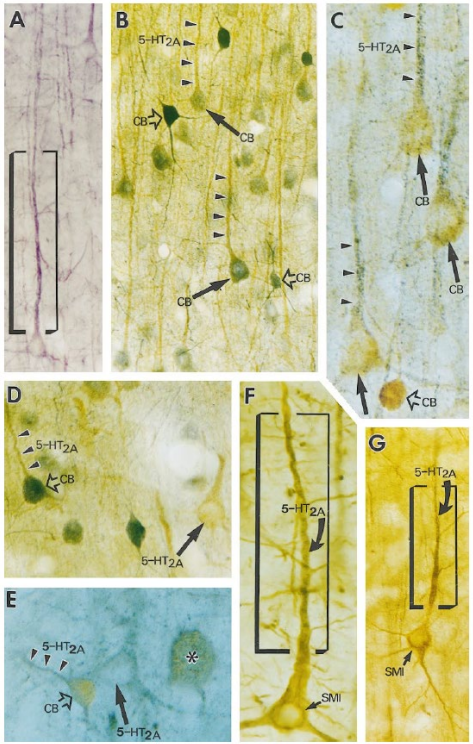
IV. Neurobiological Mechanisms of Psychedelics

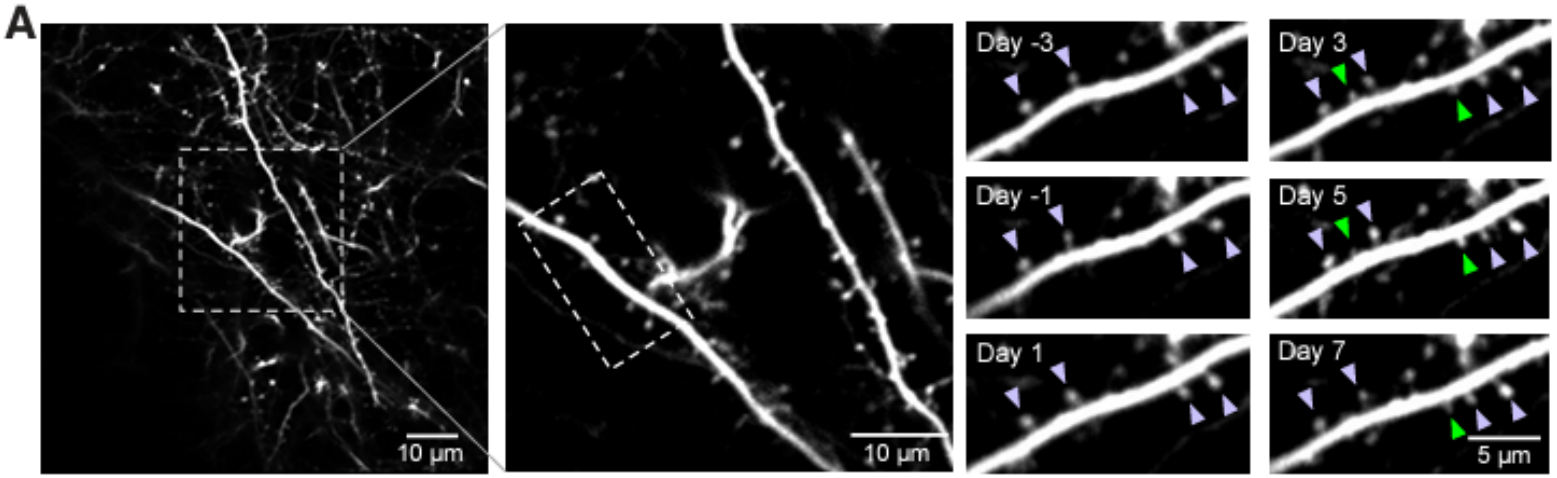
$5HT_{2A}$ Agonism & Metaplasticity



(Jakab & Goldman-Rakic, PNAS 1998)

Neuritogenesis

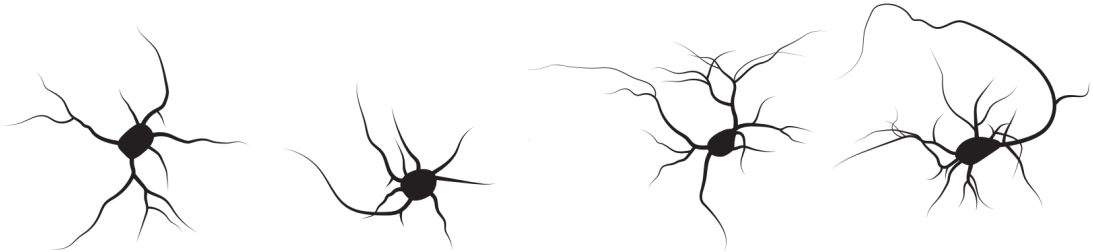
- Psilocybin increases **spine density** and **spine size** in frontal cortical pyramidal cells
- Structural remodeling is **persistent** for at least 1 month



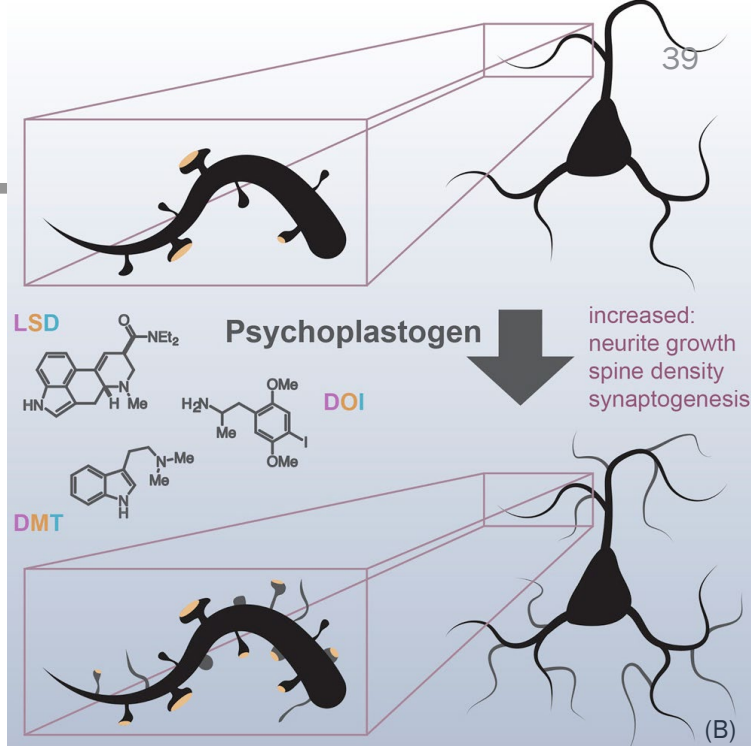
(Shao et al., Neuron 2021)

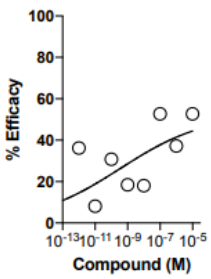
Neuritogenesis

- "...capable of robustly promoting neuritogenesis."
- MDMA twice as neuritogenic as ketamine
- Potential for TBI?

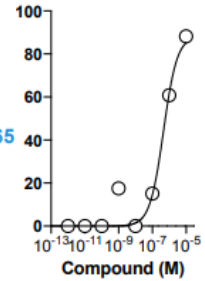


VEH AMPH MDMA PSI

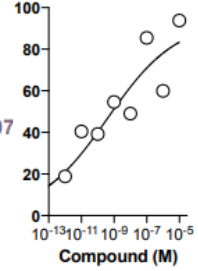




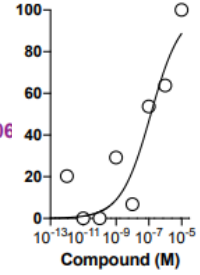
PSI
EC_{50} = 0.359 nM
Hill Slope = 0.165
E_{Max} = 53%



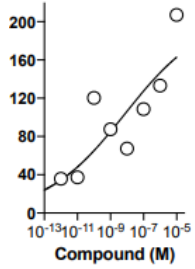
NOR
EC_{50} = 455 nM
Hill Slope = 1.07
E_{Max} = 88%



LSD
EC_{50} = 0.409 nM
Hill Slope = 0.206
E_{Max} = 94%



KET
EC_{50} = 132 nM
Hill Slope = 0.476
E_{Max} = 100%

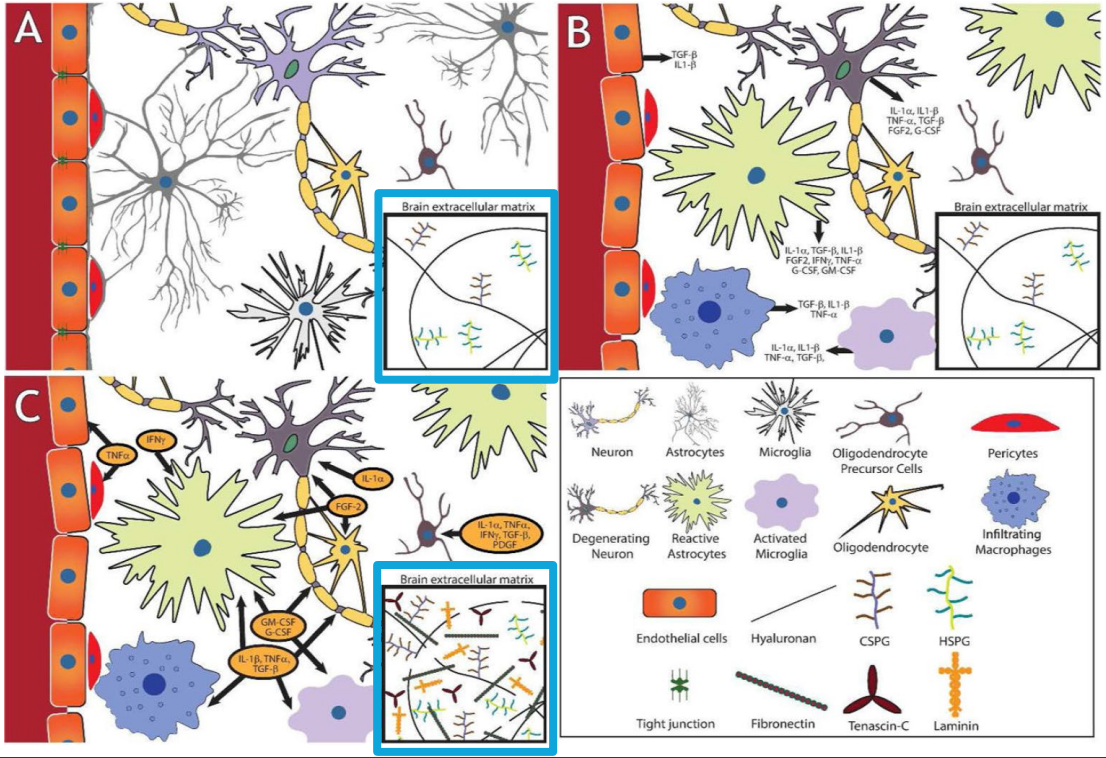


MDMA
EC_{50} = 7.41 nM
Hill Slope = 0.181
E_{Max} = 207%

Ketamine used as 100% baseline

(Ly et al., Cell 2018)

Common Pathway: Extracellular Matrix Regulation



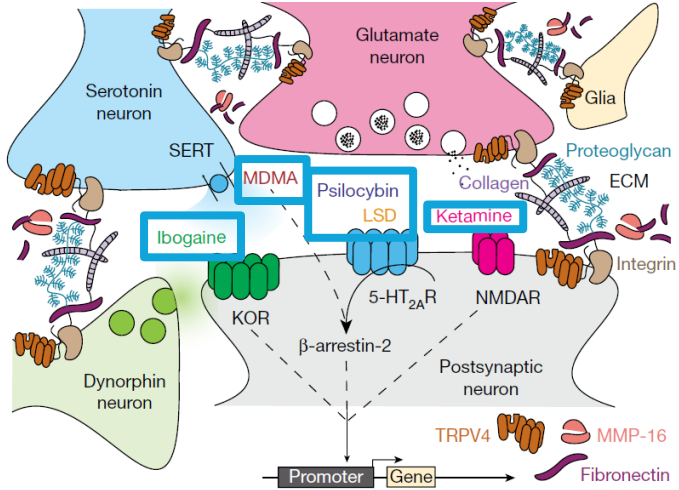
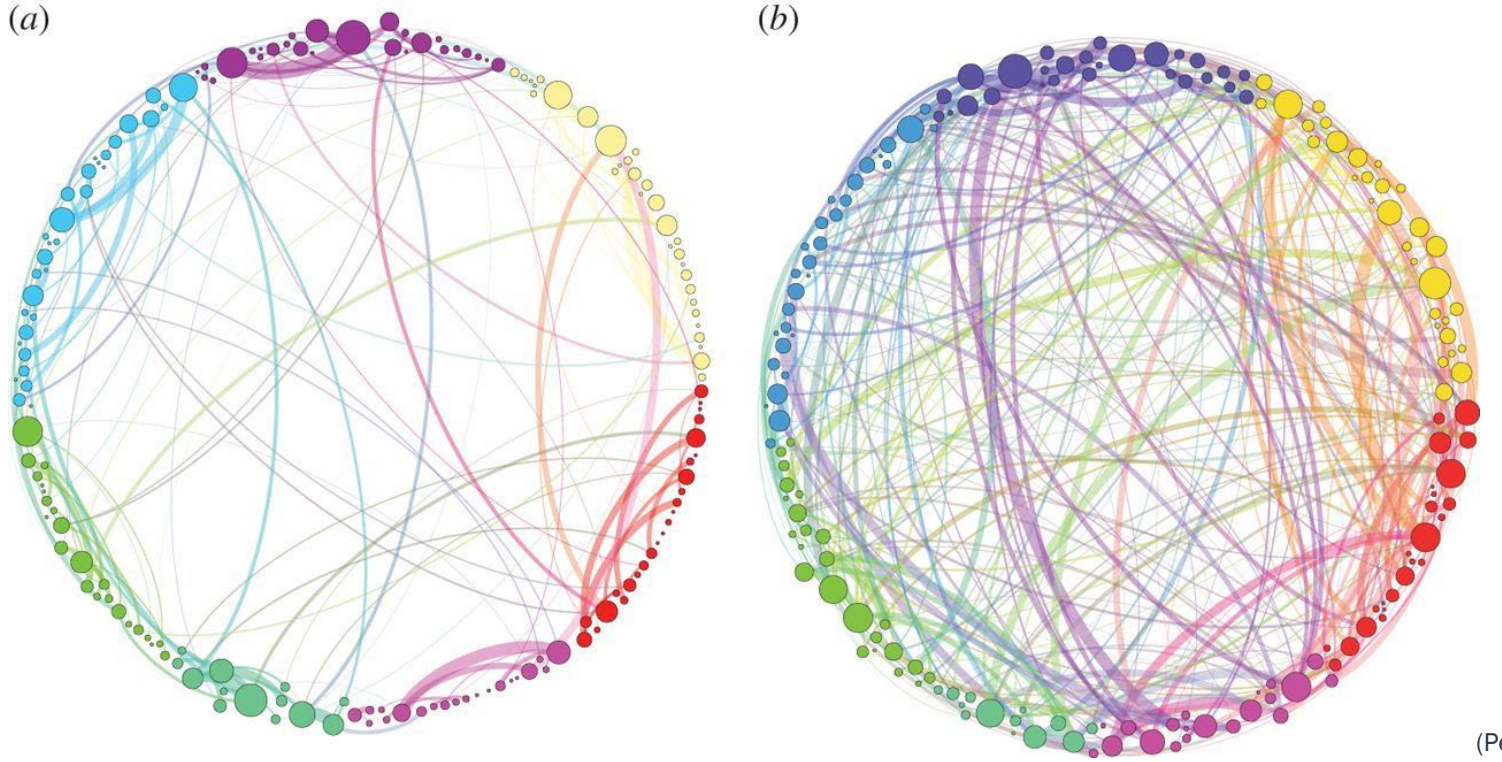


Fig. 6 | Working model of convergent cellular mechanisms of psychedelics. Psychedelics act on a diverse array of principal binding targets and downstream signalling mechanisms that are not limited to the serotonin 2A receptor (Extended Data Fig. 7) or β-arr2 (Extended Data Fig. 9). Instead, mechanistic convergence occurs at the level of DNA transcription (Fig. 5). Dynamically regulated transcripts include components of the extracellular matrix (ECM) such as fibronectin, as well as receptors (such as TRPV4) and proteases (such as MMP-16) implicated in regulating the ECM. Adapted from ref. 25.

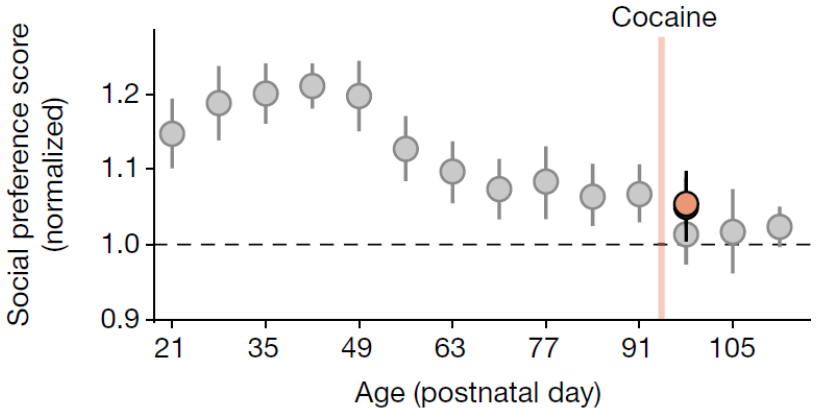
(George & Geller, J Neurosci Res 2018; Nardou et al., Nature 2023)

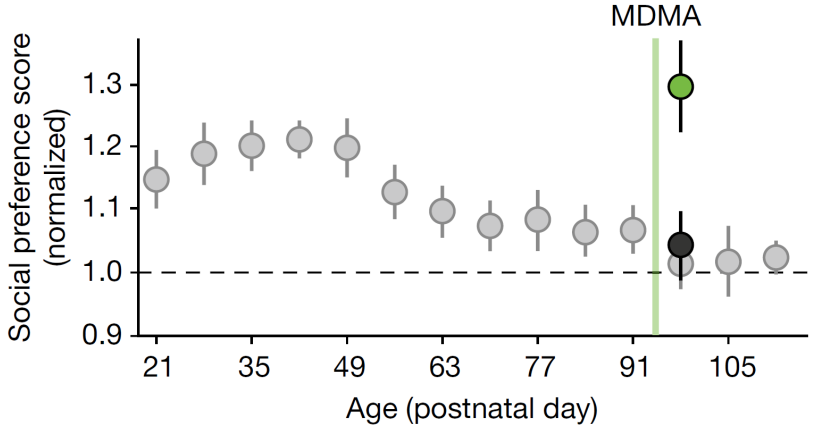
Functional Network Cross-connectivity



(Petri et al., 2014)

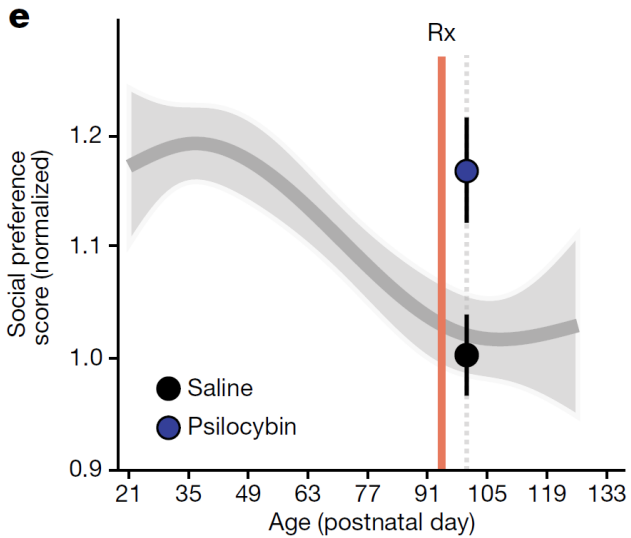
Reopen Critical Periods of Learning

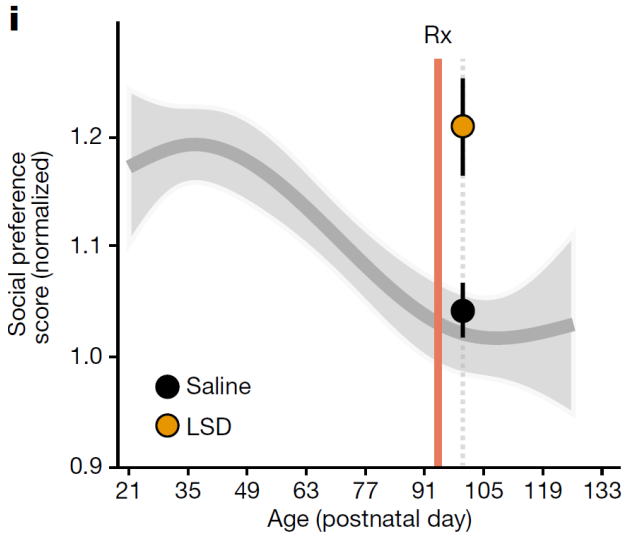


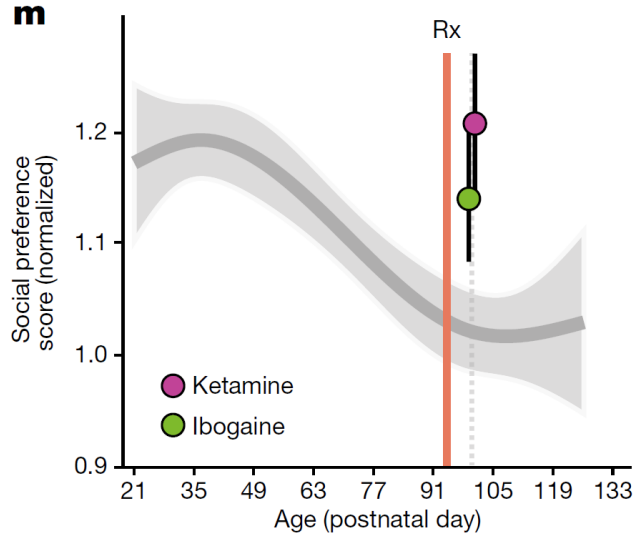


(Nardou et al., Nature 2019)

Reopen Critical Periods of Learning

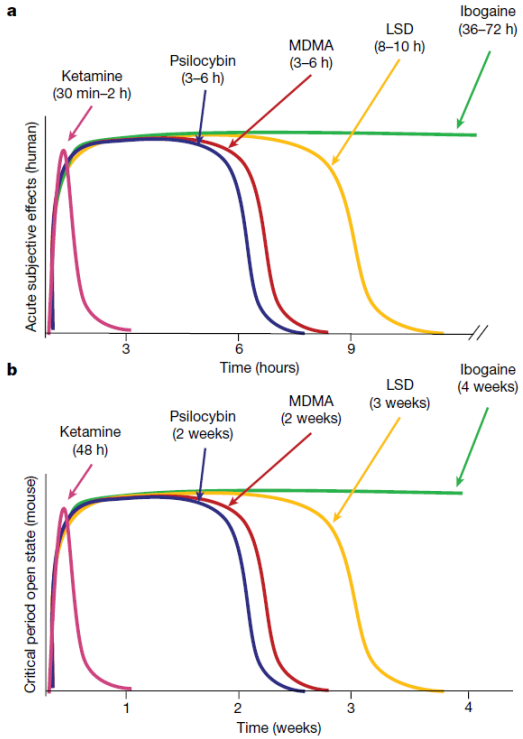






(Nardou et al., Nature 2023)

Reopen Critical Periods of Learning

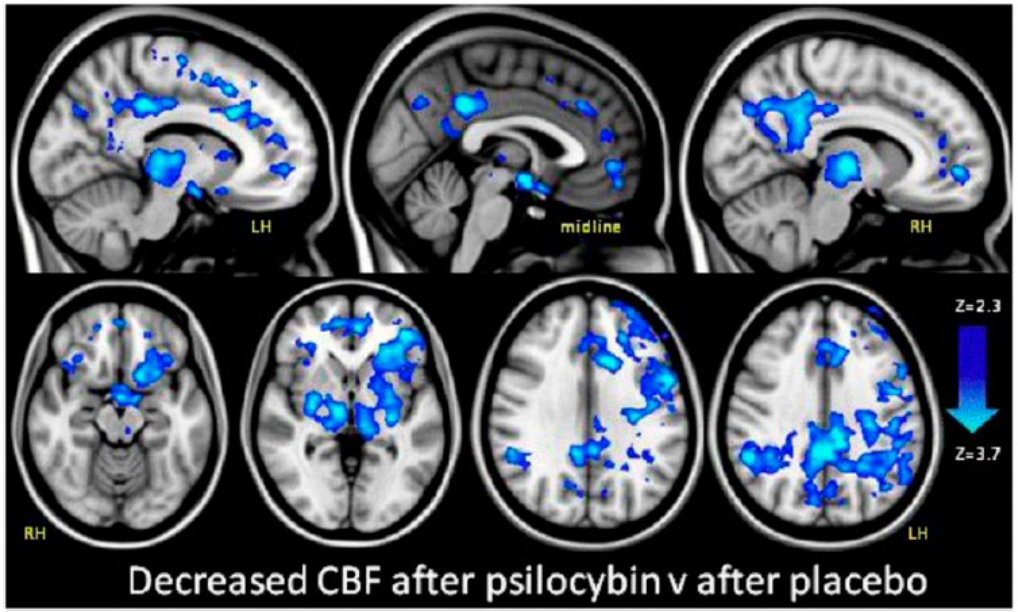


- Length of time of acute subjective effects correlates to length of time that critical periods of learning/metaplasticity remain open

(Nardou et al., Nature 2023)

Relaxed Assumptions/Expectations

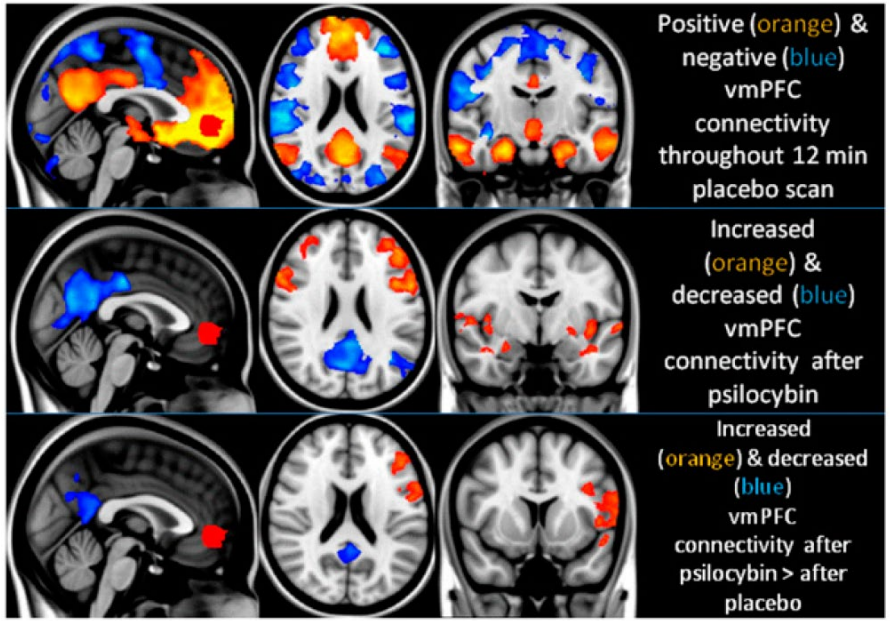
- Decrease activity in PCC (sense of self derived from collection of assumptions/expectations)



(Carhart-Harris et al., PNAS 2011)

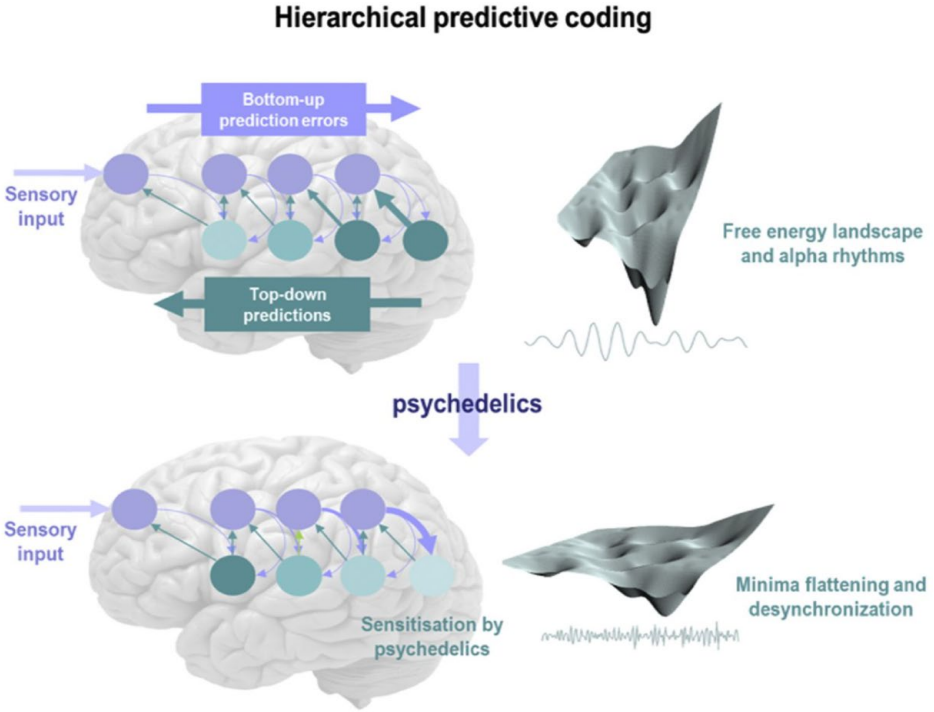
Relaxed Assumptions/Expectations

- Decoupling of PCC and vmPFC (relaxation of assumptions/expectations)



(Carhart-Harris et al., PNAS 2011)

REBUS: Relaxed Beliefs Under Psychedelics

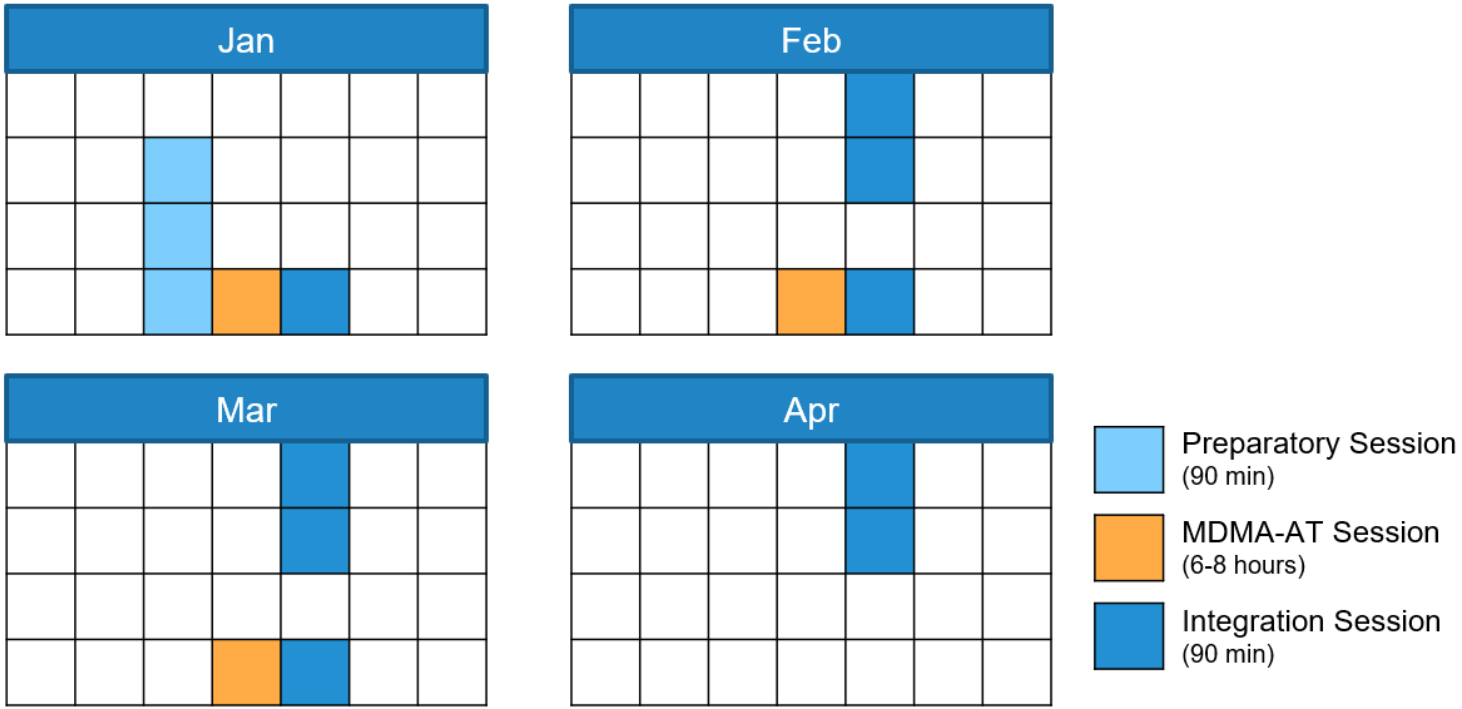


i.e. releasing from assumptions/expectations

(Carhart-Harris & Friston, 2019)

V. Psychedelic-Assisted Therapy

MDMA-AT Treatment Course




(F)


(G)


(H)


(I)

(Photos courtesy of MAJ Aaron Wolfgang)

Treatment Modality

- Role of the psychedelic
  - Emotional: Neurochemically mandate a lens of self-compassion to facilitate acute emotional processing
  - Cognitive: Catalyze insights
  - Behavioral: Promote post-medication period of cognitive flexibility/metaplasticity that facilitates behavior change
- Psychotherapeutic stance
  - Person-centered principles
  - Non-directive support
  - Integrate insights and experiential understanding into behavior change

VI. MDMA

Overview of Published RCT Evidence

Medication	PTSD RCT Data	Depress-ion RCT Data	Suicida-lity RCT Data	Pain RCT Data	TBI RCT Data	Projected FDA Approval (Indication)	Note
Ketamine	✓	✓	✓	✓✓	-	1970 (Analgesia)	VA/DoD CPGs recommend ketamine for both depression (2022) AND suicidality (2019)
Esketamine	-	✓✓	✓✓	✓	-	2019 (Depression)	Primarily used for depression
MDMA	✓✓	✓✓	-	✓	-	**2024 (PTSD)**	**Strongest evidence for PTSD**
Psilocybin	-	✓	✓	✓	-	~2027 (Depression)	Positive depression and headache RCTs
LSD	-	-	-	✓	-	~2030 (Anxiety)	Primarily anxiety (modern RCTs) and alcohol use disorder (1960s)
DMT (Ayahuasca)	-	✓	-	-	-	~2030+ (Unknown)	IV form being studied for depression
5-MeO-DMT	-	-	-	-	-	~2030+ (Unknown)	Undergoing Phase 1/2 studies
Ibogaine	-	-	-	-	-	~2030+ (Unknown)	Promising PTSD/TBI data in observational studies
Cannabinoids (Various)	✓	-	-	✓	-	1985 (Nausea, Vom.) 2018 (Seizures)	PTSD and pain data is overall equivocal, but strongest evidence is null for both

✓/✓✓ = Strongest Phase **2/3** RCT Data Positive ✓/✓✓ = Strongest Phase **2/3** RCT Data Null - = No RCT Data

Regulatory Timeline

- FDA Breakthrough Therapy designation of MDMA-AT for PTSD in 2017
- All FDA Phase 2-3 clinical trials now complete as of 2022
- FDA approval projected mid-late 2024

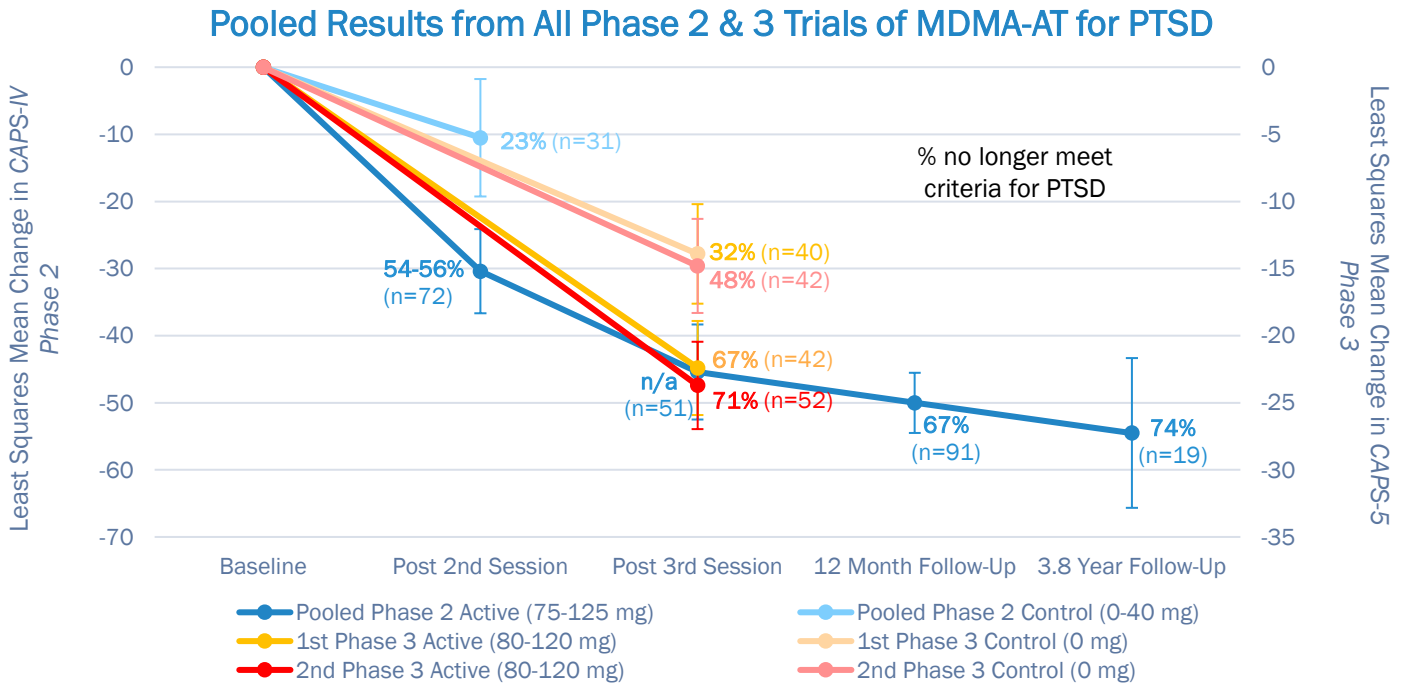
PTSD: Gold Standards Vs MDMA-AT

	Current Gold Standard PTSD Treatments (PE & CPT)	MDMA-Assisted Therapy (MDMA-AT) for PTSD
Loss of PTSD Diagnosis	~34% (28-40%)[1]	~67-71% (54-86%)[2,4,5,6]
Effect Size (Cohen's d, within-group)	~0.94 (0.78-1.10)[1]	~2.03 (1.95-2.10)[5,6]
Dropout Rate	~40% (27-55%)[2,3]	~4.0% (1.9-6.5%)[5,6]
Therapist-Hours per Treatment Course	~12-18	~80*,** (incl. 2-3x 8-hr MDMA sessions & 2 therapists)

* Research settings: 40+ therapist-hours per therapist & 2 therapists. Real-world implementation: likely to be much more efficient & less therapist-hours.
** Group models being studied in Europe for 12 patients & 3 therapists may be able to achieve average of <12 therapist-hours per course of treatment.

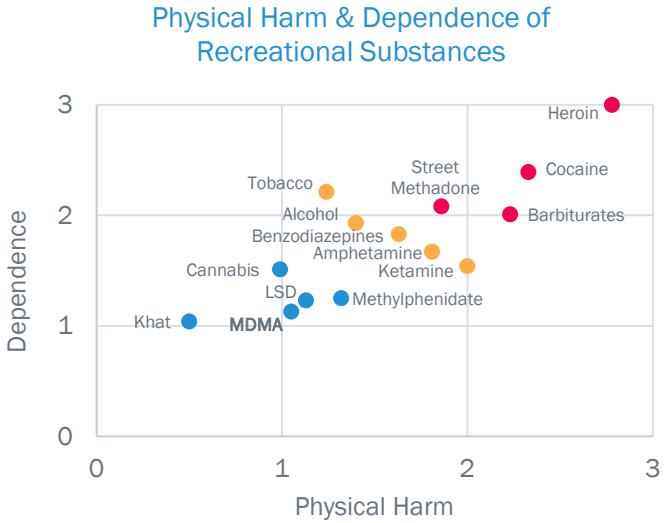
(1. Steenkamp 2015; 2. Mithoefer 2018; 3. Schnurr 2022; 4. Mithoefer 2019; 5. Mitchell 2021; 6. Mitchell 2023)

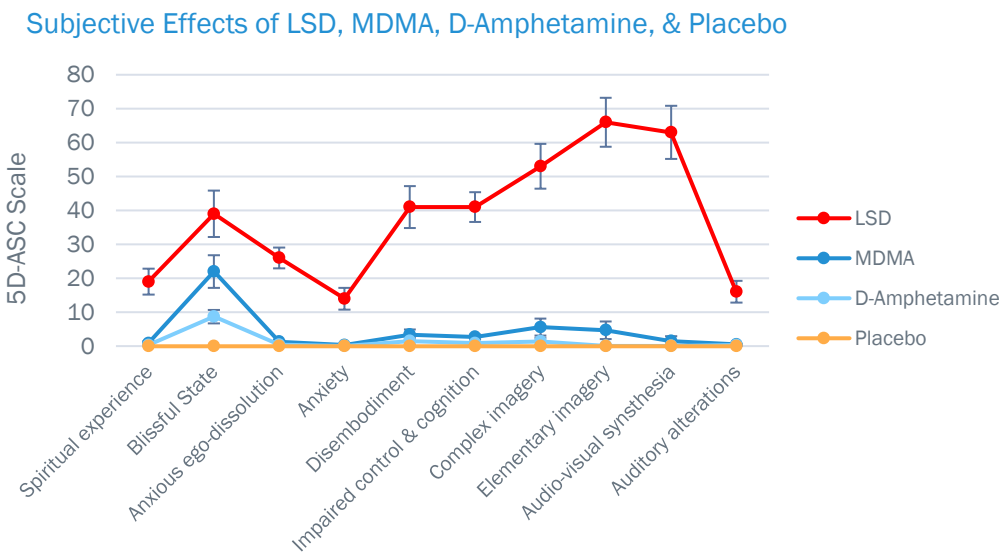
MDMA-AT for PTSD



(Wolfgang et al. in submission, Mitchell 2021 & 2023, Jerome 2020, Mithoefer 2019, Mithoefer 2018, Ot'alora 2018, Oehen 2013, Mithoefer 2011, Kotler unpub., Pacey unpub.)

Safety & Subjective Effects





- MDMA has a **LOW risk** of dependence and harm.
- Subjective effects of **MDMA ≠ other psychedelics**. With MDMA, **cognitive & perceptual lucidity remain intact**.

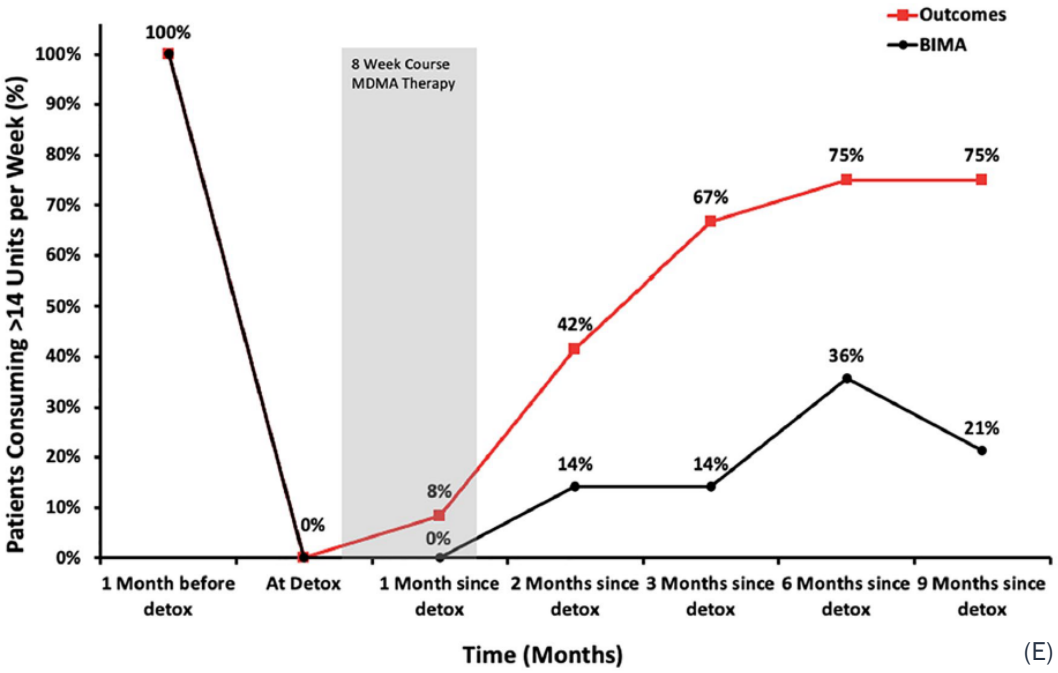
(Wolfgang & Hoge 2023; Wolfgang et al., in submission; Nutt 2007; Holze 2021)

Post-treatment Substance Use

Substance	Between Study Exit & 12-mo Follow-up	Notes
Ecstasy/MDMA	8/83 (10%)	**6/8** had used before the study. **2/2** with no previous use used in non-approved therapeutic setting, found it to be non-therapeutic, and did not use MDMA again.
Alcohol	2/55 (3.6%) Increased 17/55 (31%) No change **22/55 (40%) Decreased**	
Marijuana	10/55 (18%) Increased 6/55 (11%) No change 10/55 (18%) Decreased	

(Jerome 2020)

MDMA-AT Treatment of Alcohol Use Disorder



(E)

(Sessa 2021)

Cost-effectiveness

- Residential Treatment Program (4 weeks): ~$30k
- 3-session course of MDMA-AT in research setting: $~10-40k* depending on how costs are calculated (+/- personnel, space, etc.)
  - *Costs yet unclear in post-approval clinical implementation
- MDMA-AT "provided to patients with **severe or extreme, chronic PTSD** appears to be **cost-saving** while delivering substantial clinical benefit."[1]
- "Third-party payers are likely to **save money** within **three years** by covering this form of therapy."[1]

(Marseille 2021)

VII. Psilocybin

Overview of Published RCT Evidence

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✓/✓✓ = Strongest Phase **2/3** RCT Data Positive ✓/✓✓ = Strongest Phase **2/3** RCT Data Null - = No RCT Data

Regulatory Timeline

- FDA Breakthrough Therapy designation of Psilocybin-assisted therapy for TRD in 2018 and MDD 2019
- First FDA Phase 3 clinical trial currently underway
- FDA approval projected ~2027

ONLINE FIRST

Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer

(JAMA Psych 2010)

Charles S. Grob, MD; Alicia L. Danforth, MA; Gurpreet S. Chopra, MD; Marycie Hagerty, RN, BSN, MA; Charles R. McKay, MD; Adam L. Halberstadt, PhD; George R. Greer, MD

Psilocybin with psychological support for treatment-resistant depression: six-month follow-up

(Psychopharmacology 2018)

R. L. Carhart-Harris[1] · M. Bolstridge[1,2] · C. M. J. Day[1,2] · J. Rucker[1,3,4] · R. Watts[1] · D. E. Erritzoe[1] · M. Kaelen[1] · B. Giribaldi[1] · M. Bloomfield[5] · S. Pilling[6] · J. A. Rickard[7] · B. Forbes[8] · A. Feilding[9] · D. Taylor[10] · H. V. Curran[6,11] · D. J. Nutt[1]

Psilocybin-occasioned Mystical Experiences in the Treatment of Tobacco Addiction

(Curr Drug Abuse Rev. 2014)

Albert Garcia-Romeu, PhD[1], Roland R. Griffiths, PhD[1,2], and Matthew W. Johnson, PhD[1]

Exploratory Controlled Study of the Migraine-Suppressing Effects of Psilocybin

(Neurotherapeutics 2020)

Emmanuelle A. D. Schindler[1,2,3] · R. Andrew Sewell[4,5] · Christopher H. Gottschalk[3] · Christina Luddy[4,5] · L. Taylor Flynn[4,5] · Hayley Lindsey[1,2,3] · Brian P. Pittman[4] · Nicholas V. Cozzi[6,7] · Deepak C. D'Souza[4,5]

Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial

(Psychopharmacology 2016)

Stephen Ross[1,2,3,4,5,6], Anthony Bossis[1,2,4], Jeffrey Guss[1,2,4], Gabrielle Agin-Liebes[10], Tara Malone[1], Barry Cohen[7], Sarah E Mennenga[1], Alexander Belser[8], Krystallia Kalliontzi[2], James Babb[9], Zhe Su[3], Patricia Corby[2] and Brian L Schmidt[2]

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

(Psychopharmacology 2016)

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

Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study

Robin L Carhart-Harris, Mark Bolstridge, James Rucker, Camilla M J Day*, David Erritzoe, Mendel Kaelen, Michael Bloomfield, James A Rickard, Ben Forbes, Amanda Feilding, David Taylor, Steve Pilling, Valerie H Curran, David J Nutt*

(Lancet Psych 2016)

(JAMA Psych 2020)

JAMA Psychiatry | Original Investigation

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder
A Randomized Clinical Trial

Alan K. Davis, PhD; Frederick S. Barrett, PhD; Darrick G. May, MD; Mary P. Cosimano, MSW; Nathan D. Sepeda, BS; Matthew W. Johnson, PhD; Patrick H. Finan, PhD; Roland R. Griffiths, PhD

Trial of Psilocybin versus Escitalopram for Depression

Robin Carhart-Harris, Ph.D., Bruna Giribaldi, B.Sc., Rosalind Watts, D.Clin.Psy., Michelle Baker-Jones, B.A., Ashleigh Murphy-Beiner, M.Sc., Roberta Murphy, M.D., Jonny Martell, M.D., Allan Blemings, M.Sc., David Erritzoe, M.D., and David J. Nutt, M.D.

(NEJM 2021)

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. Páleníček, 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

(NEJM 2022)

(JAMA 2023)

JAMA | Original Investigation

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Figure 3. Comparison of GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores Between the Delayed Treatment and Immediate Treatment Groups

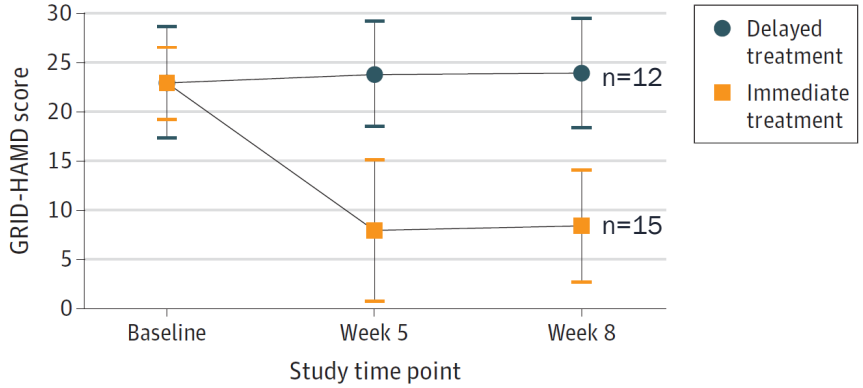
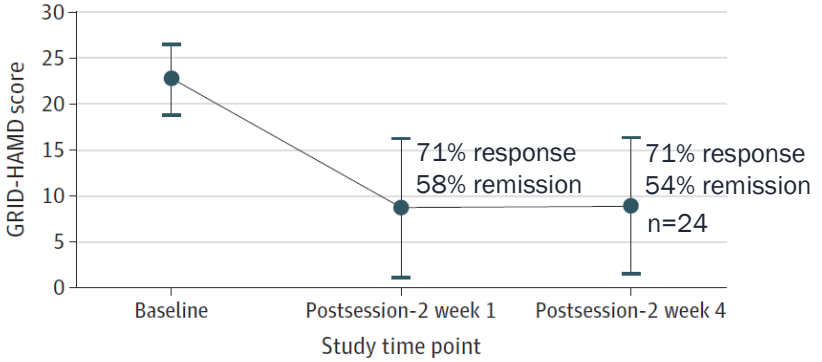


Figure 4. Decrease in the GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores at Week 1 and Week 4 Postsession-2 Follow-up in the Overall Treatment Sample



(Davis et al., JAMA Psych 2020)

Psilocybin (2 doses) v Escitalopram for TRD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trial of Psilocybin versus Escitalopram for Depression

Robin Carhart-Harris, Ph.D., Bruna Giribaldi, B.Sc., Rosalind Watts, D.Clin.Psy., Michelle Baker-Jones, B.A., Ashleigh Murphy-Beiner, M.Sc., Roberta Murphy, M.D., Jonny Martell, M.D., Allan Blemings, M.Sc., David Erritzoe, M.D., and David J. Nutt, M.D.

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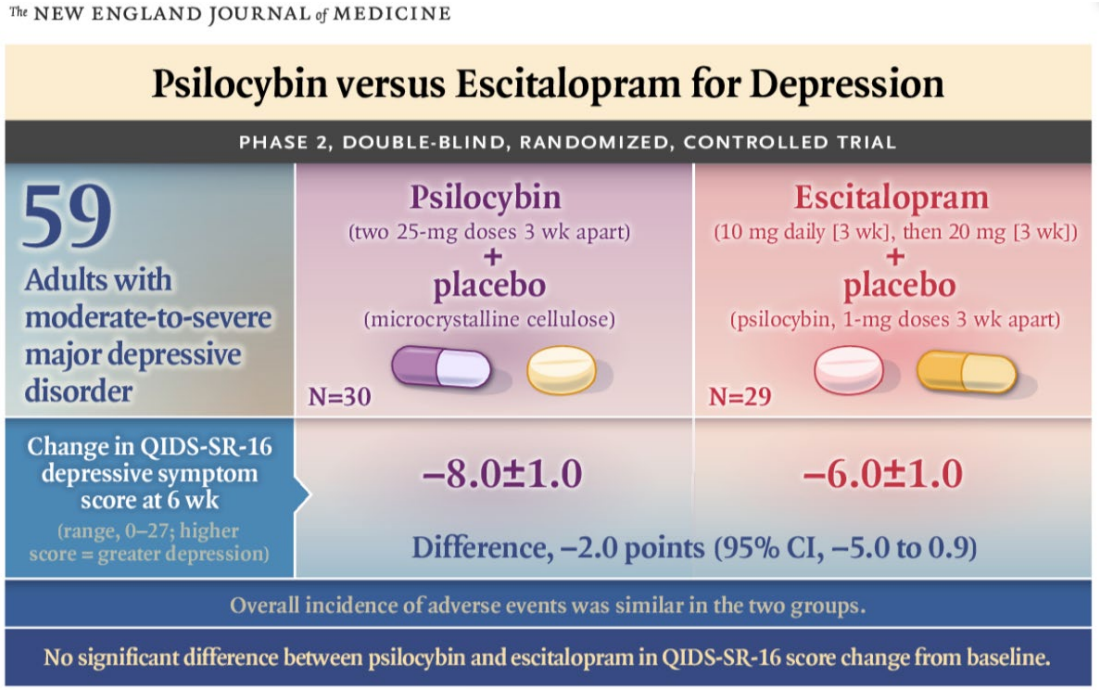


(Carhart-Harris et al., NEJM 2021)

Psilocybin (2 doses) v Escitalopram for TRD

Table 2. Primary and Secondary Outcomes.*

Outcome	Psilocybin (N=30)	Escitalopram (N=29)	Difference (95% CI)†
Primary			
Change in QIDS-SR-16 score at 6 wk — points	−8.0±1.0	−6.0±1.0	−2.0 (−5.0 to 0.9)‡
Secondary			
Depression-related outcomes			
Change in QIDS-SR-14 score from the day before to the day after dosing-day 1 — points	−5.7±0.9	−2.8±0.9	−3.0 (−5.5 to −0.4)
QIDS-SR-16 response at 6 wk — no. (%)§	21 (70)	14 (48)	22 (−3 to 48)
QIDS-SR-16 remission at 6 wk — no. (%)¶	17 (57)	8 (28)	28 (2 to 54)
Change in HAM-D-17 score at 6 wk — points	−10.5±1.0	−5.1±1.0	−5.3 (−8.2 to −2.4)
Change in MADRS score at 6 wk — points	−14.4±1.7	−7.2±1.7	−7.2 (−12.1 to −2.4)
Change in BDI-1A score at 6 wk — points	−18.4 (−22.6 to −13.8)	−10.8 (−14.3 to −7.3)	−7.6 (−13.3 to −1.8)
Change in WEMWBS score at 6 wk — points	15.4±1.9	7.3±1.9	8.1 (2.6 to 13.5)
Change in FS score at 6 wk — points	14.4±1.7	9.0±1.7	5.4 (0.5 to 10.3)
Change in STAI score at 6 wk — points	−17.6±2.2	−8.5±2.2	−9.0 (−15.2 to −2.8)
Change in BEAQ score at 6 wk — points	−10.5±2.2	−1.0±2.3	−9.5 (−15.9 to −3.1)
Change in WSAS score at 6 wk — points	−9.7±1.7	−3.8±1.7	−5.8 (−10.7 to −1.0)
Change in SHAPS score at 6 wk — points	−4.7±0.6	−2.5±0.6	−2.2 (−3.8 to −0.6)
Change in SIDAS score at 6 wk — points	−2.0 (−4.3 to 0.0)	−0.8 (−3.4 to 2.0)	−1.3 (−6.5 to −0.3)
PRSexDQ score at 6 wk	0 (0 to 0)	3 (0 to 7)	−2 (−4 to 0)
LEIS score at 6 wk	4.1±0.9	−2.2±1.0	6.3 (3.6 to 9.0)

* Changes in scores represent the mean change from baseline and are reported as mean ±SE, except for the changes in the BDI-1A and Suicidal Ideation Attributes Scale (SIDAS) scores, which are reported as mean (95% confidence interval). The PRSexDQ score at 6 weeks is reported as mean ±SE, and the LEIS score at 6 weeks is reported as mean (95% confidence interval). Scores range from 0 to 60 on the Montgomery and Asberg Depression Rating Scale (MADRS), from 20 to 80 on the Spielberger's Trait Anxiety Inventory (STAI), from 15 to 90 on the Brief Experiential Avoidance Questionnaire (BEAQ), from 0 to 40 on the Work and Social Adjustment Scale (WSAS), from 0 to 14 on the Snaith Hamilton Anhedonia Pleasure Scale (SHAPS), and from 0 to 50 on the SIDAS; greater reductions from baseline on all of these scales indicate greater reductions in symptom severity or impairment. Scores on the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ) range from 0 to 15, with higher scores indicating greater dysfunction. Scores ranges from 14 to 70 on the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) and from 8 to 56 on the Flourishing Scale (FS) range; greater increases from baseline on these scales indicate greater improvements. Scores on the Laukes Emotional Intensity Scale (LEIS) range from −34 to +34, with positive scores indicating an increased intensity of emotional responsiveness and negative scores a reduced intensity of emotional responsiveness. The analysis of each efficacy outcome was generated from statistical models, as described in the statistical analysis plan, available in the protocol. All values shown were adjusted for the baseline value. Unadjusted values are provided in Table S12 in the Supplementary Appendix.

(Carhart-Harris et al., NEJM 2021)

Psilocybin (1 dose) for TRD

The NEW ENGLAND JOURNAL of MEDICINE

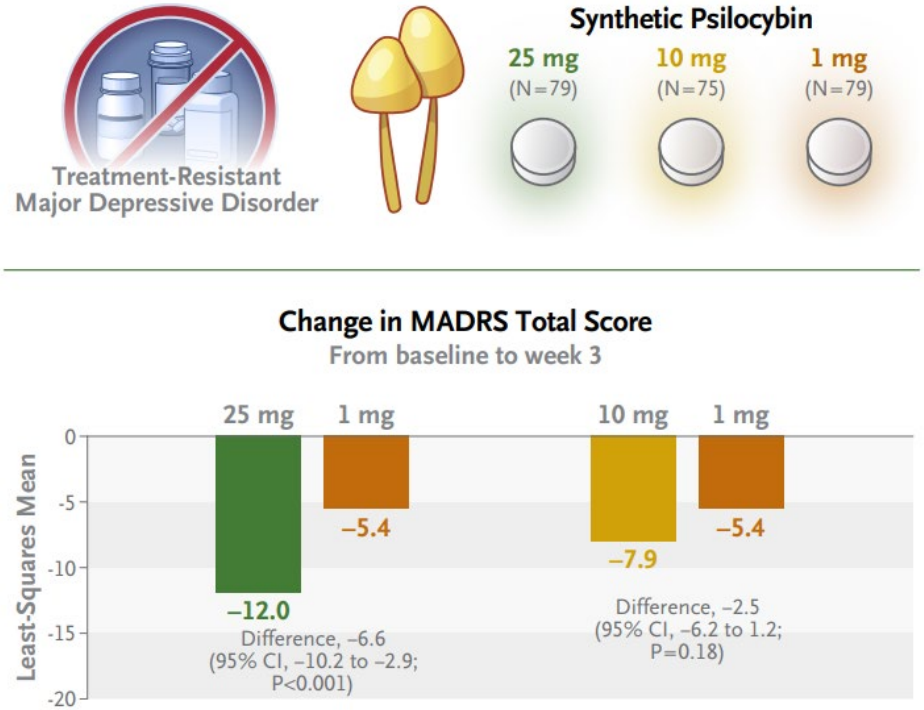
ESTABLISHED IN 1812 NOVEMBER 3, 2022 VOL. 387 NO. 18

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. Páleníček, 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

(Goodwin et al., NEJM 2022)

Psilocybin (1 dose) for TRD



(Goodwin et al., NEJM 2022)

Psilocybin (1 dose) for TRD

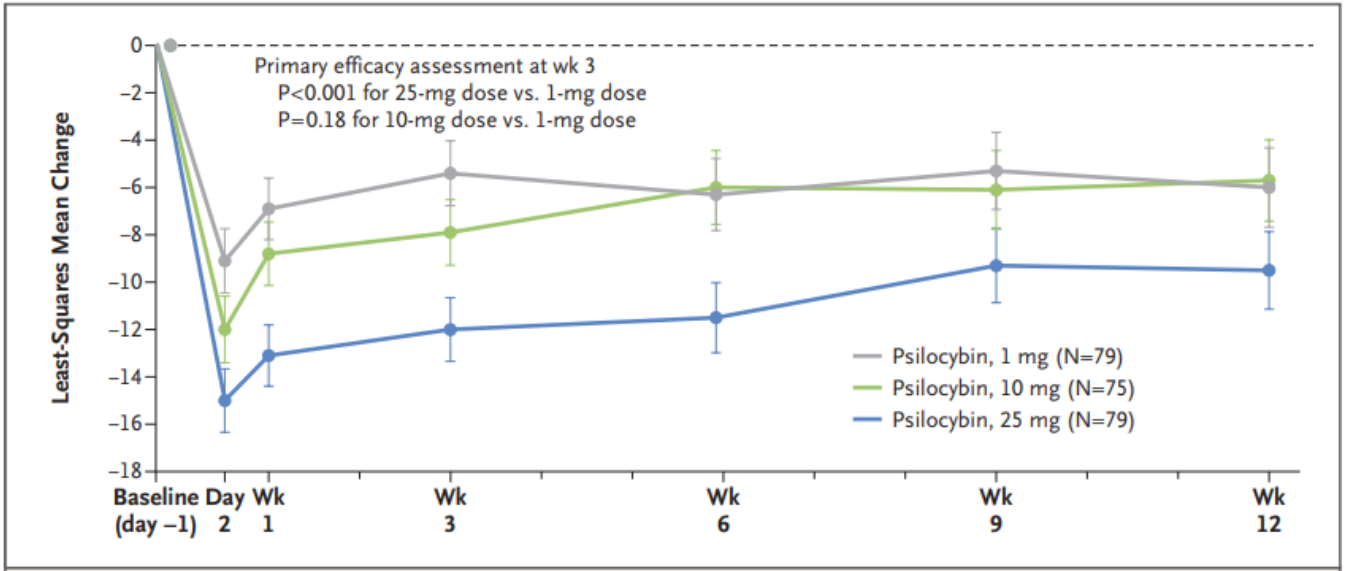
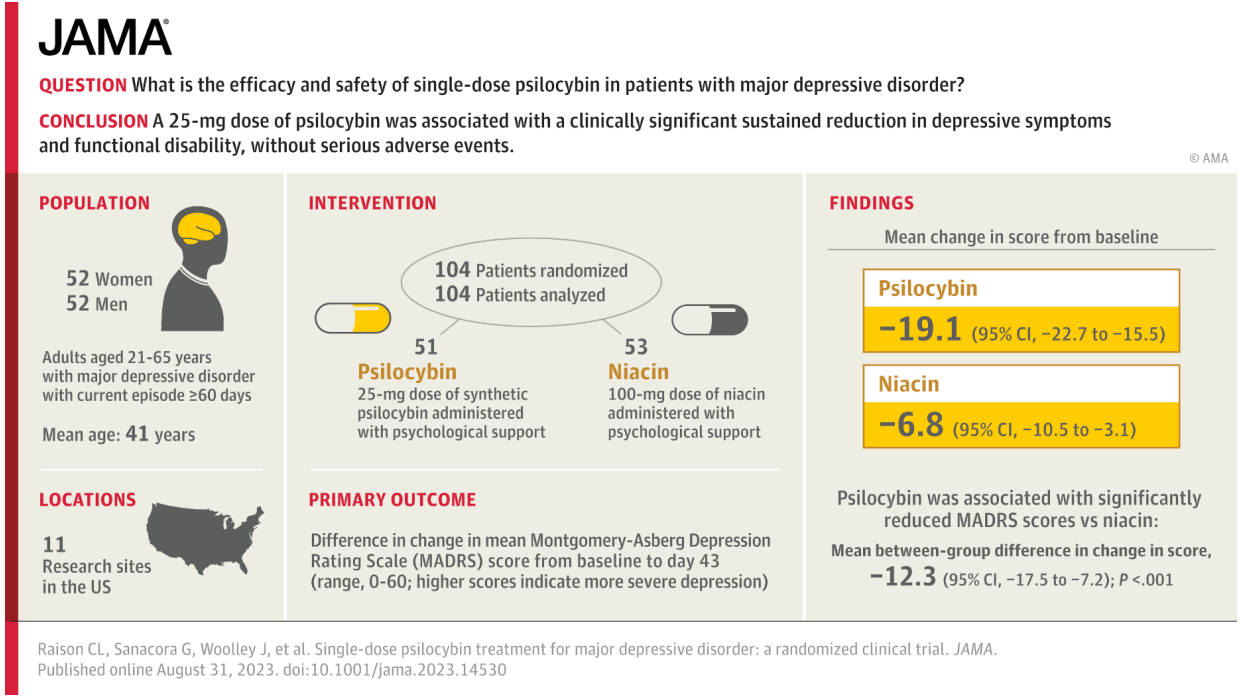


Figure 2. Change from Baseline in MADRS Total Score (Modified Intention-to-Treat Population).

Total scores on the Montgomery–Åsberg Depression Rating Scale (MADRS) range from 0 to 60, with higher scores indicating greater severity of depression. I bars represent standard errors.

(Goodwin et al., NEJM 2022)

Psilocybin (1 dose) for MDD



- Sustained remission at day 43: 42% (psilocybin) vs 11% (placebo)

(Raison et al., JAMA 2023)

Psilocybin for PTSD or TBI

- 2 small open-label studies of psilocybin for PTSD currently underway. Several other studies earlier in development.
- No studies of psilocybin yet for TBI

VIII. Ibogaine & 5-MeO-DMT

Ibogaine + 5-MeO-DMT for SOF Veterans

- All are uncontrolled observational studies, *not* clinical trials
- Protocol. Day 1: Group preparation. Day 2: Ibogaine (10 mg/kg oral). Day 3: 5-MeO-DMT (3-5 inhaled doses: 5 mg, 15 mg, 30 mg, [30 mg], [45 mg])
- Study #1 (2020)[1]
  - Retrospective Observational
  - n = 51 (of 65)
  - Suicidal ideation*
  - Symptoms of PTSD,* depression,* & anxiety*
  - Cog. impairment*
  - Psychological flexibility*
- Study #2 (2023)[1]
  - Prospective Observational
  - n = 86
  - Symptoms of PTSD,* depression,* anxiety,* & insomnia*
  - Cognitive functioning*
  - Post-concussive symptoms*
- Study #3 (2023)[1]
  - Prospective Observational
  - n = 45 (of 86)
  - Alcohol use*

* = statistically significant difference ($p<0.05$) pre vs post treatment

(Davis et al., 2020; Davis et al., 2023; Armstrong et al., 2023)

Ibogaine for Veterans with TBI

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

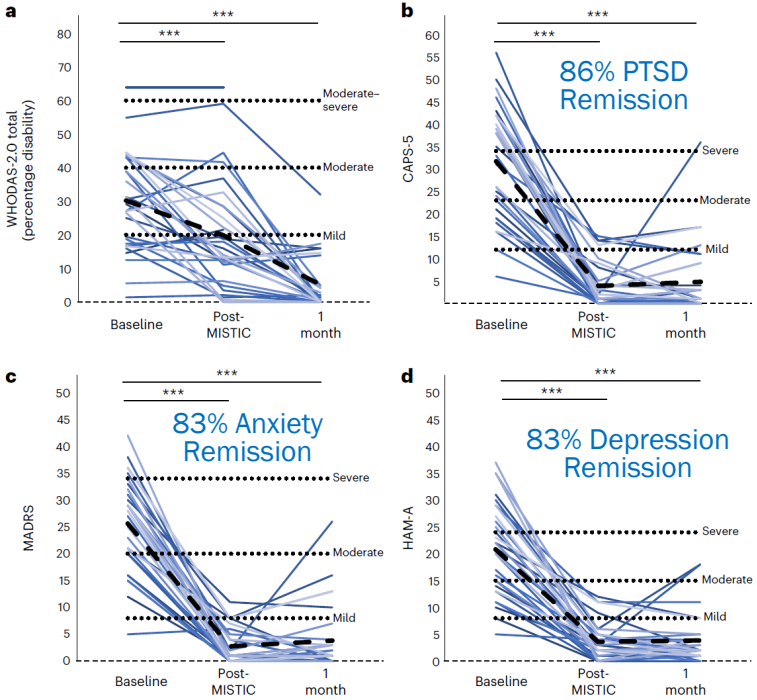
Published online: 05 January 2024

Check for updates

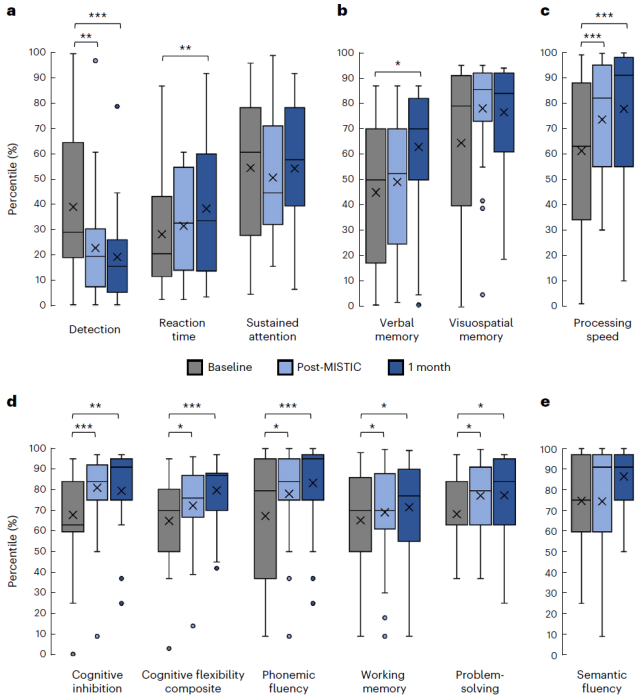
Kirsten N. Cherian[1,8], Jackob N. Keynan[1,8], Lauren Anker[1], Afik Faerman[1], Randi E. Brown[2], Ahmed Shamma[1], Or Keynan[1], John P. Coetzee[1,3], Jean-Marie Batail[1], Angela Phillips[1], Nicholas J. Bassano[1], Gregory L. Sahlem[1], Jose Inzunza[4], Trevor Millar[4], Jonathan Dickinson[4], C. E. Rolle[1], Jennifer Keller[1], Maheen Adamson[5,6], Ian H. Kratter[1,9] & Nolan R. Williams[1,7,9]

(Cherian et al., 2023)

Ibogaine for Veterans with TBI

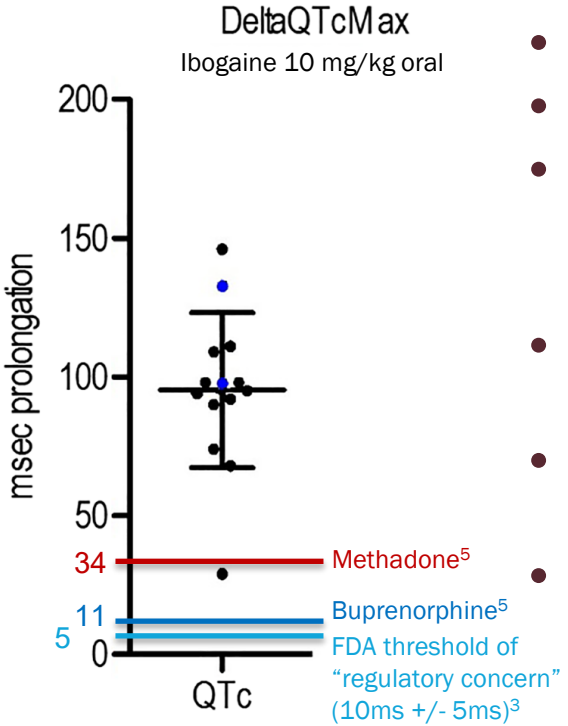


Remission rates at 1 month



Neuropsychological Testing (Cherian et al., 2023)

Ibogaine & Cardiac Safety



- 38 deaths associated with ibogaine[1]
- Ibogaine is a potent hERG blocker ⟶ ↑risk of TdP & death[1]
- 14 OUD subjects post-detox given ibogaine 10 mg/kg po (Fig)[2]
  - 7/14 (50%) with QTc prolongation >500ms = ↑risk of TdP & death
  - ΔQTcMax = 95ms (5ms is FDA threshold for "regulatory concern"[3])
- QT prolongation is the most common reason for removal from drug development[4]
- Of the psychedelics discussed today, ibogaine is least likely to be FDA-approved.
- Potential alternatives: Mg-ibogaine, analogues/derivatives (tabernanthalog), and/or active metabolites (noribogaine)

(1. Kock et al., J Sub Abuse Treat 2022; 2. Knuijver et al., Addiction 2022; 3. ICH 14 FDA Guidance; 4. Haigney, KY Ibogaine Commission Testimony 2023; 5. Wedam et al., JAMA Int Med 2007)

X. Summary & Conclusion

Summary: Overview of Published RCT Evidence

Medication	PTSD RCT Data	Depress-ion RCT Data	Suicida-lity RCT Data	Pain RCT Data	TBI RCT Data	Projected FDA Approval (Indication)	Note
Ketamine	✓	✓	✓	✓✓	-	1970 (Analgesia)	VA/DoD CPGs recommend ketamine for both depression (2022) AND suicidality (2019)
Esketamine	-	✓✓	✓✓	✓	-	2019 (Depression)	Primarily used for depression
MDMA	✓✓	✓✓	-	✓	-	**2024 (PTSD)**	**Strongest evidence for PTSD**
Psilocybin	-	✓	✓	✓	-	**~2027 (Depression)**	**Positive depression and headache RCTs**
LSD	-	-	-	✓	-	~2030 (Anxiety)	Primarily anxiety (modern RCTs) and alcohol use disorder (1960s)
DMT (Ayahuasca)	-	✓	-	-	-	~2030+ (Unknown)	IV form being studied for depression
5-MeO-DMT	-	-	-	-	-	**~2030+ (Unknown)**	**Undergoing Phase 1/2 studies**
Ibogaine	-	-	-	-	-	**~2030+ (Unknown)**	**Promising PTSD/TBI data in observational studies**
Cannabinoids (Various)	✓	-	-	✓	-	1985 (Nausea, Vom.) 2018 (Seizures)	PTSD and pain data is overall equivocal, but strongest evidence is null for both

✓/✓✓ = Strongest Phase 2/3 RCT Data Positive ✓/✓✓ = Strongest Phase 2/3 RCT Data Null - = No RCT Data

Summary

- NDAA 2024 authorizes studies of psychedelics for AD SMs
- VA already conducting & will now fund studies of MDMA & psilocybin for PTSD & depression
- Projected timeline for potential FDA approvals: MDMA-AT for PTSD (2024), psilocybin-AT for TRD & MDD (~2027), all others (2030+)
- 3 Core Principles
  - Illicit drugs ≠ pharmaceutical-grade psychedelics
  - Paradigm shift: chronic medications ⟶ medication-assisted therapy
  - Psychedelic-assisted therapy ≈ anesthesia-assisted procedure
- Psychedelics can promote neuritogenesis, metaplasticity, reopening critical periods of learning, and cognitive flexibility
- Psychedelics have a low risk of harm (except ibogaine) & dependence
- MDMA-AT is highly efficacious for PTSD (67-71% no longer diagnosable); psilocybin highly efficacious for TRD/MDD (~60% remit); effects are durable for both
- In addition to costs/benefits of access, must also consider costs/benefits of no access

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Questions?

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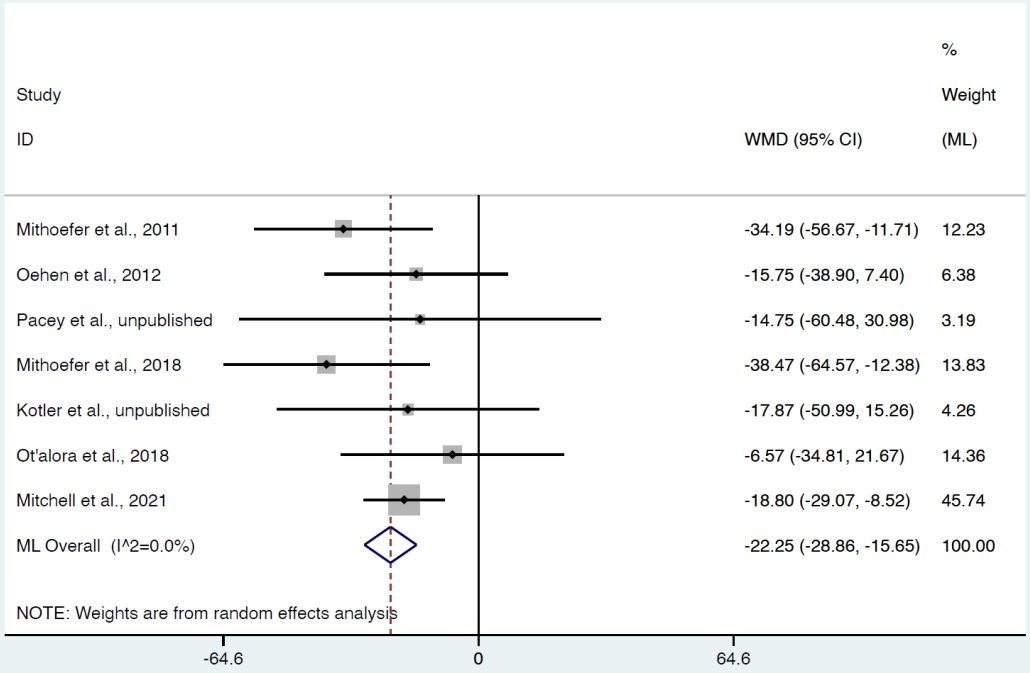
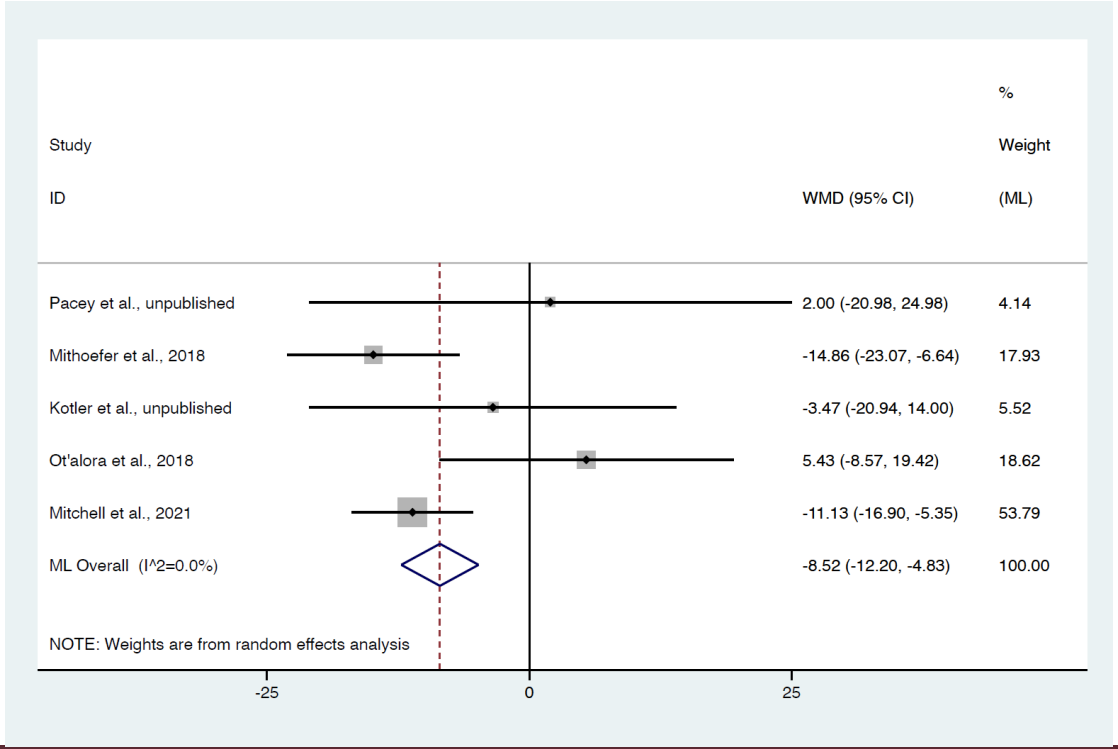
PTSD (CAPS-IV/5) Significantly Improves



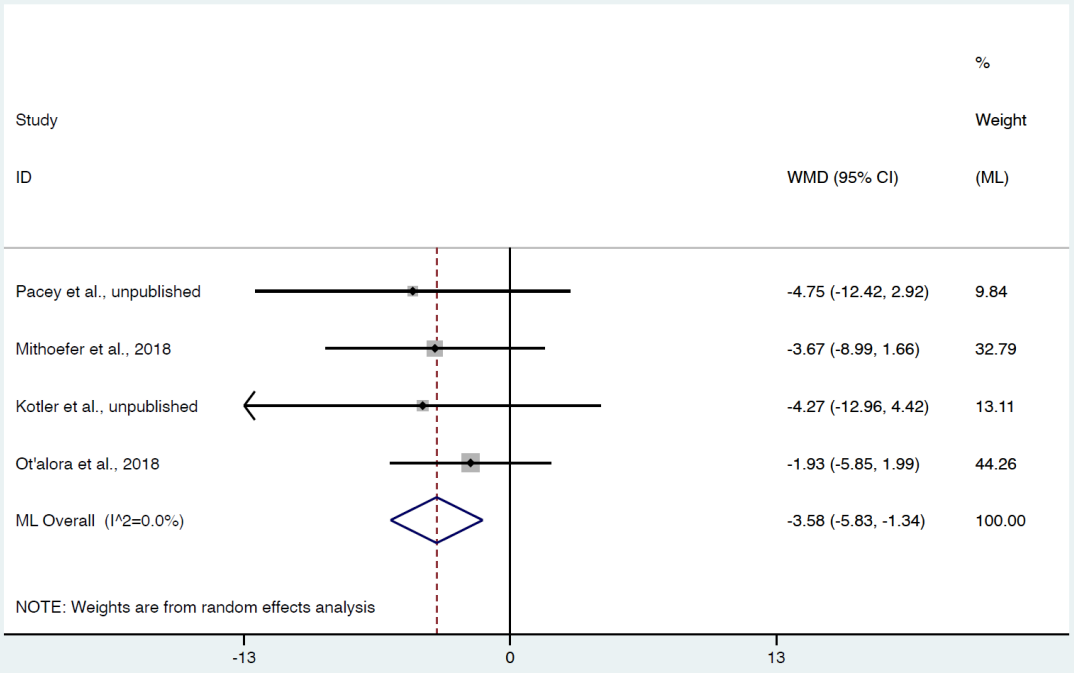
(Wolfgang et al. in prep)

Comorbid Depression (BDI-II) Significantly Improves



(Wolfgang et al. in prep)

Comorbid Insomnia (PSQI) Significantly Improves



(Wolfgang et al. in prep)

Background/Summary:
Ketamine for Depression & Suicidality

IV Ketamine for Depression

The NEW ENGLAND JOURNAL of MEDICINE

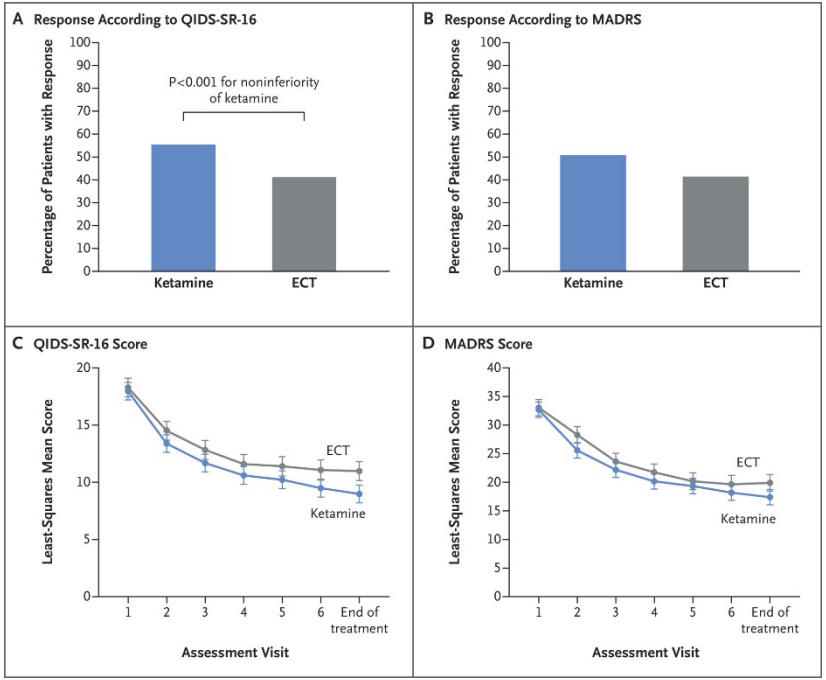
ESTABLISHED IN 1812 JUNE 22, 2023 VOL. 388 NO. 25

Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression

A. Anand, S.J. Mathew, G. Sanacora, J.W. Murrough, F.S. Goes, M. Altinay, A.S. Aloysi, A.A. Asghar-Ali, B.S. Barnett, L.C. Chang, K.A. Collins, S. Costi, S. Iqbal, M.K. Jha, K. Krishnan, D.A. Malone, S. Nikayin, S.E. Nissen, R.B. Ostroff, I.M. Reti, S.T. Wilkinson, K. Wolski, and B. Hu

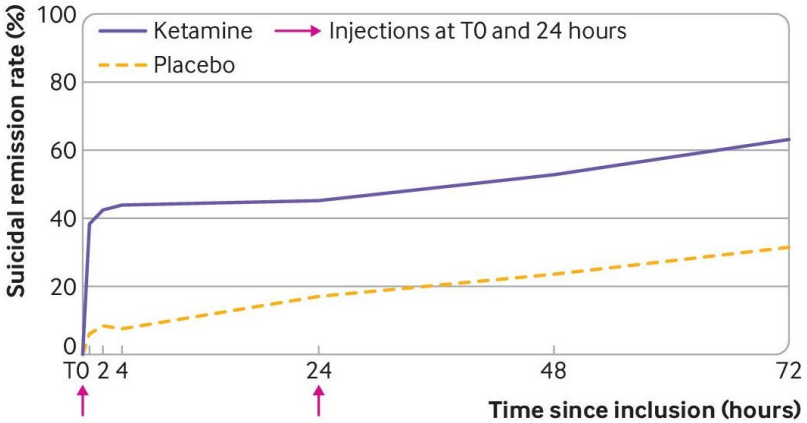
CONCLUSIONS

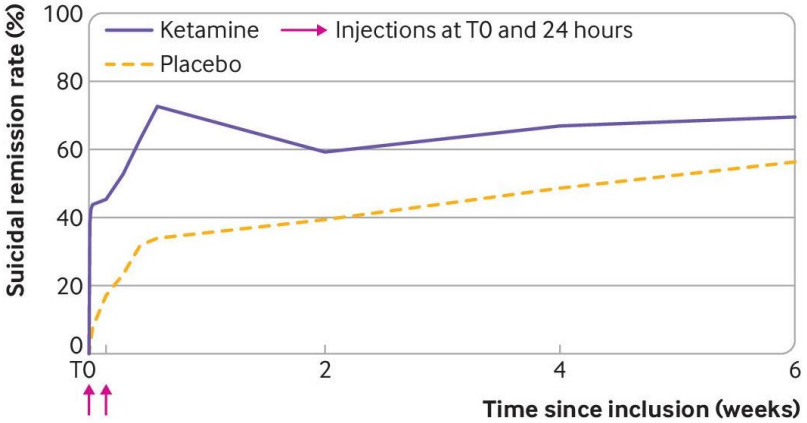
Ketamine was noninferior to ECT as therapy for treatment-resistant major depression without psychosis. (Funded by the Patient-Centered Outcomes Research Insti-



(Anand A et al 2023)

IV Ketamine for Suicidality



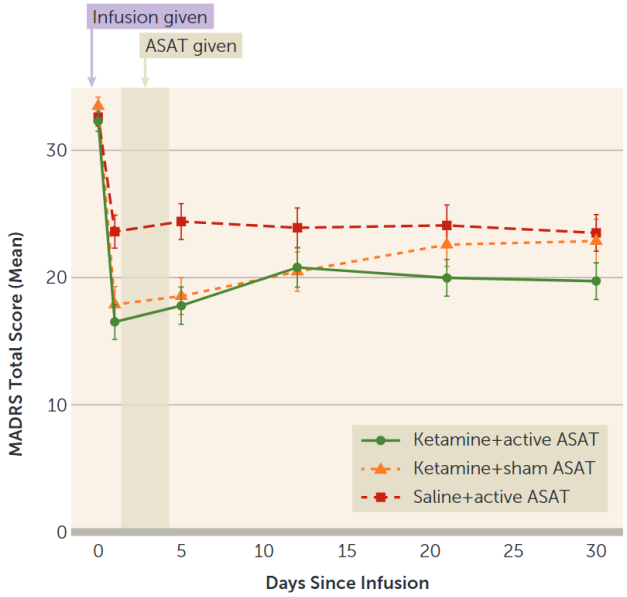


- Remission at day 3: 63% (active) vs 32% (placebo)
- Remission at week 6: 70% (active) vs 56% (placebo) [p>0.05]

(Abbar M et al 2022)

Ketamine-Assisted Therapy

FIGURE 2. Depression severity scores in a randomized controlled trial of ketamine and automated self-association training (ASAT), by treatment allocation and days since infusion[a]



[a] Ketamine+active ASAT, N=53; ketamine+sham ASAT, N=50; saline+active ASAT, N=51. Error bars indicate standard error of the mean.

- Combining ketamine with therapy sustains long-term antidepressant effects
- Paradigm Shift
  - Ketamine ⟶ Ketamine-Assisted Therapy
- Logistical considerations and physical space requirements similar between ketamine-assisted therapy and MDMA-assisted therapy

(Price RB et al 2022)

IV Ketamine in DoD/VA Clinical Practice Guidelines

- Ketamine now recommended in the DoD/VA Clinical Practice Guidelines for both Suicidality (2019) *and* Treatment-Resistant Depression (2022)
  - Only other pharmacotherapy recommended in DoD/VA CPGs for suicidality are lithium & clozapine; neither are compatible with AD service
  - Whereas a time-limited course of ketamine is the only recommended treatment for suicidality that *is* compatible with AD service
- VA now has national protocol to implement ketamine for suicidality & treatment-resistant depression across entire VA
- Yet, ketamine is *not* systematically implemented in the DoD for either suicidality or treatment-resistant depression