



Unlocking the Doors of Depression: *Neuroplastic and Psychedelic Therapies in MDD*

MasterClass

Faculty

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Faculty Disclosures

- **Andrew Penn, MS, PMHNP-BC:** Advisory Board—Alkermes PLC, Definium Therapeutics, NACCME, Osmind, Otsuka, Tactogen; Consultant—1440 Foundation, Alkermes PLC, Board of Psychedelic Medicine and Therapies, California Institute of Integral Studies, Compass Pathways, Fireside Project, Luciem, NACCME, Otsuka; Employee—UCSF, Salma Health; Grant/Research Support—Filament, MAPS, Usona
- **Charles L. Raison, MD:** Consultant—Usona Institute, AbbVie, Otsuka, Eli Lilly; Grant/Research Support—Tiny Blue Dot Foundation, Vail Health Foundation, ARPA-H

Disclosures

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Learning Objectives

- Describe glutamatergic and serotonergic pathways to neuroplasticity in MDD
- Differentiate investigational serotonergic psychedelics from traditional serotonergic antidepressants and novel glutamatergic antidepressants in MDD
- Evaluate neurobiological and clinical evidence associated with investigational serotonergic psychedelics and their potential therapeutic role in MDD
- Assess current movements towards psychedelic-assisted psychotherapies in MDD

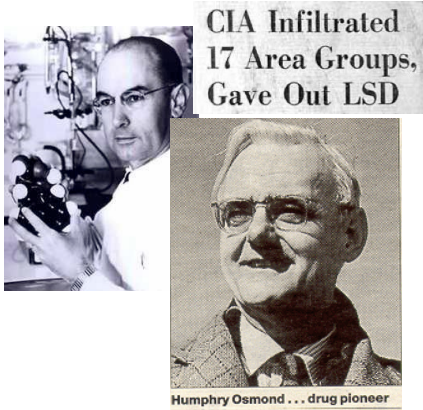
Psychedelics in Psychiatry

Andrew Penn

Psychedelics – 1943 to Today



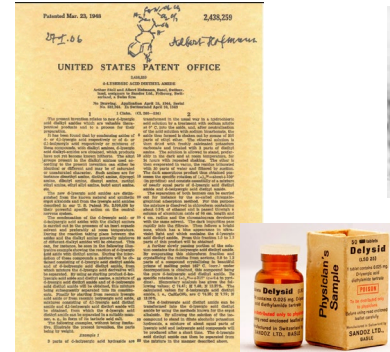
Premodern
Use



Discovery and Research



Thalidomide
Crisis/ Kefauver-Harris Act /



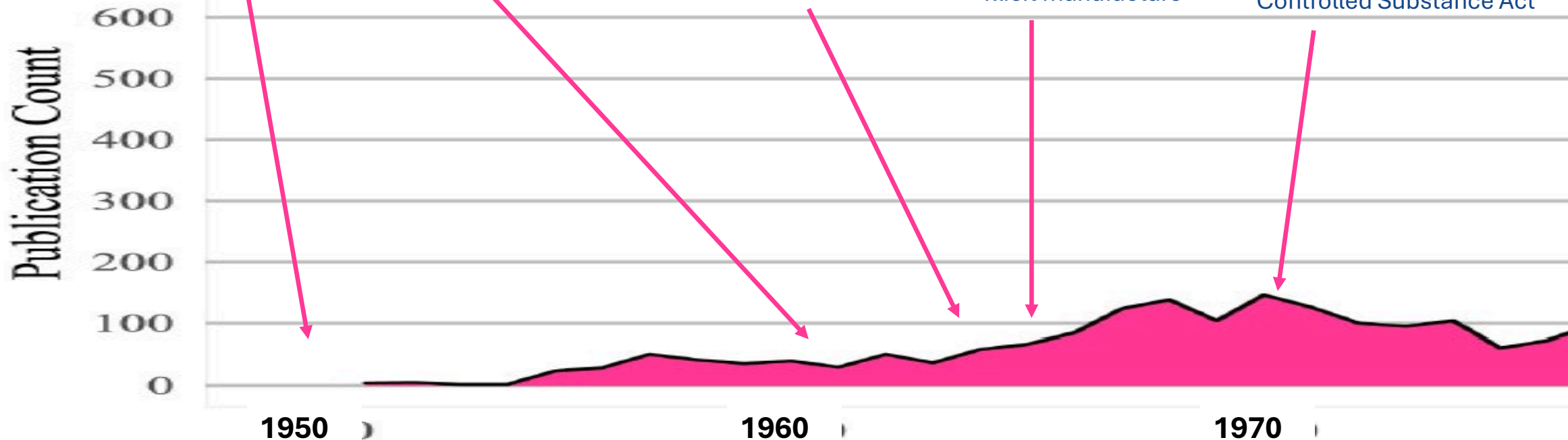
LSD Patent/Sandoz
stops manufacture



Youth culture/
Illicit manufacture



Backlash/
Controlled Substance Act



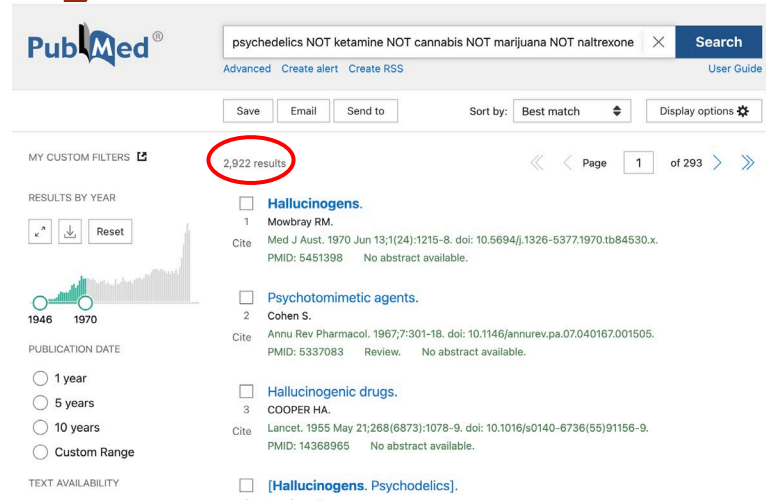
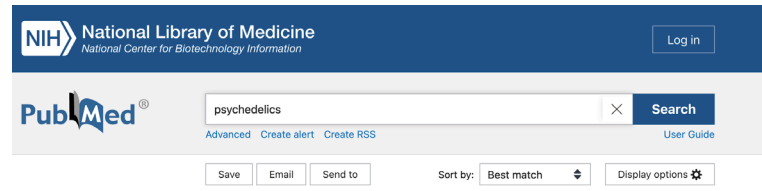
No, there weren't thousands of clinical trials on psychedelics in the 50's and 60's

1946-1970 (27y)

2922 papers

68 Clinical trials

1 RCT

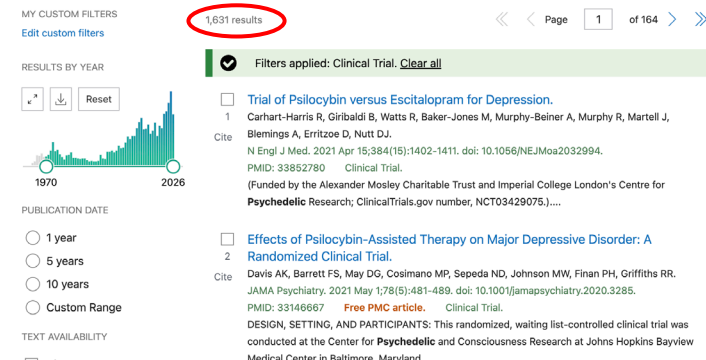
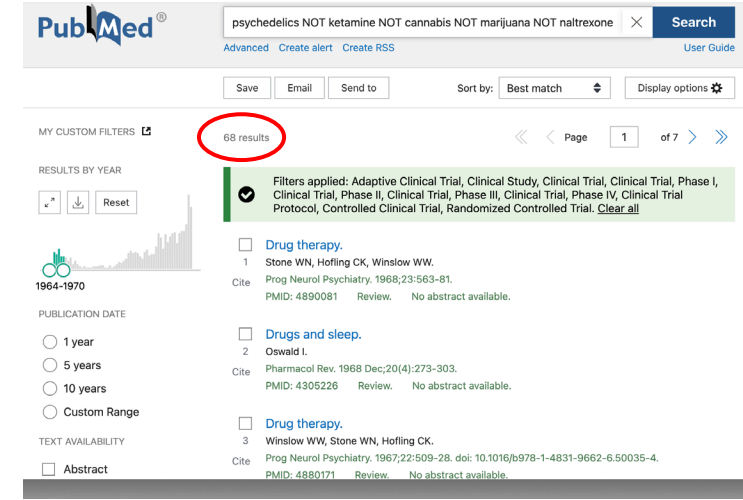
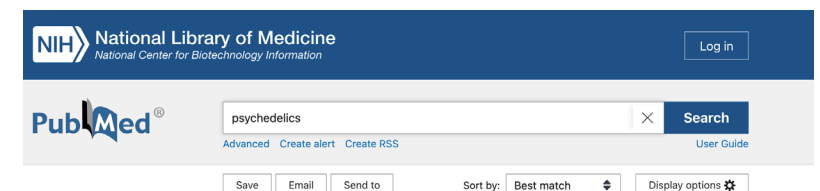
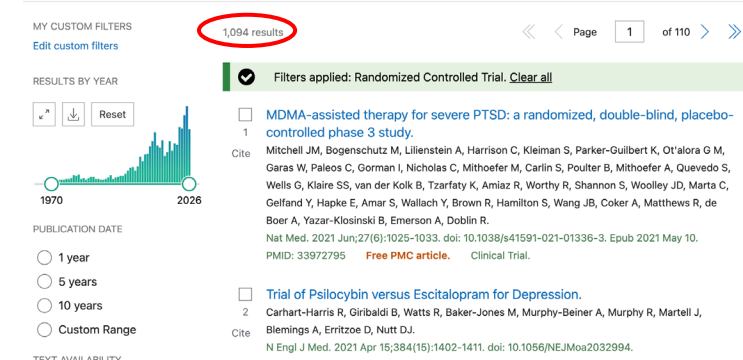


1970-2026 (32y)

33,378 papers

1631 Clinical trials

1094 RCT's



Pre-prohibition “trials” were mostly case reports, small studies, and basic science

The Effects of LSD-25 on Creativity and Tolerance to Regression

Leonard S. Zegans, MD; John C. Pollard, MD; and Douglas Brown, MS, New Haven, Conn

IN RECENT years, the interest shown by behavioral scientists in creativity has reflected what has for a long time been a popular preoccupation.¹⁻⁶ Willing authors have come forward, informing us how to acquire it, whether we must be neurotic to use it, and how to discover if we have that “divine fire.” Attempts have been made to define

emerged an outline of characterological and cognitive traits related to the ability to do creative work.^{5,13-15}

Recently there has been a growing interest in the manner in which physiological and environmental conditions interact with personality factors in facilitating or hindering creative productivity. A few of the factors considered have been the immediate physi-

structed to refrain from eating within two hours of reporting for the experiment. This was requested so that the differences in absorption of the drug could be minimized.

Two subjects were tested at each session. Upon arrival each subject was introduced to his tester and the first battery of tests was given. Certain physiological measures were also taken at this time (blood pressure and pulse rate). Upon completion of the first half of the test, each subject was given a glass of distilled water. A dose equal to 0.57/kg body weight was added to the water of those randomly selected to receive LSD-25. Nineteen subjects received LSD and 11 did not. The subject following ingestion was escorted to the lounge where he could read or relax while waiting for two hours to elapse before he would be retested. Immedi-

Method

Subjects.—Thirty-one subjects, all males, 21 years of age or older were selected from a pool of 50 such volunteers. They did not know prior to volunteering for this experiment that psychoactive drugs were to be used. All were paid for their participation. The amount paid to the subjects was not in any way related to their performance of whether or not they received the active drug. A candidate was rejected if he displayed any obvious psychological or physical contraindications to his participation. Fourteen subjects were rejected at this state. The remaining subjects were seen by a clinical psychologist and given a battery of projective tests, consisting of a Rorschach, Holtzman, and Min-

LSD and Chromosomes

A Controlled Experiment

Joe-Hin Tjio, PhD; Walter N. Pahnke, MD, PhD; and Albert A. Kurland, MD

The chromosomes of lymphocytes were studied in 32 patients before and after they took lysergic acid diethylamide (LSD) as part of double-blind, controlled research of the effects of the drug in psychotherapy and in five black-market LSD users who volunteered to take pure LSD in a research setting. Statistical analysis revealed no significant difference between the before- and after-LSD chromosomal aberration rates. In addition, a post-LSD study of eight normal subjects who had received LSD in previous research experiments was also performed with the same cytogenetic methods. The results of these ex-

Thus far, in studies in vivo, Hungerford et al¹¹ and Abuzzahab et al (unpublished data) have attempted to control this factor by analyzing WBC chromosomes both before and after LSD had been taken. No long-term chromosomal changes were demonstrated in either study, but the findings did not agree completely in regard to transient changes. In each project only a small group of patients was studied. ing a prospective study in the Institute.

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A Controlled Comparison of Lysergic Acid Diethylamide (LSD) and Dextroamphetamine in Alcoholics

BY LEO E. HOLLISTER, M.D., JACK SHELTON, M.D., AND GEORGE KRIEGER, M.D.

Seventy-two alcoholic patients were admitted to a controlled comparison of LSD and dextroamphetamine as treatments. In the context of little associated psychotherapeutic intervention, LSD produced slightly better results early, but after six months the results were alike for both treatment groups. Controlled studies of such treatments are not only possible but mandatory, the authors conclude, if one is not to be misled into ascribing special therapeutic attributes to a specific treatment.

tients(5). Single doses of 200 µg. of LSD were given to 68 chronic alcoholics, 26 of whom attained sobriety during an average follow-up period of 38 weeks. Personality factors were explored during the drug-induced state(4). Doses of 400 to 1500 µg. were used along with psychotherapy for 61 alcoholics followed for three to 18 months. Thirty were much improved, while 16 showed some degree of improvement(3).

An attempt to replicate the work of the Saskatchewan group, which has reported the most outstanding results, using a situa-

LYSERGIC ACID DIETHYLAMIDE AS A VARIABLE IN THE HOSPITAL TREATMENT OF ALCOHOLISM

A FOLLOW-UP STUDY

WILLIAM T. BOWEN, M.S.W., ROBERT A. SOSKIN, Ph.D., AND JOHN W. CHOTLOS, Ph.D.¹

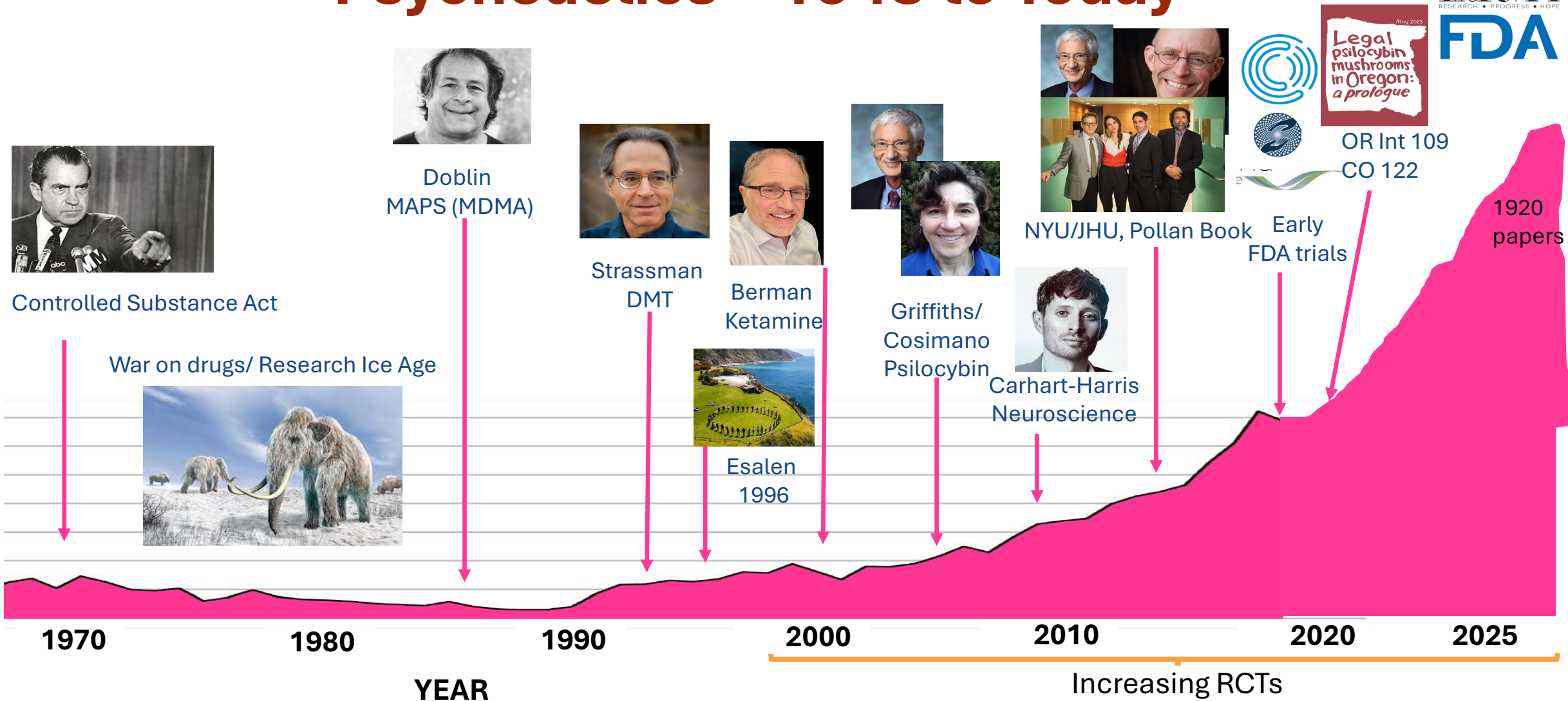
The use of lysergic acid diethylamide (LSD) in the treatment of alcoholism has led to many claims as to the drug's efficacy, but without a controlled study of both in-hospital application and posthospital adjustment of patients. The present paper is concerned with the use of LSD in placebo and maximum dosages as a concomitant of a Human Relations Training Laboratory treatment program. Patients receiving LSD were also compared with patients completing the Laboratory program but not receiving LSD. Findings were such as to indicate that the long term gains through use of LSD are negligible. A successful post-treatment adjustment seems more closely associated with pretreatment employment level, marital status, and whether or not the patient completes the treatment program.

Arch Gen Psychiat—Vol 16, June 1967

Zegans LS, Pollard JC, Brown D. Arch Gen Psychiatry. 1967;16(6):740–749; Tjio J, Pahnke WN, Kurland AA. JAMA. 1969;210(5):849–856; BOWEN, WILLIAM T. et al., 150(2):p 111-118, February 1970.

Hollister, L. E., Shelton, J., & Krieger, G. (1969). *The American journal of psychiatry*, 125(10), 1352–1357.

Psychedelics – 1943 to Today



What's in a Name?

“Anxious
Neurosis”
”Melancholia”
“Alcoholic”

“Shell Shock”

“Rape Trauma
Syndrome/ Post-
Vietnam Syndrome”

Major Depressive Disorder
Generalized Anxiety Disorder
PTSD
Substance abuse/ dependence

Substance use disorder

Phantastica (19thC)
Hallucinogen

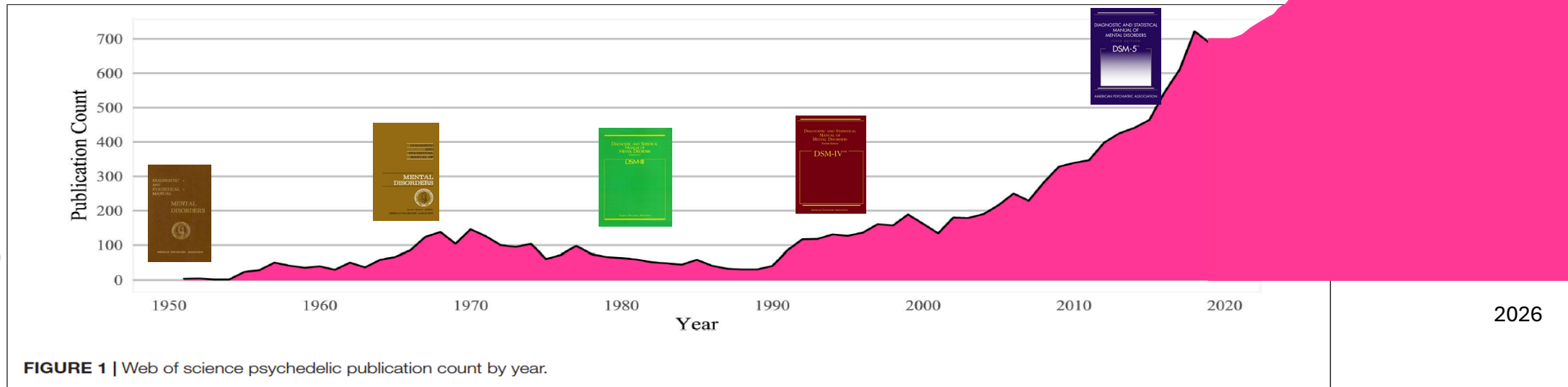
Psychotomimetic

Psychedelic/Phanerothyme
Hallucinogen

Psychedelic

Neuroplastogen

DSM-I: 1952
DSM-II: 1968
DSM-III: 1980
DSM-III-R: 1987
DSM-IV: 1994
DSM-IV-TR: 2000
DSM-5: 2013
DSM-5-TR: 2022



Psychedelics Today

FDA Approved – 1 drug
Phase 3 – 9 programs
Phase 2 – 29 programs
Phase 1 – 18 programs
Preclinical – 59 programs

Q3 2026

PSYCHEDELIC ALPHA

Psychedelic Drug Development Tracker

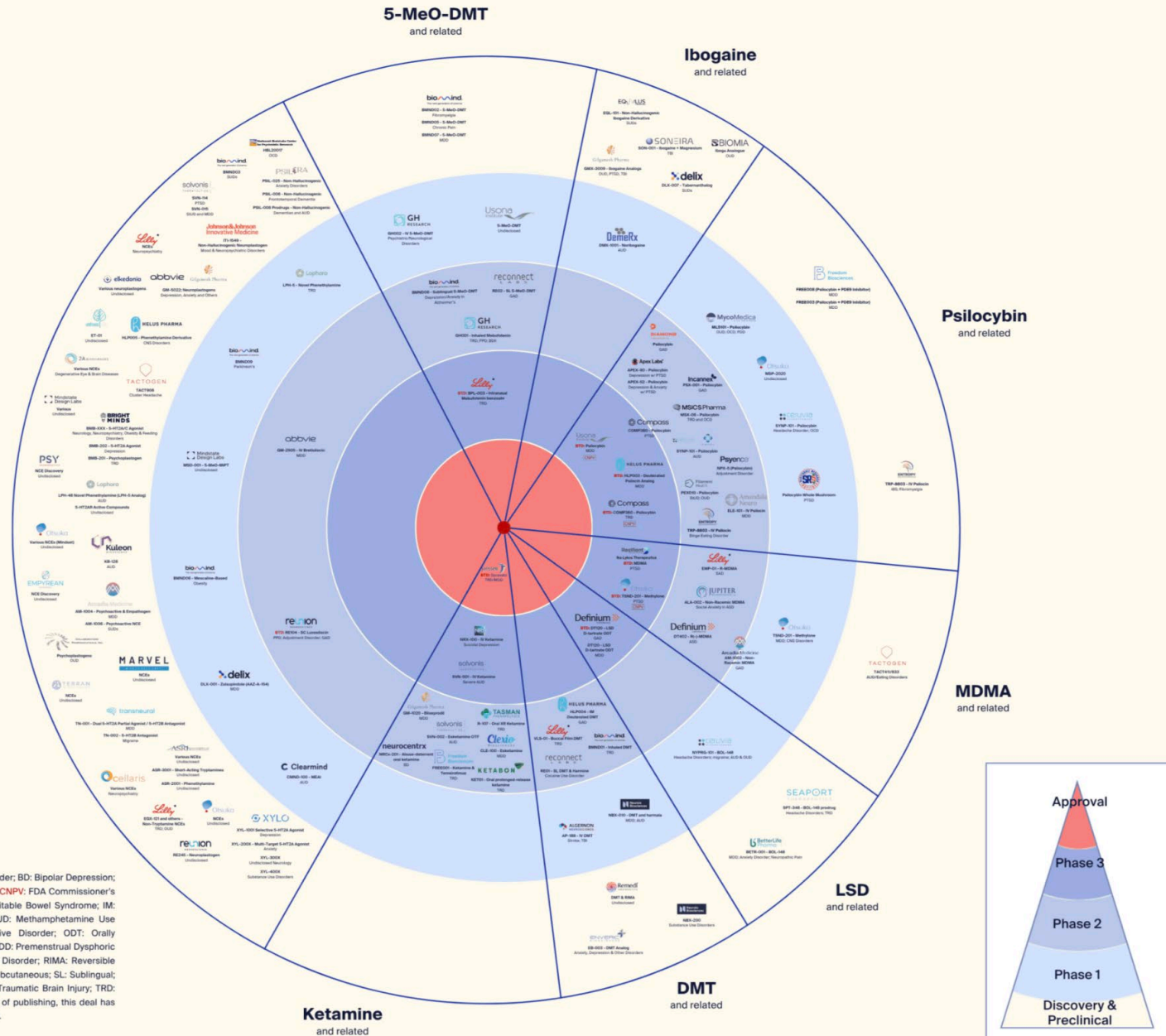
Supported by



Abbreviations: ASD: Autism Spectrum Disorder; AUD: Alcohol Use Disorder; BD: Bipolar Depression; BDII: Bipolar 2 Disorder; BTD: FDA Breakthrough Therapy Designation; CNPV: FDA Commissioner's National Priority Voucher; GAD: Generalized Anxiety Disorder; IBS: Irritable Bowel Syndrome; IM: Intramuscular; IV: Intravenous; MDD: Major Depressive Disorder; MUD: Methamphetamine Use Disorder; NCE: New Chemical Entity; OCD: Obsessive Compulsive Disorder; ODT: Orally Disintegrating Tablet; OTF: Oral Thin Film; OUD: Opioid Use Disorder; PDD: Premenstrual Dysphoric Disorder; PPD: Postpartum Depression; PTSD: Post-Traumatic Stress Disorder; RIMA: Reversible Inhibitor of Monoamine Oxidase A; SAD: Social Anxiety Disorder; SC: Subcutaneous; SL: Sublingual; SIUD: Stimulant Use Disorder; SUDs: Substance Use Disorders; TBI: Traumatic Brain Injury; TRD: Treatment-Resistant Depression; XR: Extended Release; * At the time of publishing, this deal has been announced by both AtaiBeckley and Eli Lilly, but has not yet closed.

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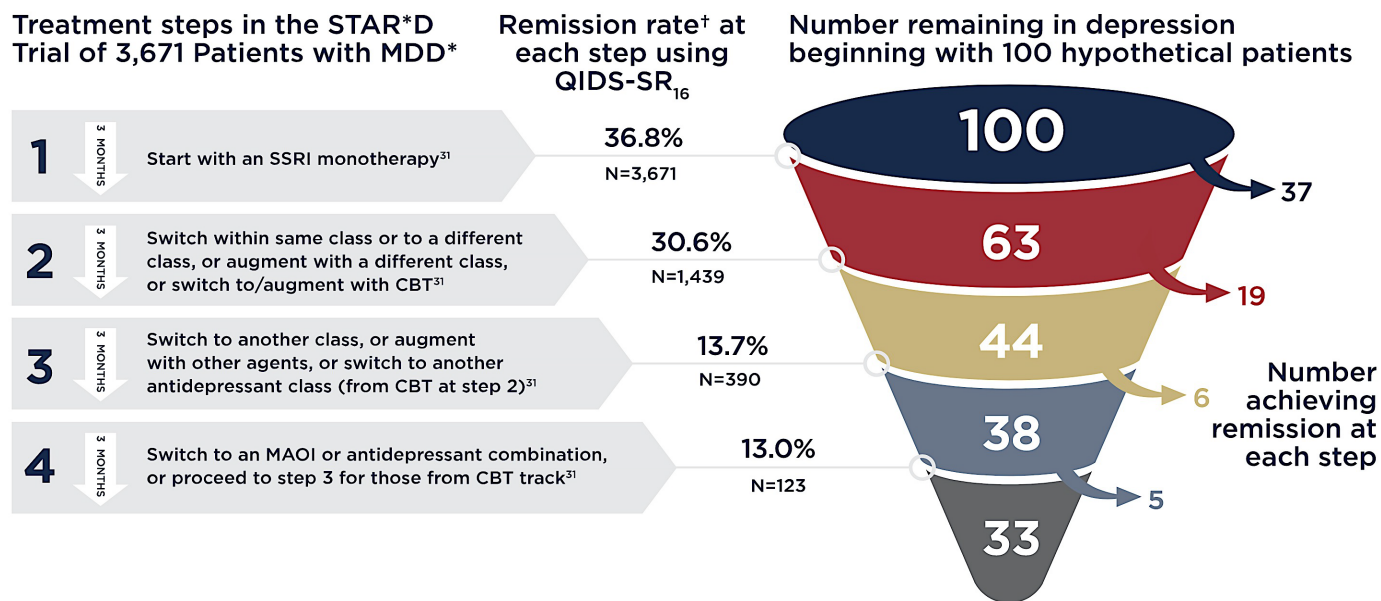
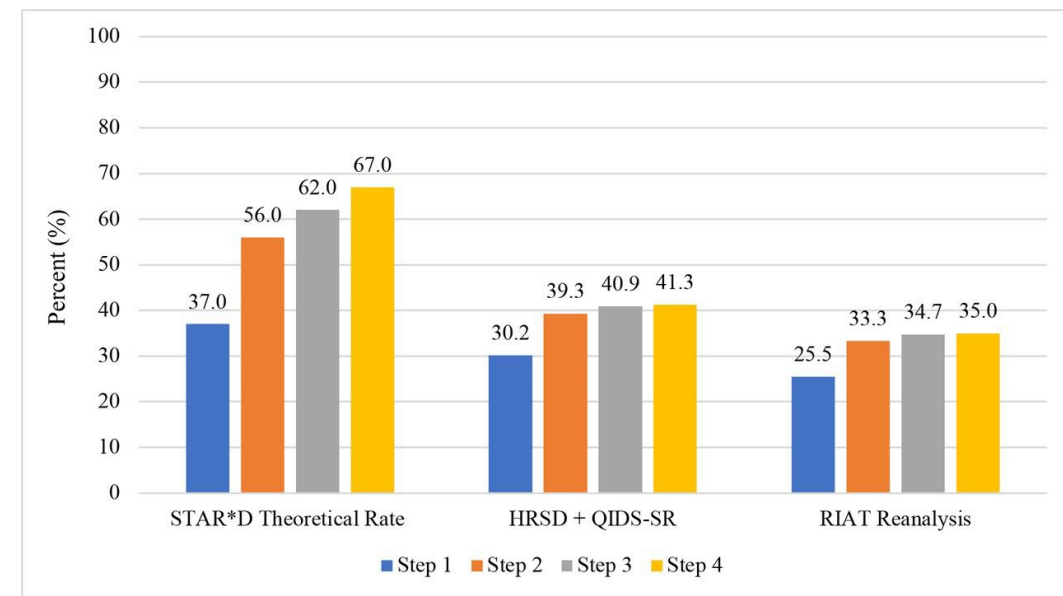
Other



Why Psychedelics in Psychiatry?

Because what we have isn't working so great

Lessons from STAR*D



STAR*D originally concluded that **67%** of people went into remission after 4 drug treatments

*But might be closer to
only 35% who went into remission*

STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

Dunner DL. *Primary Psychiatry*. 2007;14(3). Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917. H Edmund Pigott et al. *BMJ Open* 2023;13:e063095

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

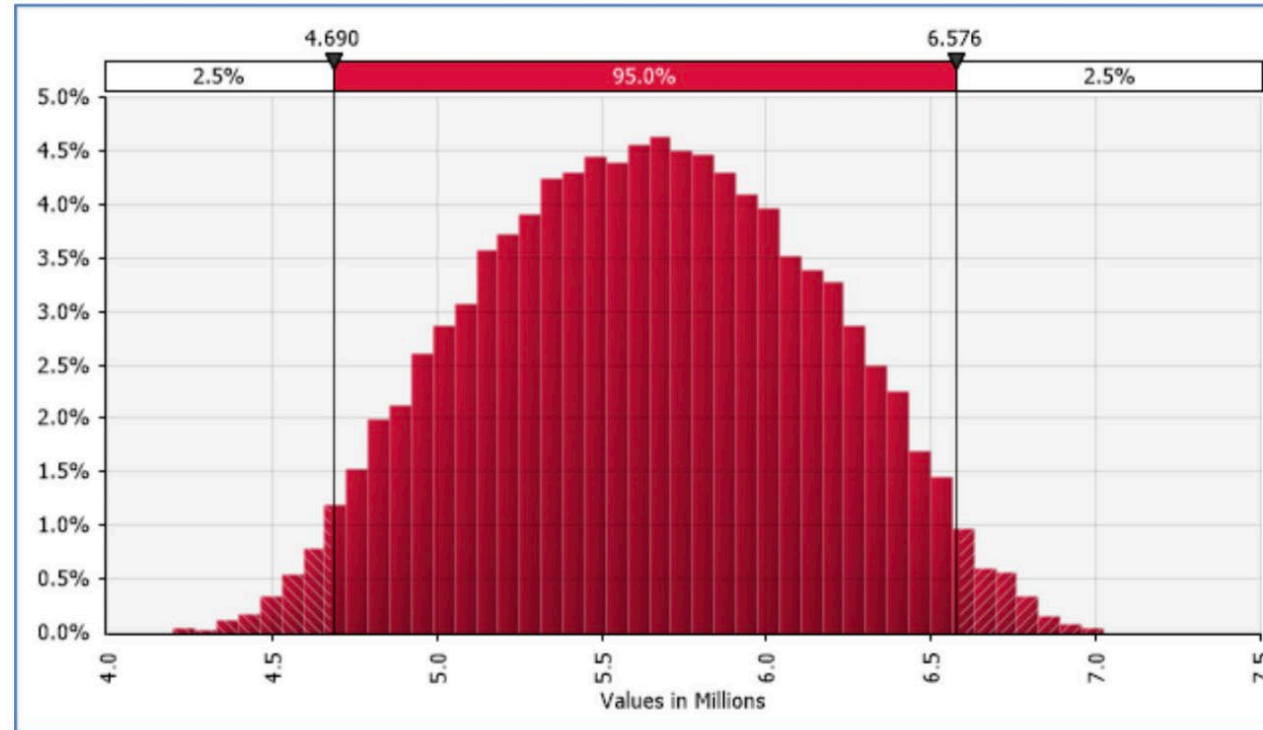


Figure 1. Patients being treated for MDD who are eligible for PSIL-AT. Multi-variate sensitivity analyses, 20,000 iterations.

PSIL-AT = psilocybin-assisted therapy; MDD = major depressive disorder.
Rab SF, et al. *Psychedelics*. 2024;1(2):26-30.

Choosing a Psychedelic vs a Conventional Psychiatric Treatment

- Those who do not want daily side effects from taking a medication
- Not bothered by psychedelic effects
- Those who get greater durability and like infrequent treatment
- Those who find benefit in psychedelic-insight
- Those who have insurance coverage for an expensive treatment
- Clinics that can build the infrastructure to support



- Those who do not want psychedelic effects
- Those who cannot make the time for a procedure
- Those who are less interested in their own psychological experience
- First preference of payors
- Not bothered by side effects
- Clinics that don't have the infrastructure to support

Key Learning Points

- Psychedelics have a complex history and became a part of medicine in 1938 with the discovery of LSD
- Psychedelic research has steadily grown in the last 30 years, leading to multiple FDA-registry trials
- Psychedelics represent a novel approach to treating mood and other psychiatric disorders that have not been adequately addressed with extant treatments

Exploration of Glutamatergic Neuroplastogens in MDD

Chuck Raison

Glutamate vs Monoamine Neurobiology

Neurotransmitter Comparison

Feature	Monoamines	Glutamate
Abundance	~10% of synapses	~60% of synapses
Signal speed	Slow, modulatory	Fast, direct
Receptor diversity	Moderate (7-14 subtypes)	High (>30 subtypes)
Synaptic plasticity	Days to weeks	Minutes to hours
Clinical effect onset	2 to 6 weeks	Hours to days

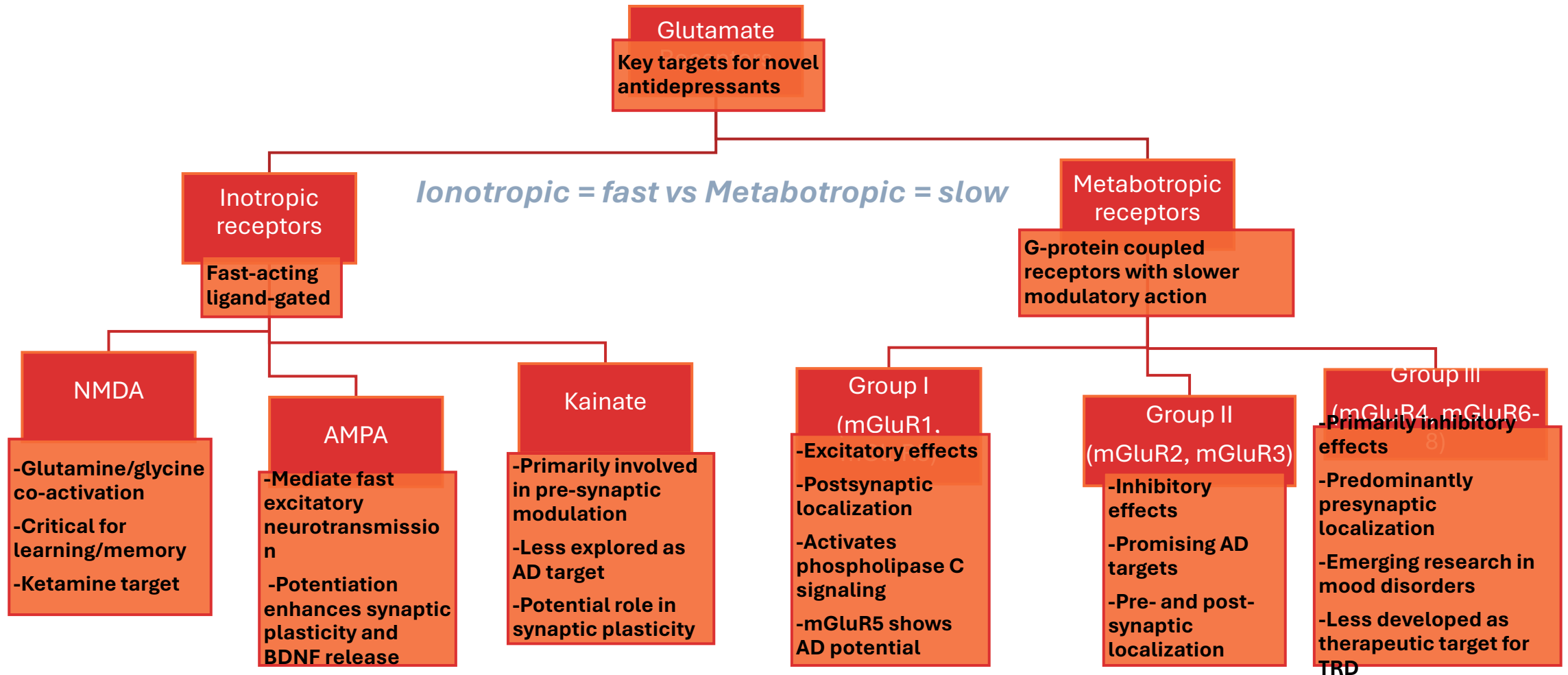
The **glutamate model** emphasizes rapid synaptic modulation and neuroplasticity, potentially enabling faster symptom relief.

Clinical implications

- Faster onset potential
- Different mechanism
- More precise targeting options

Greengard P. *Science*. 2001;294(5544):1024-1030. Hansen KB, et al. *Pharmacol Rev*. 2021;73(4):298-487. Niciu MJ, et al. *J Neural Transm (Vienna)*. 2014;121(8):907-924. Ren L. *Prog Neuropsychopharmacol Biol Psychiatry*. 2024;129:110910.

Glutamate Receptor Types



AD = antidepressant.

Freudenberg F, et al. *Pharmacol Res.* 2025;220:107918. Niciu MJ, et al. *J Neural Transm (Vienna).* 2014;121(8):907-924. Xia CY, et al. *Pharmacol Ther.* 2021;226:107875.

Glutamatergic Dysfunction in Depression

Human Neuroimaging

- **Increased** glutamate in the anterior cingulate cortex (MRS studies)
- **Decreased** prefrontal Glx ratio in TRD
- Normalization of glutamate levels with successful treatment
- Ketamine normalizes glutamate connectivity patterns

Post-Mortem Studies

- **Decreased** NMDA receptor subunit expression
- Altered AMPA:NMDA receptor ratio
- **Decreased** glutamate transporter density in PFC
- **Decreased** glial cell density in mood regions

Animal Models

- Stress-induced glutamate surge in PFC and hippocampus
- Ketamine rapidly reverses stress-induced synaptic deficits
- NMDA-NR2B knockout shows antidepressant phenotype

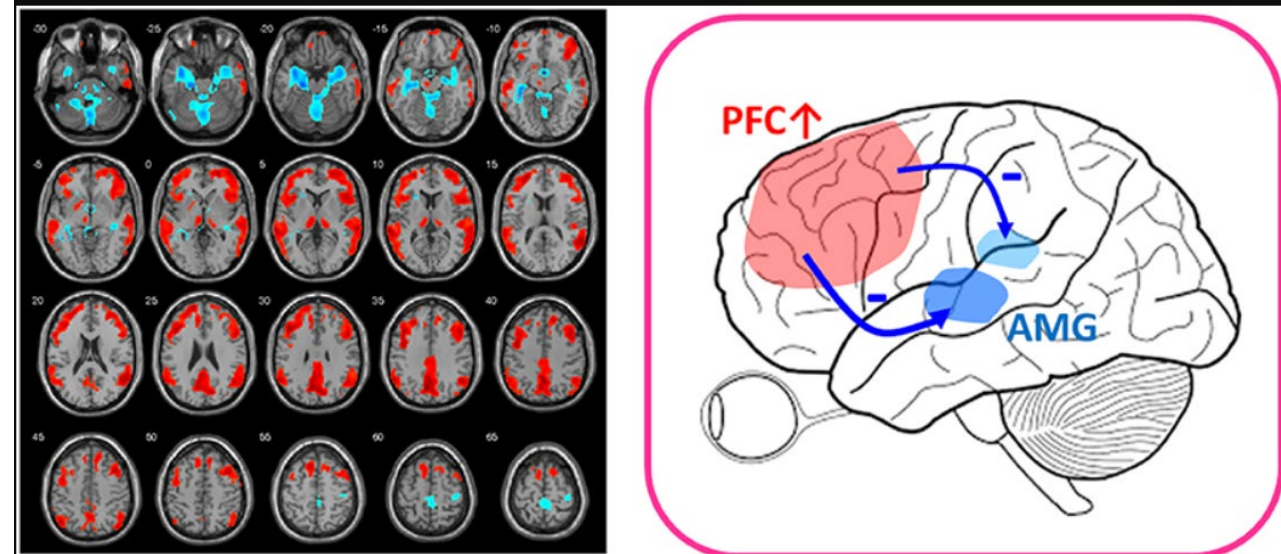


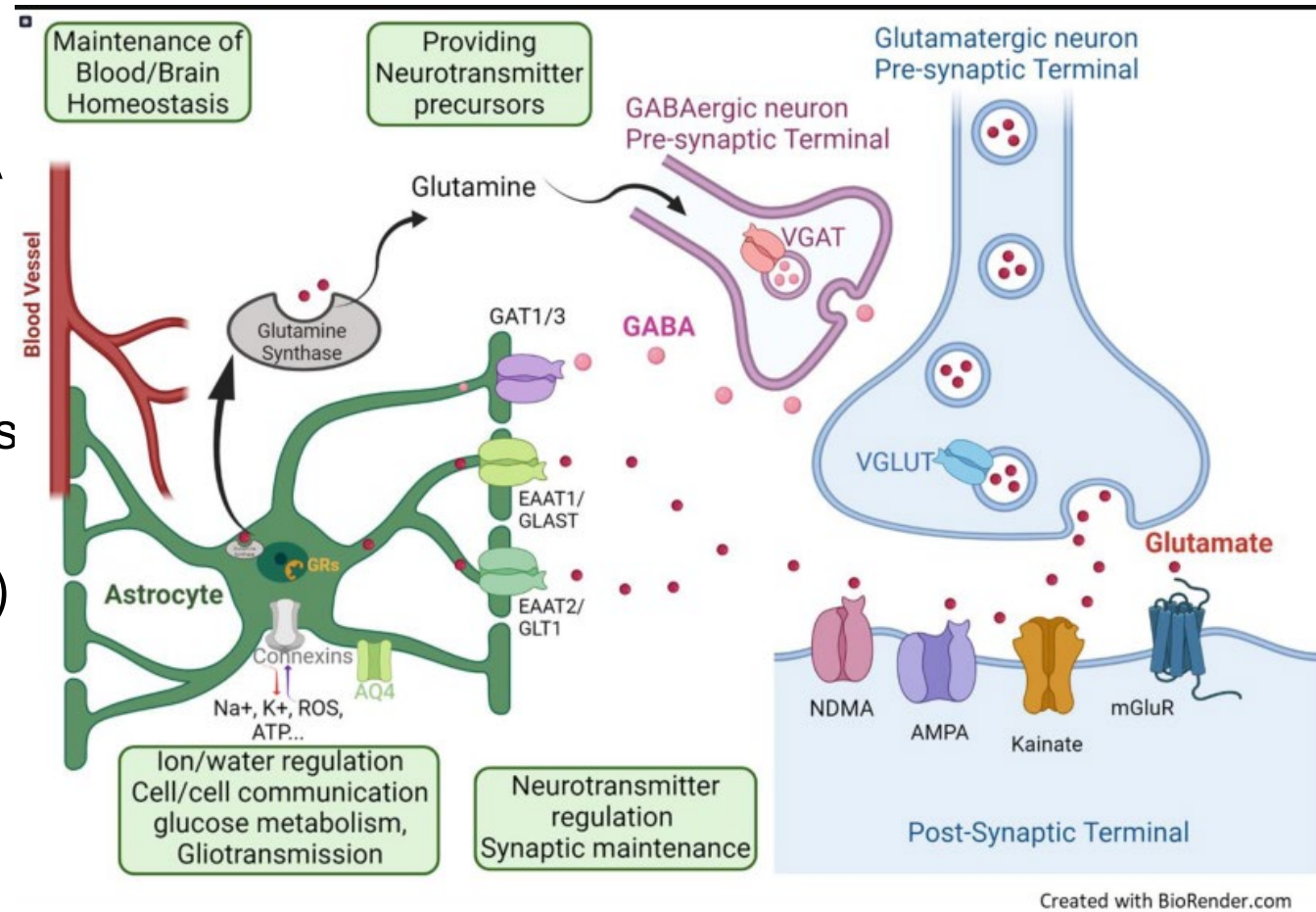
Figure 1. After vs before changes of glucose metabolism in response to low-dose ketamine in treatment-resistant depressives (FWE-corrected, $p < 0.001$). **Patients showed decreased glucose metabolism in limbic structures, such as amygdala (AMG) and hippocampus (shown in blue color), and increased function in prefrontal cortex (PFC) (shown in red color) after ketamine treatment.** The placebo group lacked the PFC activation. The findings of prefronto-amygdala changes in response to ketamine provided supports that low-dose ketamine could reverse glutamatergic dysfunction of the mood circuit.

MRS = magnetic resonance spectroscopy.

Halaris A, Cook J. *Adv Exp Med Biol.* 2023;1411:487-512. Kim YK, Na KS. *Prog Neuropsychopharmacol Biol Psychiatry.* 2016;70:117-126. Niciu MJ, et al. *J Neural Transm (Vienna).* 2014;121(8):907-24. Li CT, et al. *Psychiatry.* 2019;9:767.

Role of Astrocytes in Glutamate/GABA Balance

- **Glutamate-GABA cycle**
 - Uptake of synaptic glutamate, conversion to glutamine, transfer to neurons for GABA synthesis
- **Excitotoxicity prevention**
 - Removal of excess glutamate to prevent neuronal damage via EAAT1/2 transporters
- **Synaptic modulation**
 - Release of gliotransmitters (D-serine, ATP) that regulate synaptic strength
- **Energy support**
 - Glycogen storage and lactate provision to neurons during high activity



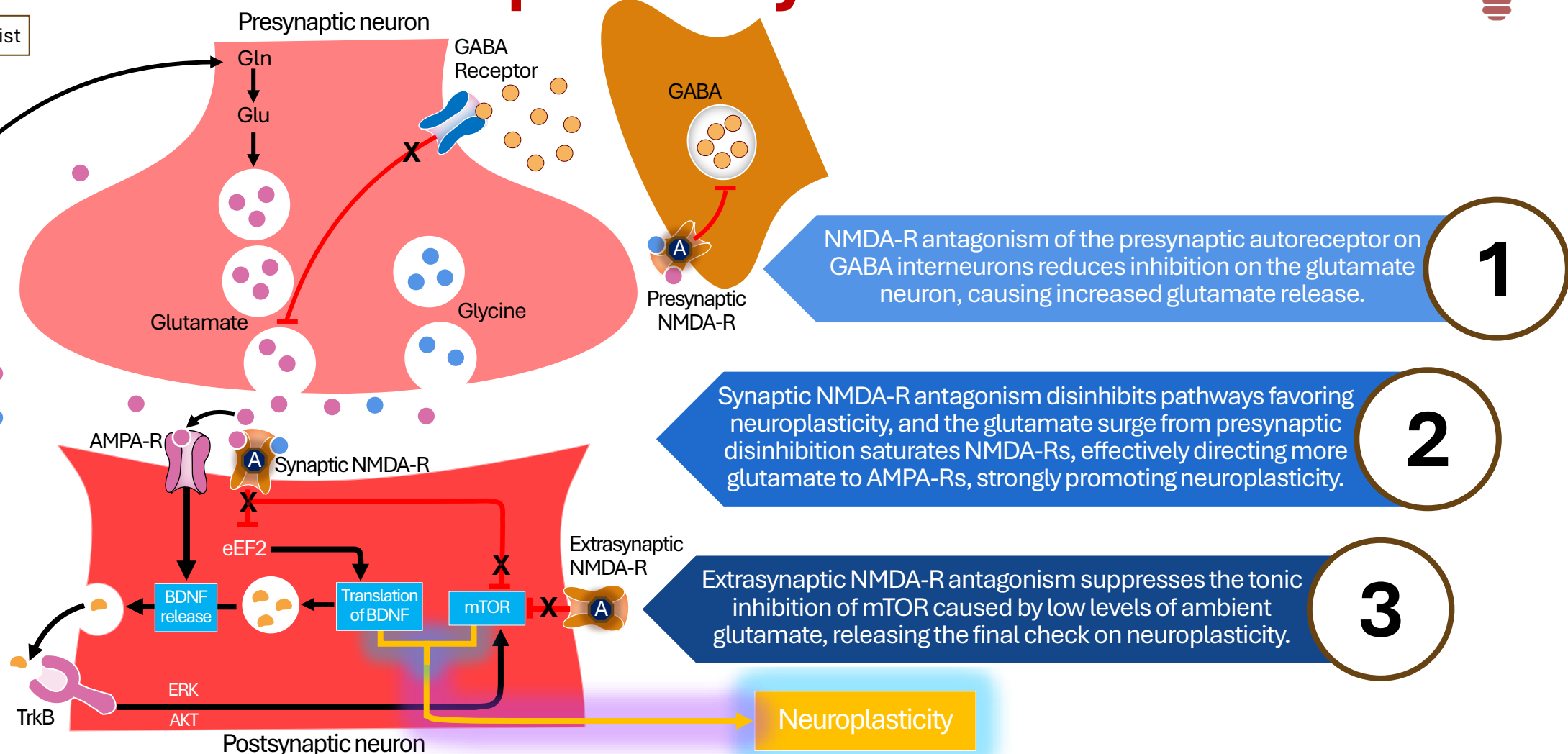
ATP = adenosine triphosphate.

Li S, et al. *Prog Neuropsychopharmacol Biol Psychiatry*. 2025;141:111475. Musazzi L, et al. *Biol Psychiatry*. 2013;73(12):1180-1188. McGrath T, et al. *Nutrients*. 2022;14(5):917. Bansal Y, et al. *Int J Mol Sci*. 2024;25(12):6357.

NMDA-Receptor Antagonists May Promote Neuroplasticity in MDD



A = NMDA Antagonist



NMDA = N-methyl-D-aspartate; AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF = Brain-Derived Neurotrophic Factor; eEF2 = eukaryotic elongation factor 2; ERK = extracellular signal-regulated kinase; AKT = Protein kinase B; mTOR = mechanistic Target of Rapamycin; TrkB = Tropomyosin receptor kinase B.

Kadriu B, et al. *Int. J. Pharm.* 2019;22(2) 119-135. Murrough J, et al. *Nat Rev Drug Discovery.* 2017;16:472. Niciu, MJ. *Pharmacology Biochemistry and Behavior.* 2012;100(4): 656-664.

The Contributory Role of Sigma-1 Receptors

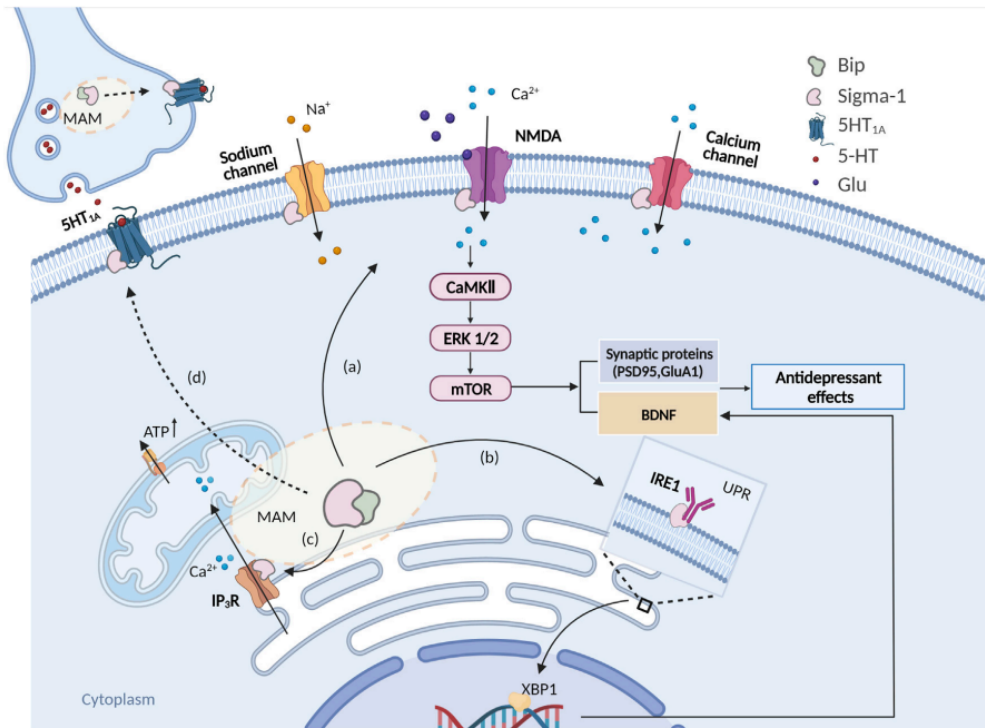
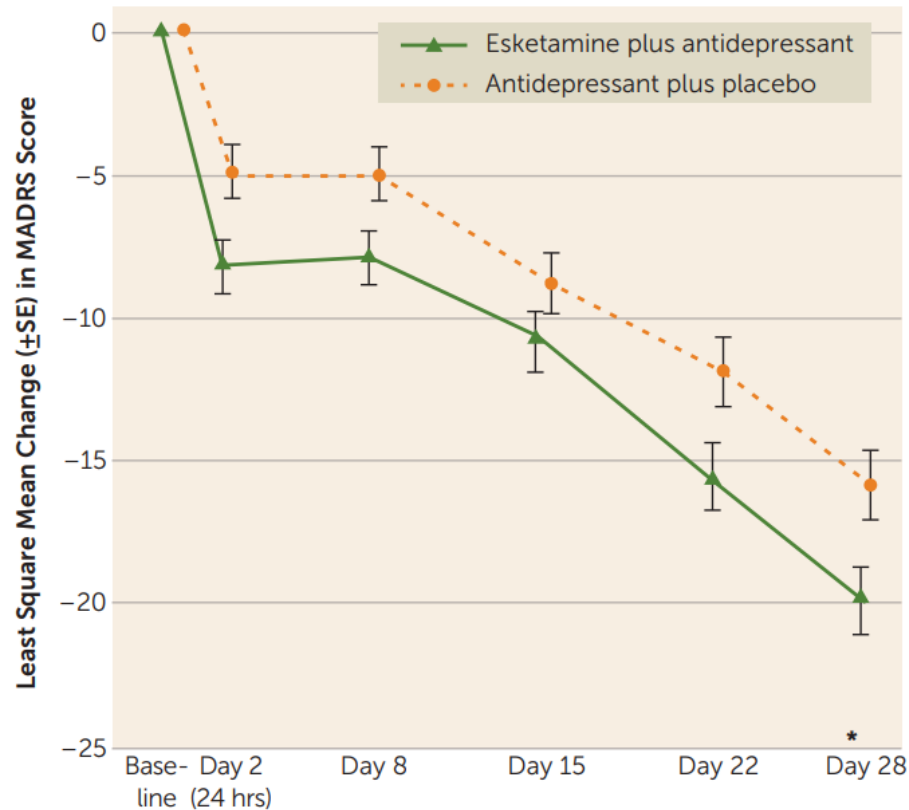


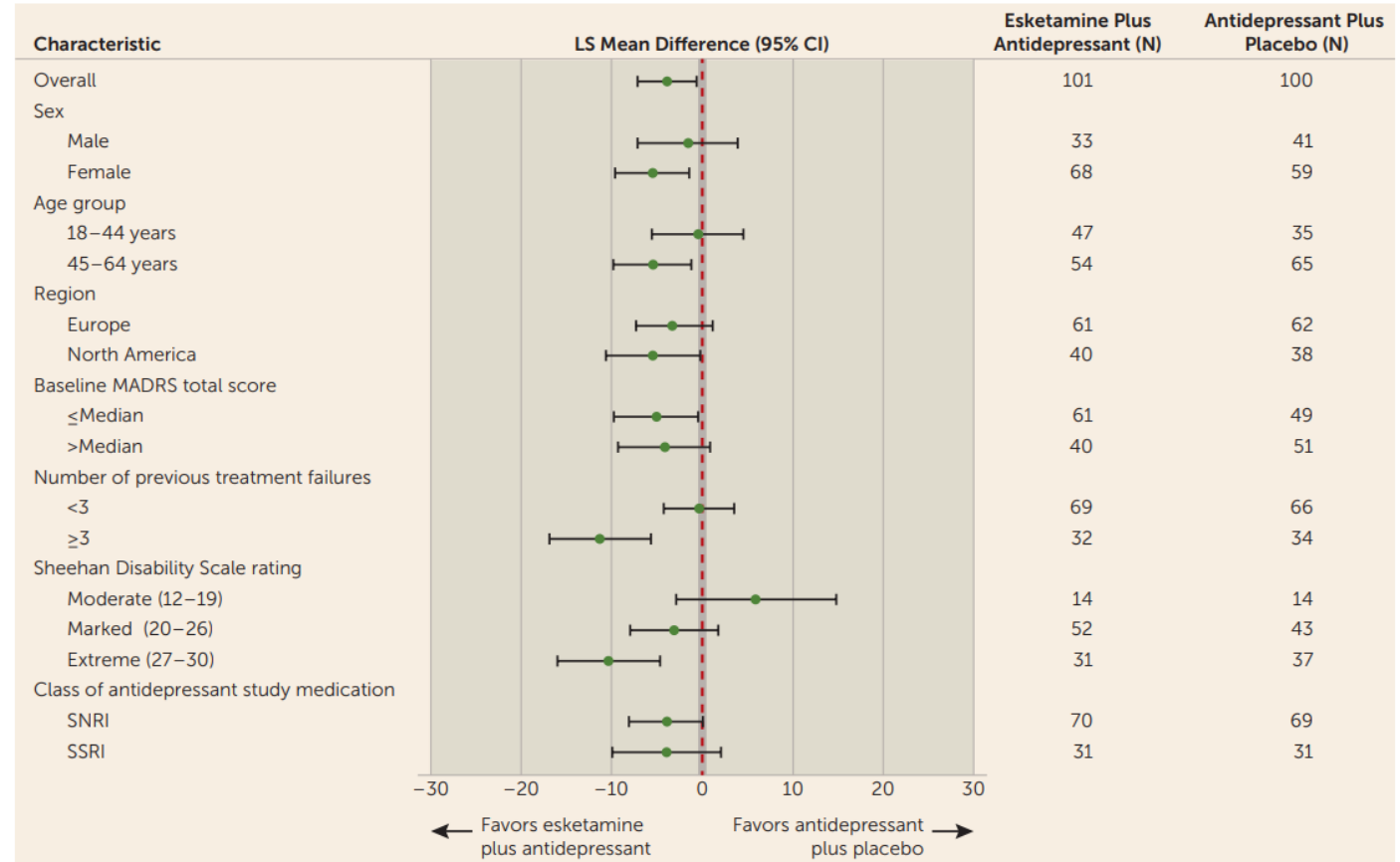
FIGURE 1 | Schema of intracellular signaling pathways involved in the antidepressant-like effects of sigma-1 receptors. **(A)** Sigma-1 receptors are activated and translocated to the plasma membrane to interact with the NMDAR of pyramidal cells, which would result in a rapid intracellular activation of CaMKII that would eventually activate (phosphorylate) intermediates in the ERK1/2 and mTOR pathways, thus inducing a rapid synthesis of PSD95, BDNF etc; **(B)** Sigma-1 receptors are activated and then disassociate from Bip thus stabilizing IP3R, maintaining the Ca²⁺ flow from the ER to mitochondria and ATP production; **(C)** Sigma-1 receptor activates and thus binds and modulates the ER stress response via ER stress sensors IRE1 and facilitates BDNF expression via the IRE1-XBP1 signaling pathway. **(D)** Sigma-1 receptors may also modulate 5HT_{1A} function through sigma-1 receptor-5HT_{1A} interaction.

- **Chaperones NMDA receptors:** activated sigma-1 moves to the synaptic membrane and binds NMDA receptor subunits directly, making them more responsive to glutamate — amplifying, not initiating, the signal.
- **Feeds a plasticity cascade:** boosted NMDA activity triggers CaMKII, then ERK1/2, then mTOR, turning glutamate pulse into new BDNF and synaptic proteins (PSD95, GluA1).
- **Keeps the energy supply running:** sigma-1 also stabilizes IP3 receptors at the ER-mitochondria junction, maintaining calcium transfer that fuels the ATP production needed to build new synapses.
- **Pharmacologically relevant:** agonists like dextromethorphan or ketamine enhance NMDA-driven plasticity, while antagonists like BD1063 block it.
- **Protective when glutamate is excessive:** under excitotoxic conditions (too much glutamate, calcium overload, ER stress), dials signaling back down, keeping glutamate transmission in a healthy range.

Esketamine Augmentation of Standard Antidepressants for Treatment Resistant Depression



Esketamine plus antidepressant (N)	114	109	109	107	103	101
Antidepressant plus placebo (N)	109	102	105	102	104	100



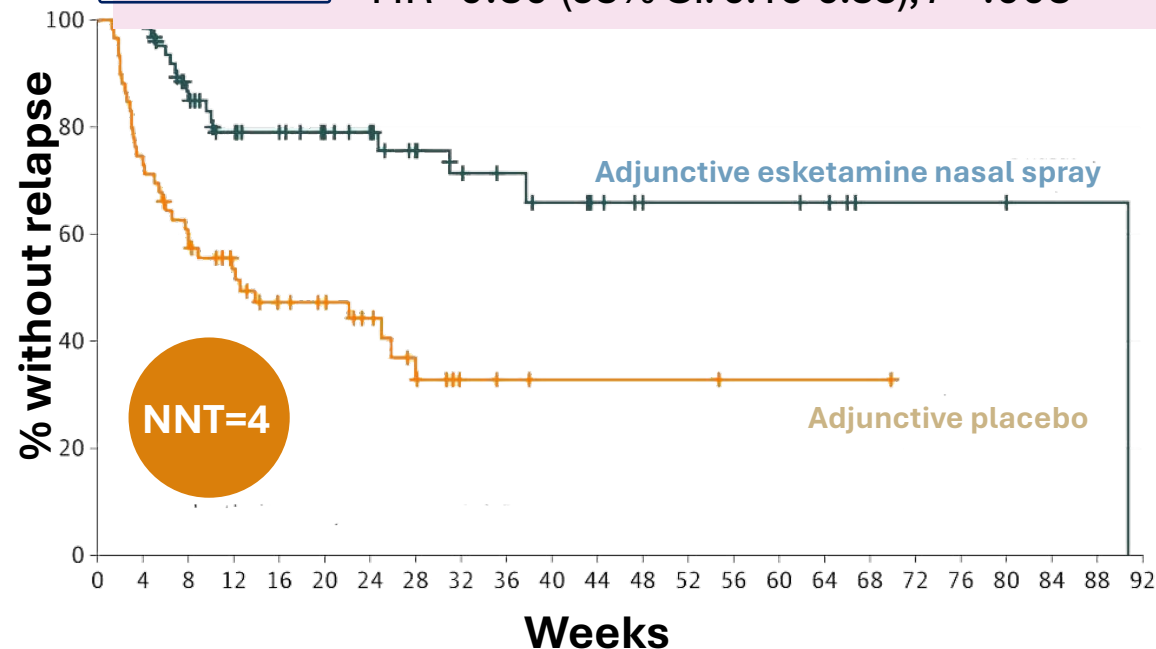
Esketamine Treatment & Relapse Prevention

Patients who responded to treatment

70%

were less likely to relapse

HR=0.30 (95% CI: 0.16-0.55), $P=.003$

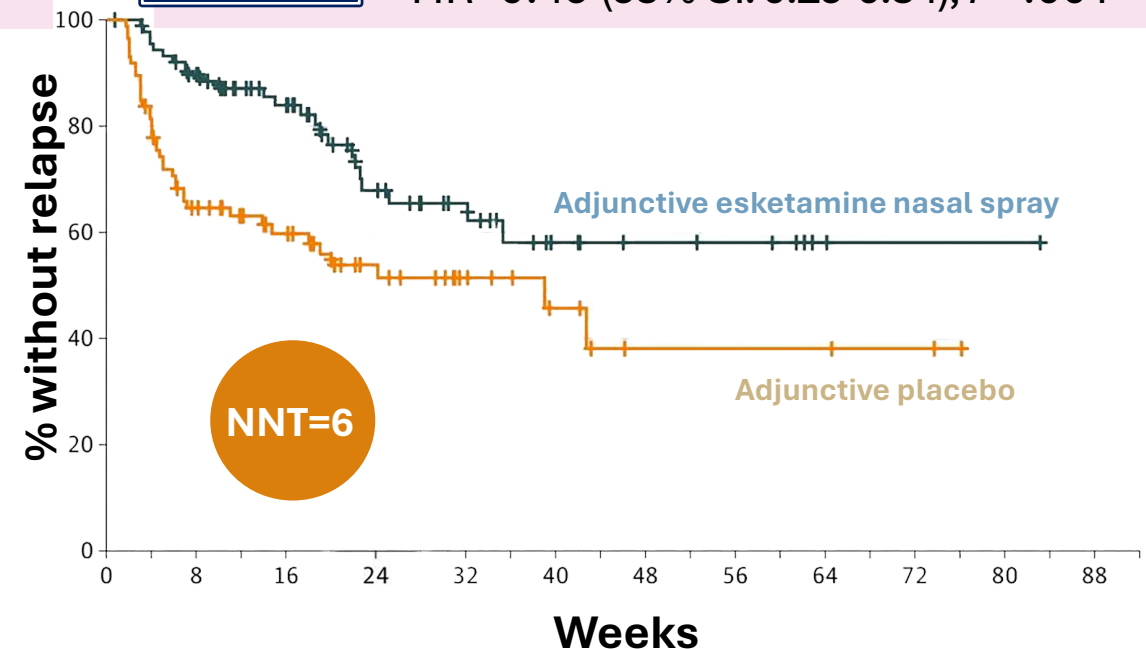


Patients who reached remission

51%

were less likely to relapse

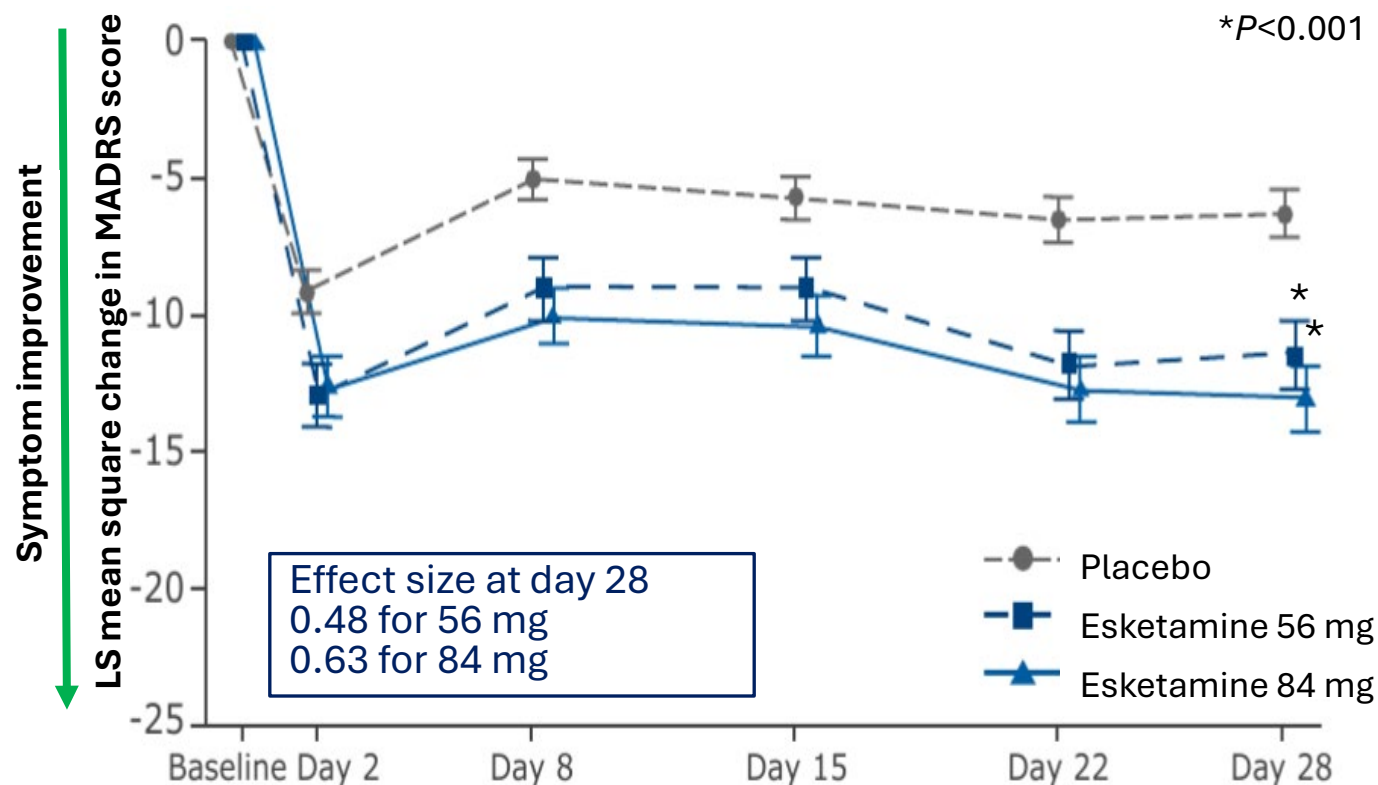
HR=0.49 (95% CI: 0.29-0.84), $P=.001$



HR = hazard ratio.

Daly E, et al. *JAMA Psychiatry*. 2019;76(9):893-903.

Esketamine Monotherapy for TRD: Phase 4 Trial



Adverse Events in Double-Blind Phase

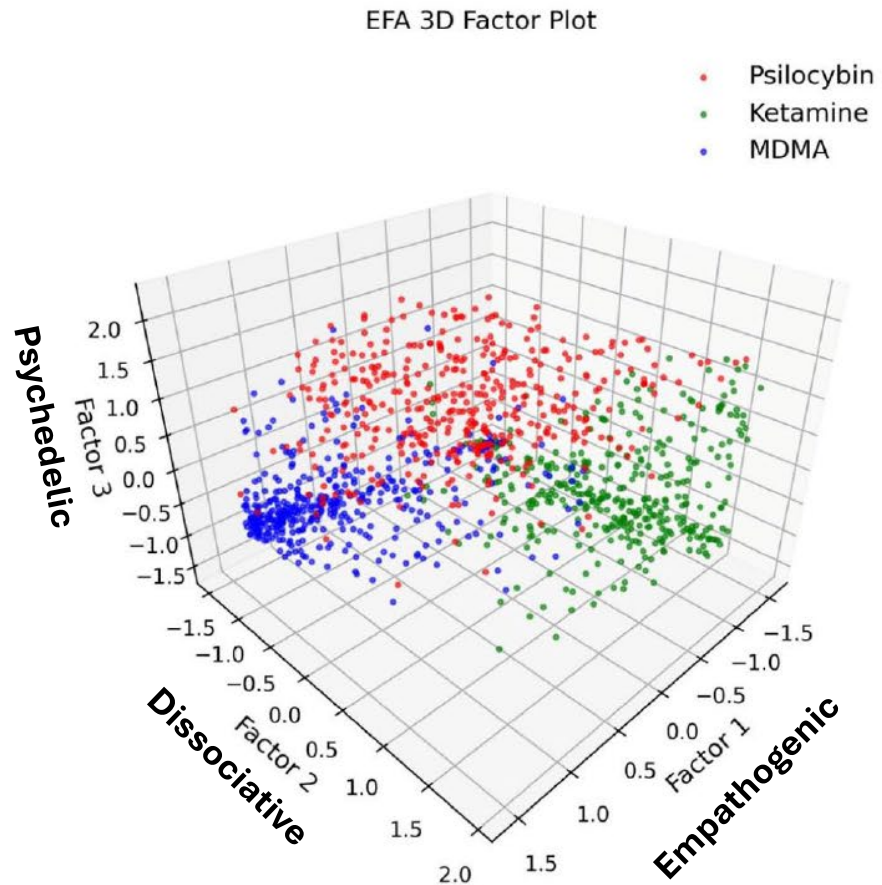
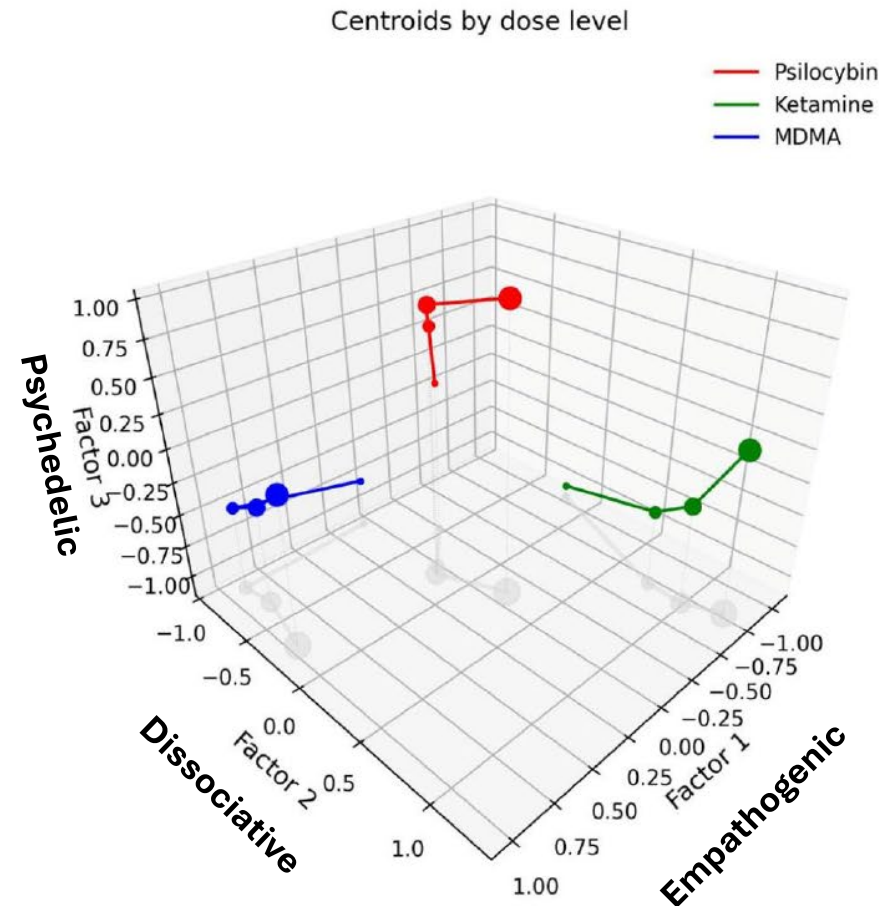
	Esketamine		Placebo
	56 mg (N=105)	84 mg (N=121)	N=250
Nausea	23%	26%	8%
Dissociation	22%	26%	3%
Dizziness	21%	22%	7%
Headache	18%	20%	9%
Feeling drunk	8%	7%	1%
Anxiety	5%	8%	1%
Fatigue	8%	6%	4%
Vomiting	5%	8%	<1%
Insomnia	6%	4%	4%
Somnolence	6%	3%	1.6%
D/C due to AEs	1%	4%	1%

Esketamine monotherapy produced significantly greater reductions in MADRS scores at day 28 versus placebo, with treatment differences of 5.1 points for 56 mg and 6.8 points for 84 mg (both $P < .001$).

D/C = discontinuation.

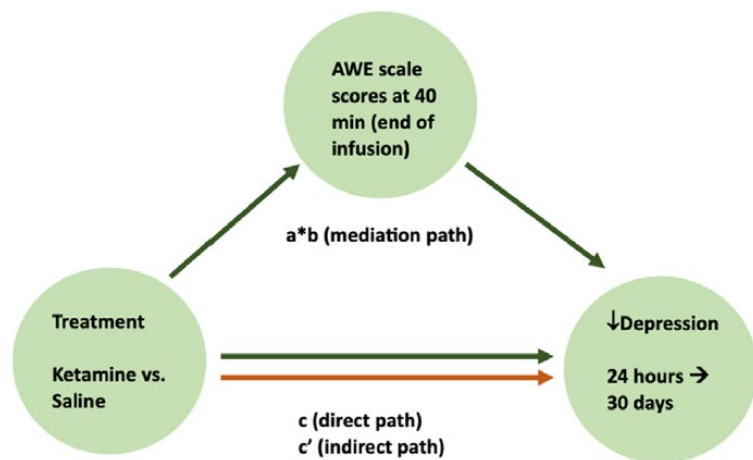
Janik A, Qiu X, Lane R, et al. *JAMA Psychiatry*. 2025;82(9):877-887.

These Neuroplastogens Are Not Psychedelics or Psychoplastogens: Or Are They (at Least a Little Bit)?

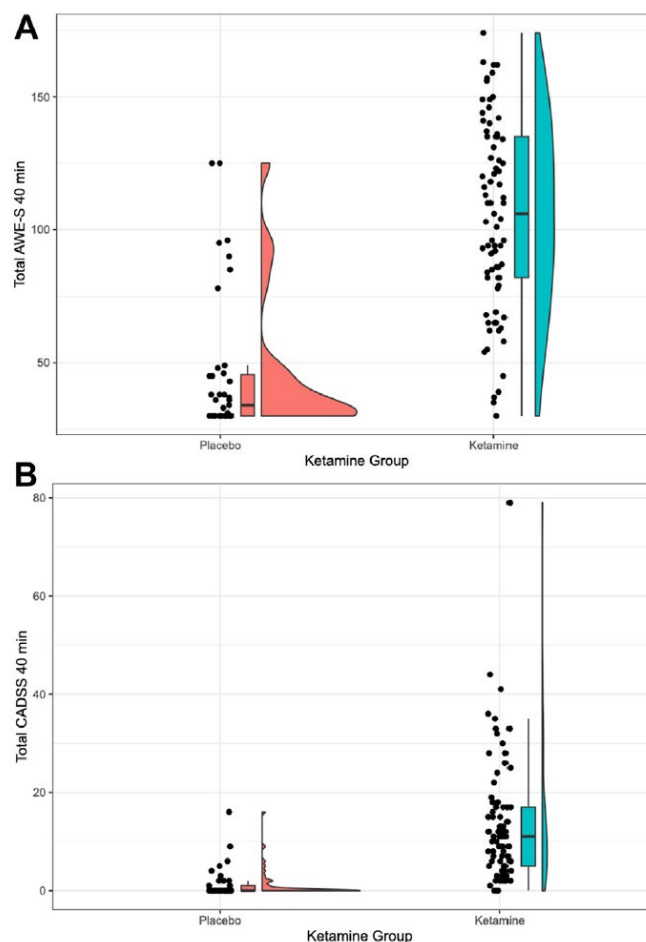
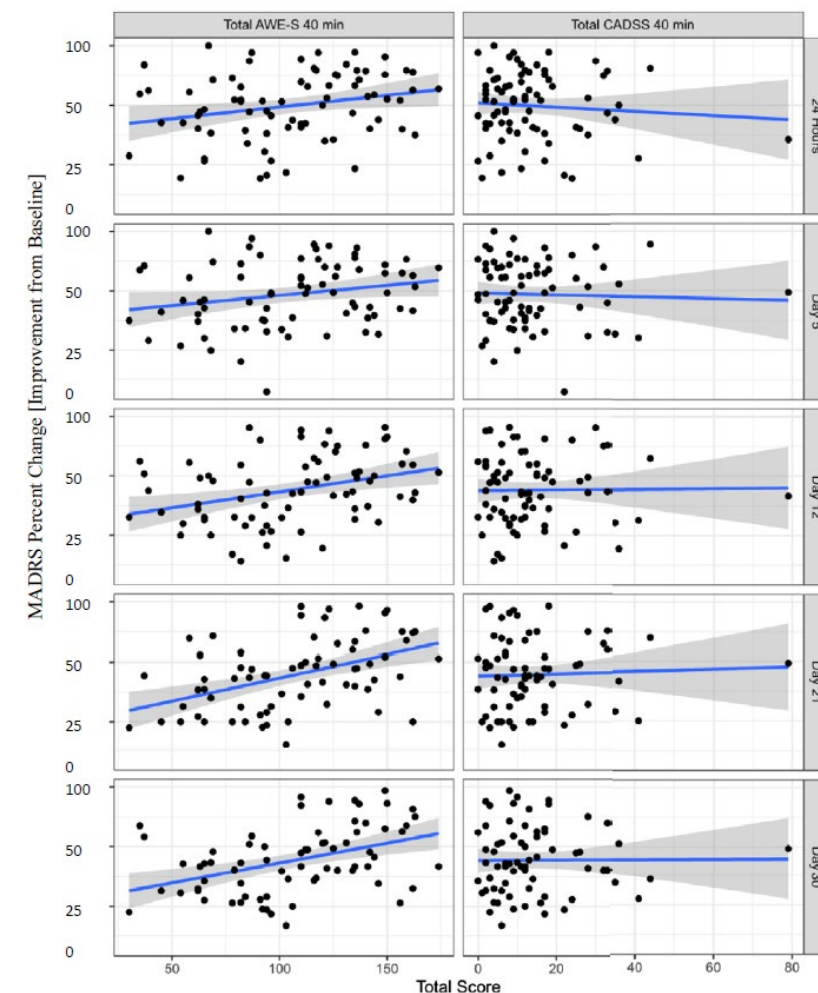


Over 200 participants rated Delphi-generated subjective rating scale items based on their personal experiences with all 3 drugs. Factor analyses revealed three or four sufficiently independent dimensions of subjective experience (variable label, Effects). A machine-learning classifier successfully predicted Drug from Effects, validating the hypothesis that psilocybin, ketamine and MDMA have categorically distinct subjective effect profiles, differentiable by (1) visions and psychological insight (psilocybin), (2) dissociation (ketamine) and (3) pro-social and loving feelings (MDMA).

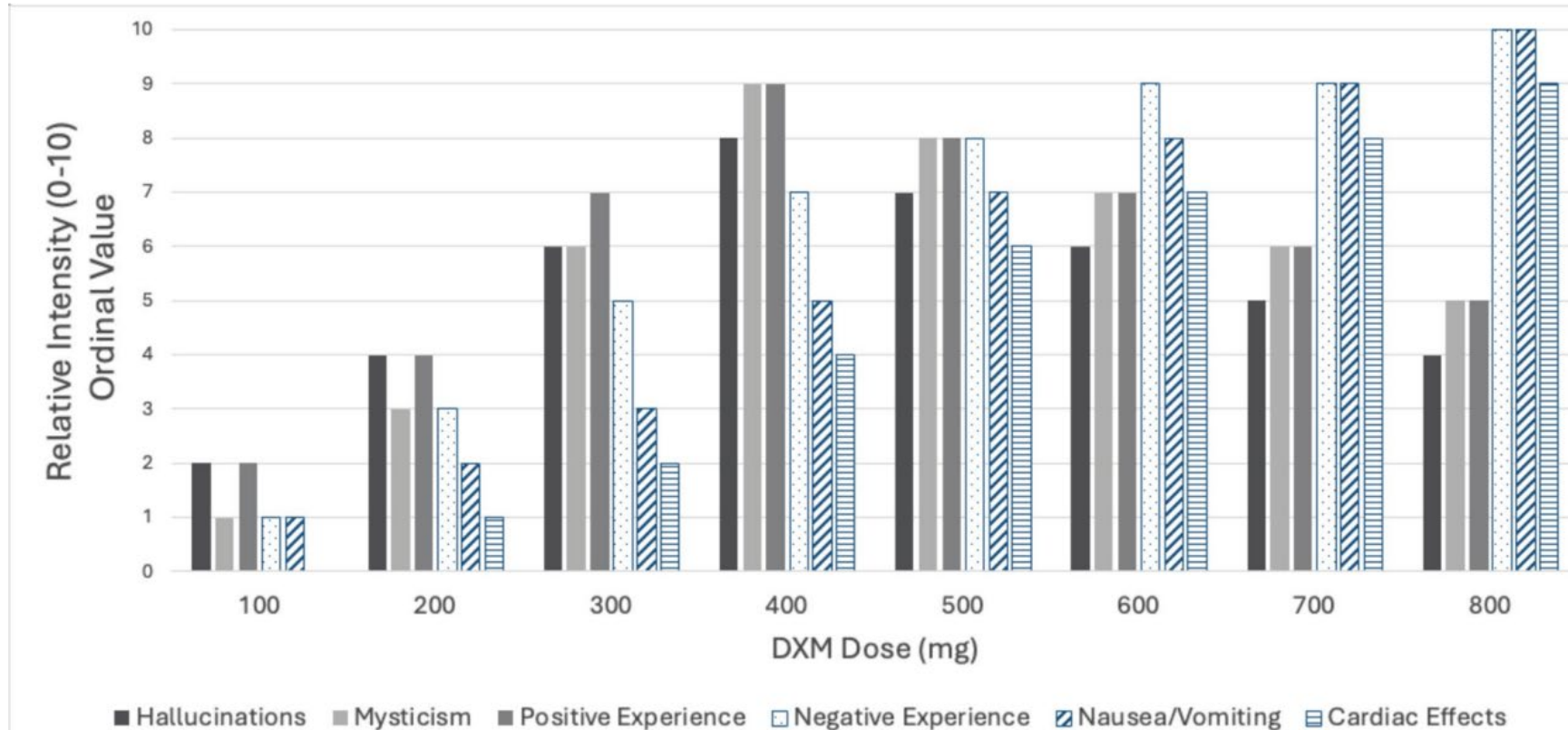
Is Ketamine a Simple Neuroplastogen or Does It Have Untapped Psychedelic-Like Properties?



One hundred sixteen participants with depression, 77 of whom received a ketamine infusion (0.5 mg/kg over 40 minutes) and 39 patients who received saline placebo, completed a validated measure of awe (the Awe Experience Scale [AWE-S]) at 40 minutes post infusion. the psychological experience of awe was strongly reported by participants during ketamine infusion, but not saline infusion, and there were significant associations between total AWE-S scores and Montgomery-Åsberg Depression Rating Scale score improvement (% change) in the ketamine arm at all 5 time points.



Neuroplastogen? Acute Psychological and Perceptual Effects of Dextromethorphan-Bupropion Unknown



- DXM-BUP delivers 45 mg of DXM, but the addition of bupropion increases the exposure levels many times, likely far into the range at which DXM induces psychedelic effects.
- No such effects have been reported for DXM-BUP, reason not known; theoretically because bupropion shunts DXM away from a primary metabolite believed to be the primary psychedelic element.

Key Learning Points

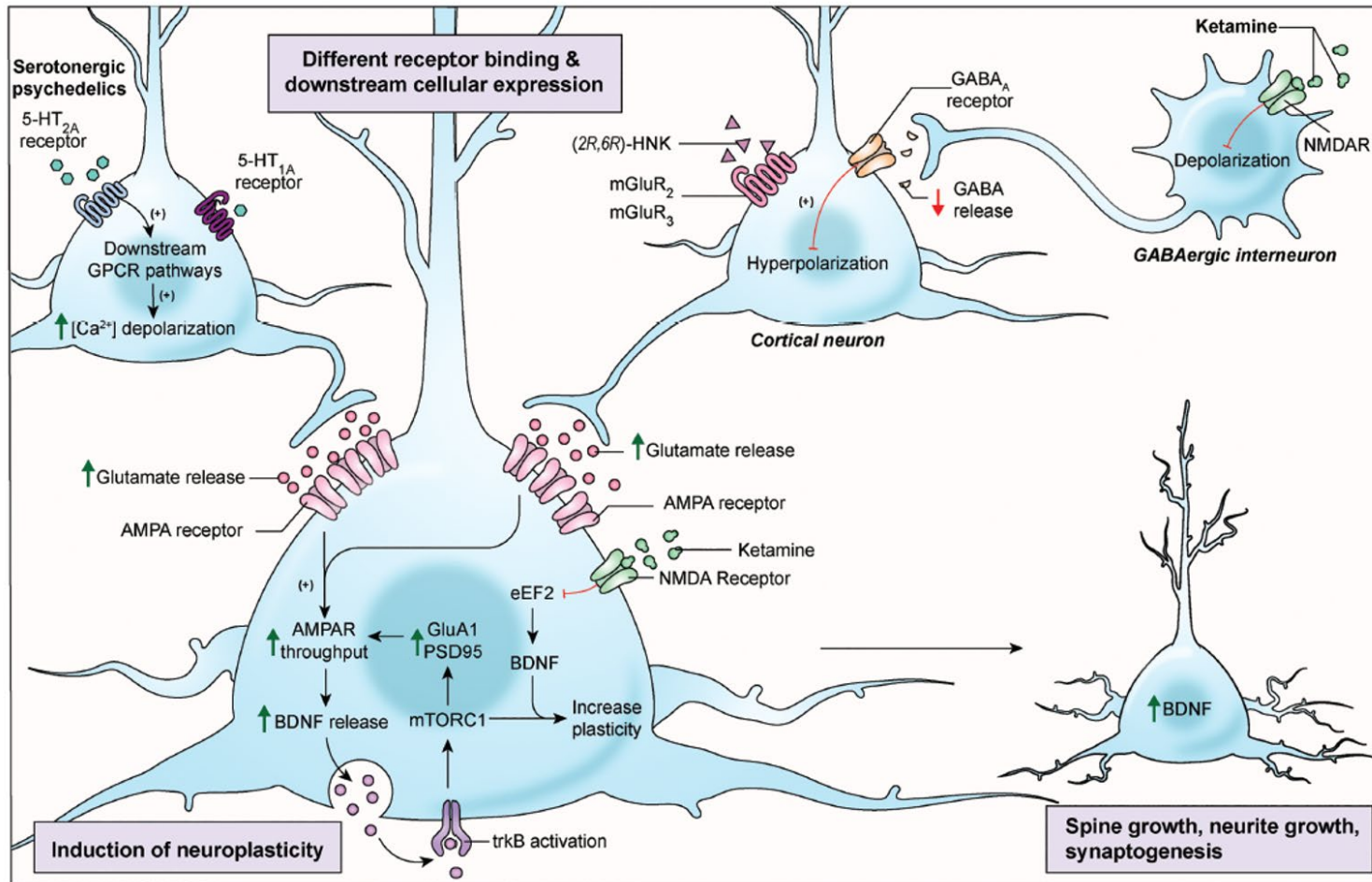
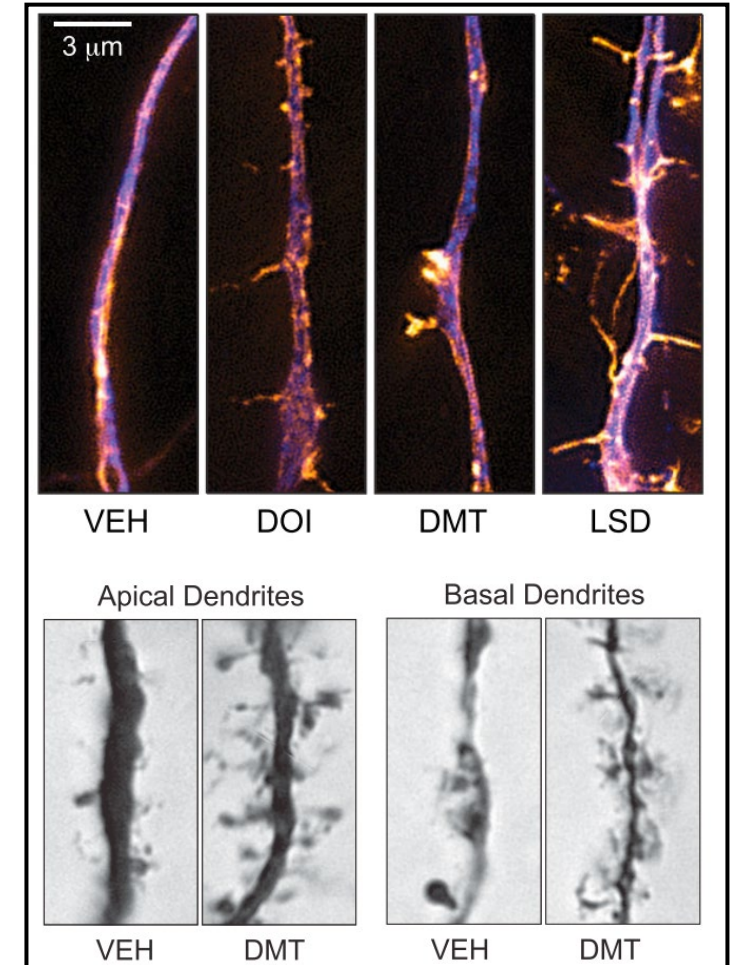


- **NMDA receptor antagonism on GABAergic interneurons reduces inhibitory control of glutamatergic neurons**, increasing glutamate release and activating downstream neuroplasticity pathways
 - Sigma-1 receptor modulation may provide an additional route to synaptic restoration
- FDA-approved glutamatergic treatments offer clinically relevant antidepressant effects through distinct, potentially neuroplastic mechanisms
 - Including esketamine for TRD and depressive symptoms associated with acute suicidal ideation or behavior, and DXM-BUP for MDD

Exploration of Serotonergic Neuroplastogens (Psychedelics) in MDD

Chuck Raison

Preclinical Evidence that Psychedelics Are Neuroplastogens: Neuroplasticity as Mechanism?



Psychedelic Compounds Farthest Along the FDA Path for Treatment of MDD or TRD: Part 1



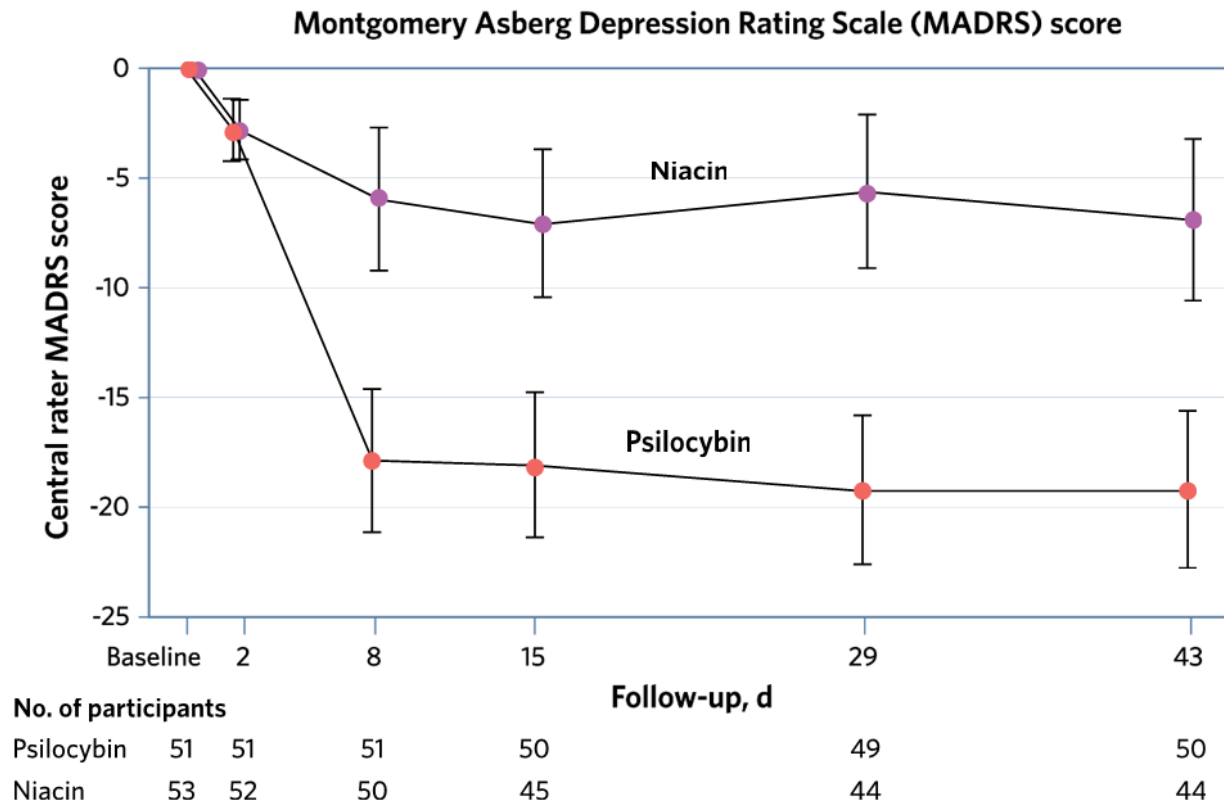
Compound	PD Profile	Duration	Company	Status
COMP360 (synthetic psilocybin)	5-HT2A agonist (+ 5-HT1A, 5-HT2C)	~4–6 hrs	Compass Pathways	Phase 3 (TRD). COMP005 positive Feb 2026; NDA planned Q4 2026
Psilocybin (synthetic psilocybin)	5-HT2A agonist (+ 5-HT1A, 5-HT2C)	~4–6 hrs	Usona Institute (nonprofit)	Phase 3 (uAspire, MDD). Enrollment complete Nov 2025; topline pending
HLP003 (formerly CYB003; deuterated psilocin)	5-HT2A agonist; deuterated to reduce PK/PD variability	~4–6 hrs (estimated)	Helus Pharma (formerly Cybin)	Phase 3 (PARADIGM program, adjunctive MDD). Topline Q4 2026. BTD held
Bretisilocin (formerly GM-2505)	5-HT2A agonist + 5-HT (serotonin) releaser — dual mechanism	Short-acting by design; retains extended benefit (exact duration TBD)	AbbVie (acquired from Gilgamesh Pharmaceuticals, Aug 2025, up to \$1.2B)	Phase 2 (MDD). Positive Phase 2a: –21.6-pt MADRS at Day 14 (10mg) vs –12.1-pt (1mg comparator), p=0.003. FDA Fast Track (distinct from BTD)

Psychedelic Compounds Farthest Along the FDA Path for Treatment of MDD or TRD: Part 2



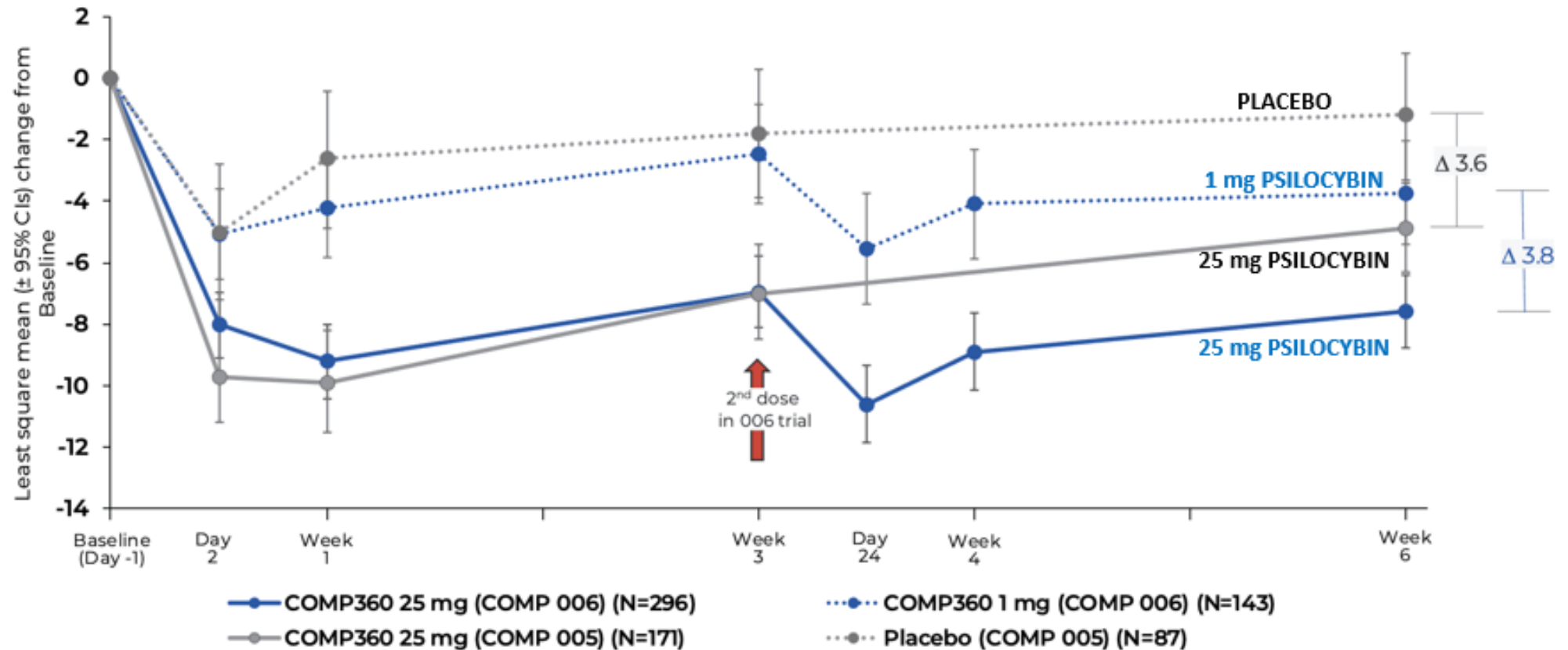
Compound	PD Profile	Duration	Company	Status
BPL-003 (intranasal 5-MeO-DMT / mebufotenin benzoate)	Preferential 5-HT1A agonism over 5-HT2A — distinct from psilocybin/LSD	~1–1.5 hrs	atai Beckley (Eli Lilly)	Phase 2b positive (TRD). Hit endpoints July 2025; 8mg dose advancing to Phase 3
GH001 (inhaled 5-MeO-DMT / mebufotenin)	Same active molecule as BPL-003; inhaled for ultra-rapid onset	~30–60 min; in-clinic visit ~1–3 hrs	GH Research	Phase 2b positive (TRD). –15.5-pt placebo-adjusted MADRS at day 8 (Jan 2026)
Luvesilocin (formerly RE104; prodrug of 4-OH-DiPT)	5-HT2A agonist; engineered for a short acute experience	Shorter than psilocybin by design (exact duration TBD)	Reunion Neuroscience	Phase 2 positive, FDA BTB (Feb 2026) — for postpartum depression specifically, not general MDD/TRD
DT120 (formerly MM120; lysergide/LSD)	5-HT2A agonist + meaningful 5-HT1A / dopaminergic affinity	~8–12 hrs (longest of the class)	Definium Therapeutics (formerly MindMed)	Phase 3 positive (MDD). Emerge trial hit primary endpoint June 2026. Received FDA Breakthrough Therapy designation for MDD in Sept. 2026.

Single 25 mg Dose of Psilocybin for Major Depressive Disorder



	Psilocybin			Niacin		
Outcome/Study Visit	N	n (%)	95% CI	N	n (%)	95% CI
Depressive Symptom Response						
Post-Dose Day 8	51	27 (53)	38.5, 67.1	50	5 (10)	3.3, 21.8
Post-Dose Day 15	50	25 (50)	35.5, 64.5	45	8 (18)	8.0, 32.1
Post-Dose Day 29	49	26 (53)	38.3, 67.5	44	7 (16)	6.6, 30.1
Post-Dose Day 43	50	29 (58)	43.2, 71.8	44	9 (20)	9.8, 35.3
Depressive Symptom Remission						
Post-Dose Day 8	51	18 (35)	22.4, 49.9	50	4 (8)	2.2, 19.2
Post-Dose Day 15	50	20 (40)	26.4, 54.8	45	6 (13)	5.1, 26.8
Post-Dose Day 29	49	18 (37)	23.4, 51.7	44	5 (11)	3.8, 24.6
Post-Dose Day 43	50	22 (44)	30.0, 58.7	44	5 (11)	3.8, 24.6

COMP360: Single and Double 25 mg Dose Psilocybin for Treatment-Resistant Depression

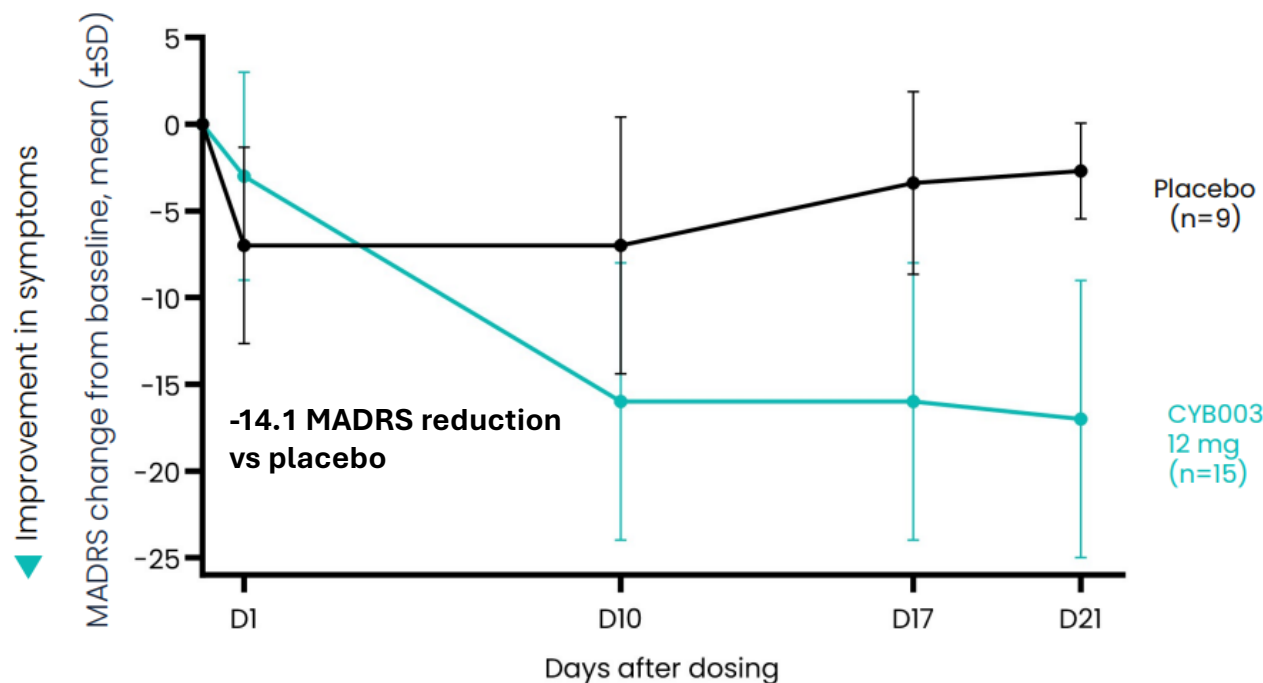
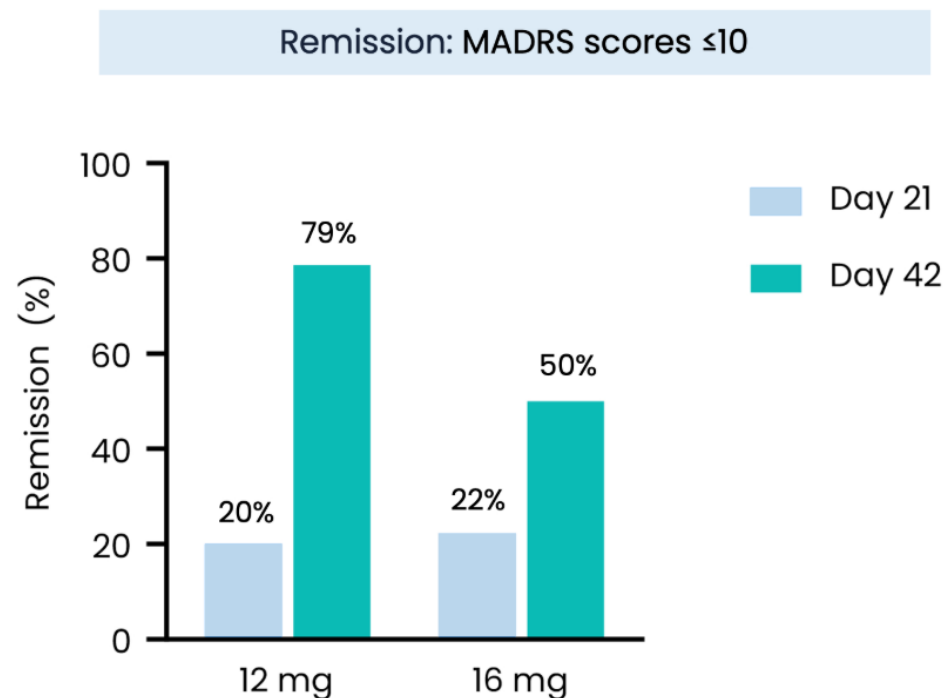


*Cross-trial comparisons should be interpreted with caution. Differences between these trials, including but not limited to study designs, protocols, timing of assessments, number or timing of doses and participant populations can meaningfully influence outcomes and limit the validity of any comparison.

Psychedelic Alpha. February 17, 2026. Accessed April 28, 2026.

<https://psychedelicalpha.com/news/compass-provides-fuller-phase-3-picture-madrs-curves-on-webcast/>.

Complex Phase 2 Program for Deuterated Psilocybin Analog



In complex phase 2 program in patients with major depressive disorder (MDD) were randomized to placebo or 12 or 16 mg of a deuterated psilocybin analog. Participants were allowed to remain on stable antidepressant dose. Phase 3 development program is specifically focused on the product as an augmentation strategy for standard antidepressants

Hot Off The Press: Additional Long-Term Open-Label Data on Psilocybin Durability of Effect in TRD

Notable Reduction in MADRS with Durability to 52 Weeks for 25mg Arm after Additional Dose in Part C

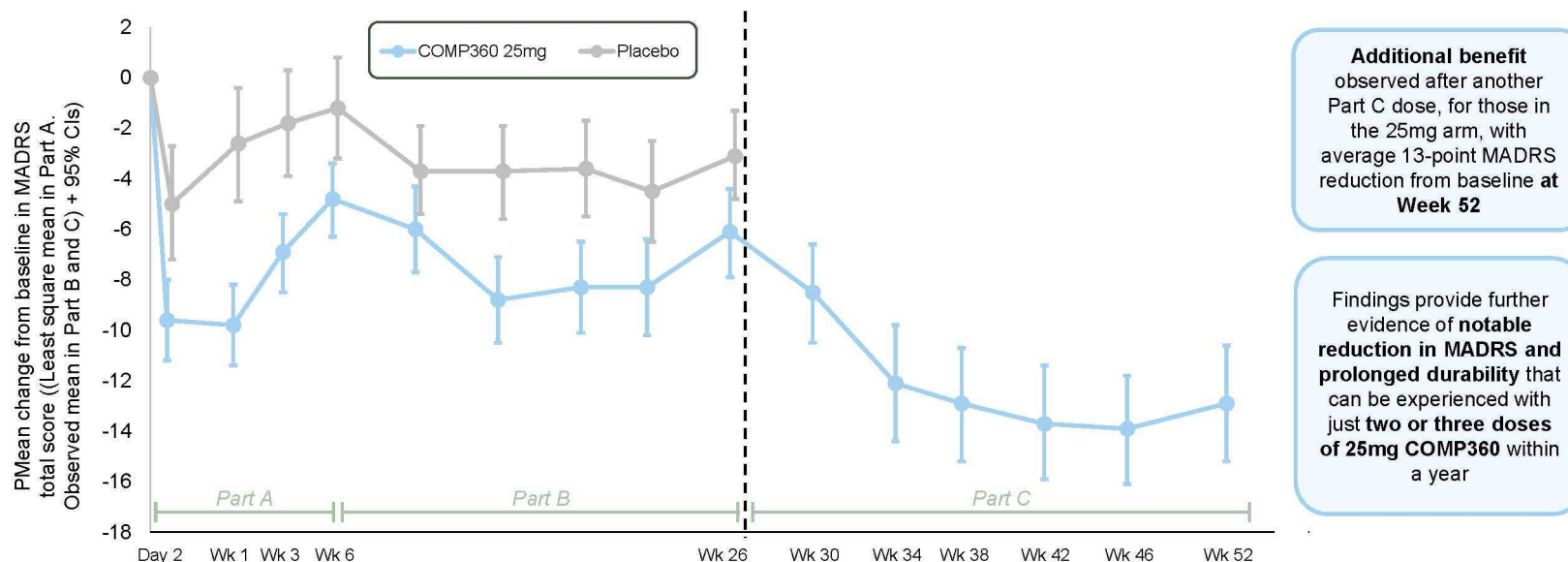


Figure 1: 25 mg participants who continued through Part C with 80% receiving retreatment in Part C

Note: Total 258 participants allocated to arms in trial, n=171 in 25mg arm, n=87 in placebo arm. 118 participants from 25mg arm entered Part C and 113 of those met eligibility criteria for open-label treatment of which 90 (80%) were dosed

MADRS = Montgomery-Åsberg Depression Rating Scale; n = number of participants

compass

Compass Pathways plc. Compass Pathways' new 52-week topline open-label data from phase 3 COMP005 trial demonstrates additional benefit from another COMP360 dose in Part C extending durability out to 1 year. Published September 9, 2026. Accessed September 9, 2026.

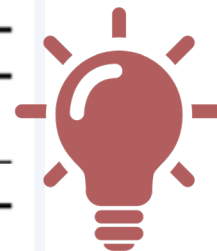
Novel 5HT2A Agonist (Bretisilocin) with Potential Serotonergic-Releasing Properties for MDD

Randomized, double-blind, double-dosing, active comparator-controlled trial in 40 patients with major depressive disorder (MDD)

MADRS CHANGES FROM BASELINE AND REMISSION RATES

	ARM 1	ARM 2
GM-2505 DOSING	Day 1, 1 mg Day 15, 15 mg	Day 1, 10 mg Day 15, 15 mg
BASELINE	31.9	33.4
DAY 14	n=20	n=20
- CHANGE FROM BASELINE	-12.1	-21.6
- REMISSION	25%	70%
DAY 29	n=20	n=17
- CHANGE FROM BASELINE	-21.1	-28.0
- REMISSION	55%	94%
DAY 74 FOLLOW-UP	n=20	n=17
- CHANGE FROM BASELINE	-19.7	-25.1

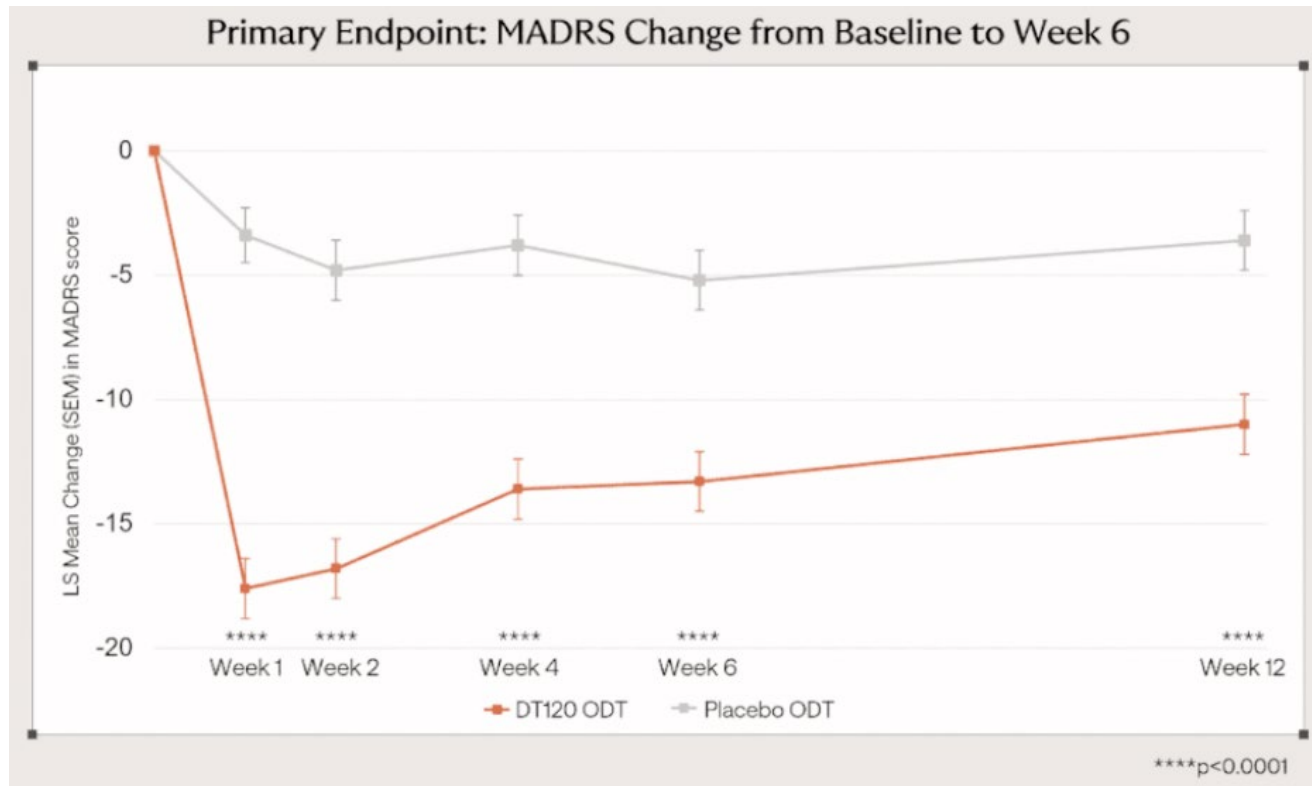
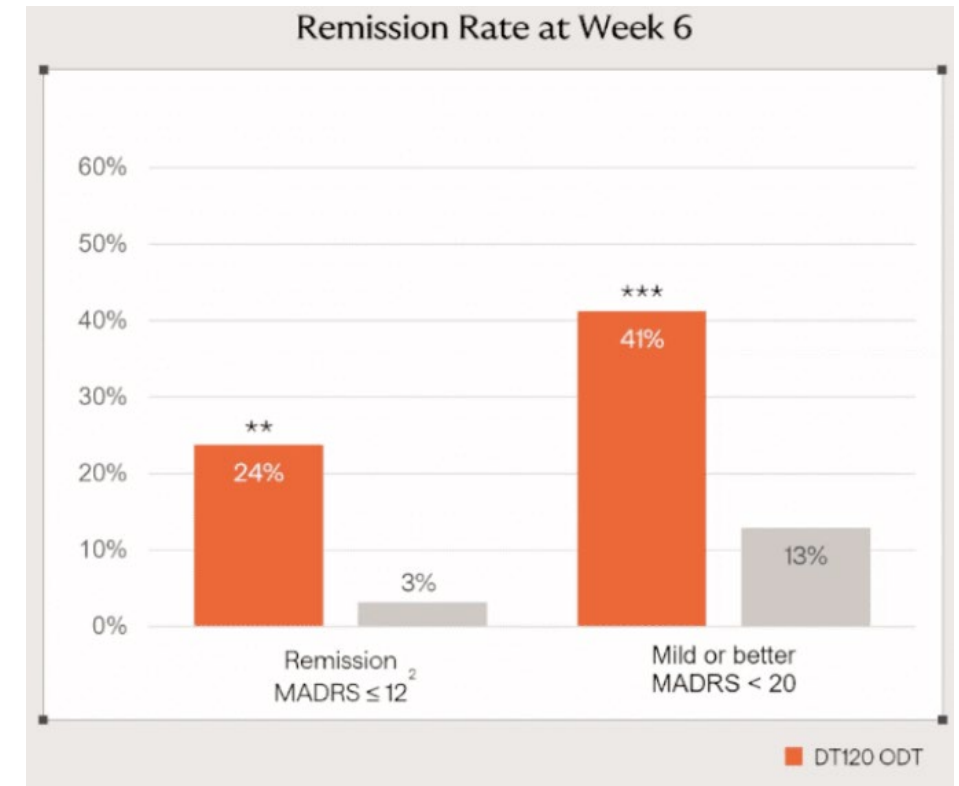
Change from baseline values reported are least squares mean estimates from MMRM analysis
Remission is defined as MADRS total score ≤ 10



- Novel serotonin 5HT2A agonist and serotonin releasing agent delivered intravenously (intramuscular in development) with a 60–90-minute psychedelic experience administered with only “psychosocial support” by facilitators not required to have therapy training/licensure

Marek GJ. *Robust antidepressant efficacy of the novel 5-HT2A receptor agonist GM-2505 in a double-blind, randomized, controlled phase 2a trial in patients with MDD.* Presented at: American Society of Clinical Psychopharmacology Annual Meeting; May 27-30, 2025; Scottsdale, AZ. PR Newswire. Gilgamesh Pharmaceuticals. May 27, 2025. Accessed September 2025.

Single 100 Microgram Dose of LSD (DT120) for Major Depressive Disorder



149 MDD patients across 20 sites randomized to receive either 100 µg of the company's orally disintegrating tablet (ODT) form of LSD or placebo. Primary end point at 6 weeks, double-blind follow-up to week 12 with a 40-week open-label extension.

Inhaled 5-MeO-DMT Monotherapy for Treatment-Resistant Depression

RCT: GH001 vs Placebo in Patients With Treatment-Resistant Depression

POPULATION

35 Male, 46 Female

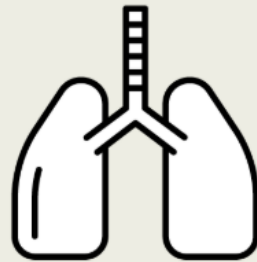


Adults with treatment-resistant depression

Mean (SD) age, 42.8 (11.2) y

INTERVENTION

81 Patients randomized



40 Inhaled mebufotenin (GH001)

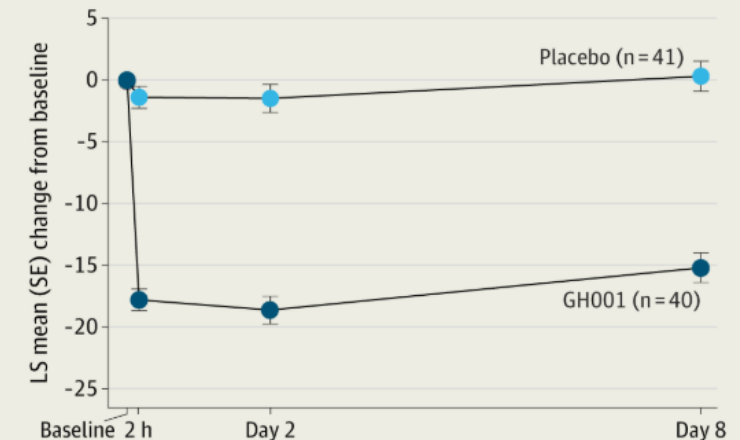
GH001 individualized dosing regimen (up to 3 escalating doses: 6, 12, 18 mg)

41 Inhaled placebo

Inhaled placebo individualized dosing regimen

FINDINGS

Mean change in MADRS total score from baseline to day 8 was statistically significantly greater for GH001 vs placebo



Least-squares mean (SE) change in MADRS score:

GH001 group: -15.2 (1.2)

Placebo group: 0.3 (1.2)

Between-group difference: -15.5 (1.7); $P < .001$

SETTINGS / LOCATIONS

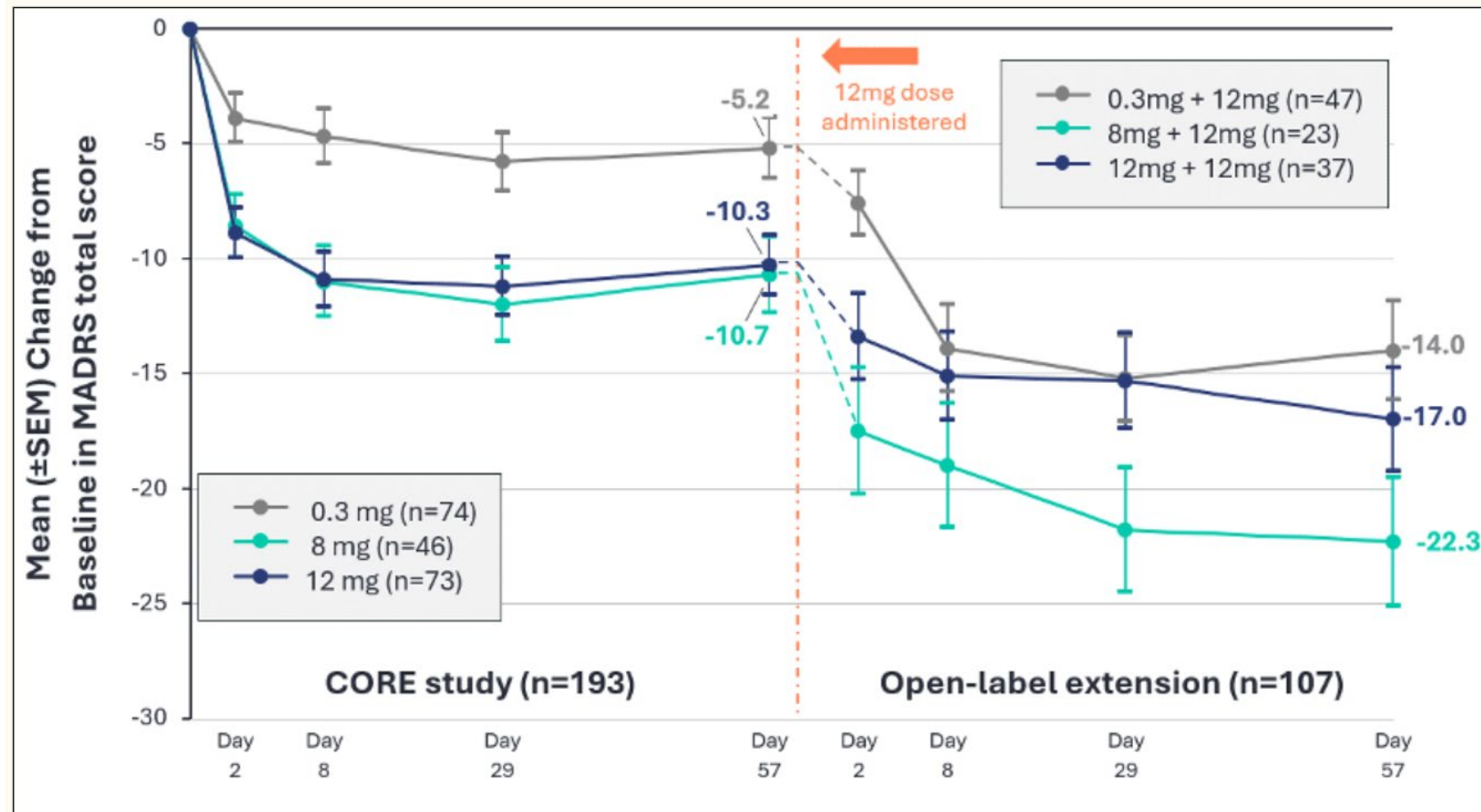


16 Clinics
in Europe

PRIMARY OUTCOME

Change from baseline to day 8 in Montgomery-Åsberg Depression Rating Scale (MADRS) total score (range, 0-60) with GH001 individualized dosing regimen vs placebo individualized dosing regimen

Intranasal 5-MeO-DMT Monotherapy for Treatment Resistant Depression



Luvesilocin (4-OH-DiPT Prodrug) Monotherapy and as Augmentation for Postpartum Depression



Study Design

- RECONNECT trial (NCT06342310) — multicenter, randomized, double-blind, active dose-controlled, parallel-group
- N=84 adult female patients with moderate-to-severe postpartum depression (PPD)
- Single subcutaneous dose: 30mg luvesilocin vs. 1.5mg (subperceptual low-dose active control)
- Primary endpoint: change from baseline in MADRS total score at Day 7
- Secondary endpoints: response/remission rates, additional mood and anxiety measures, follow-up through Day 28



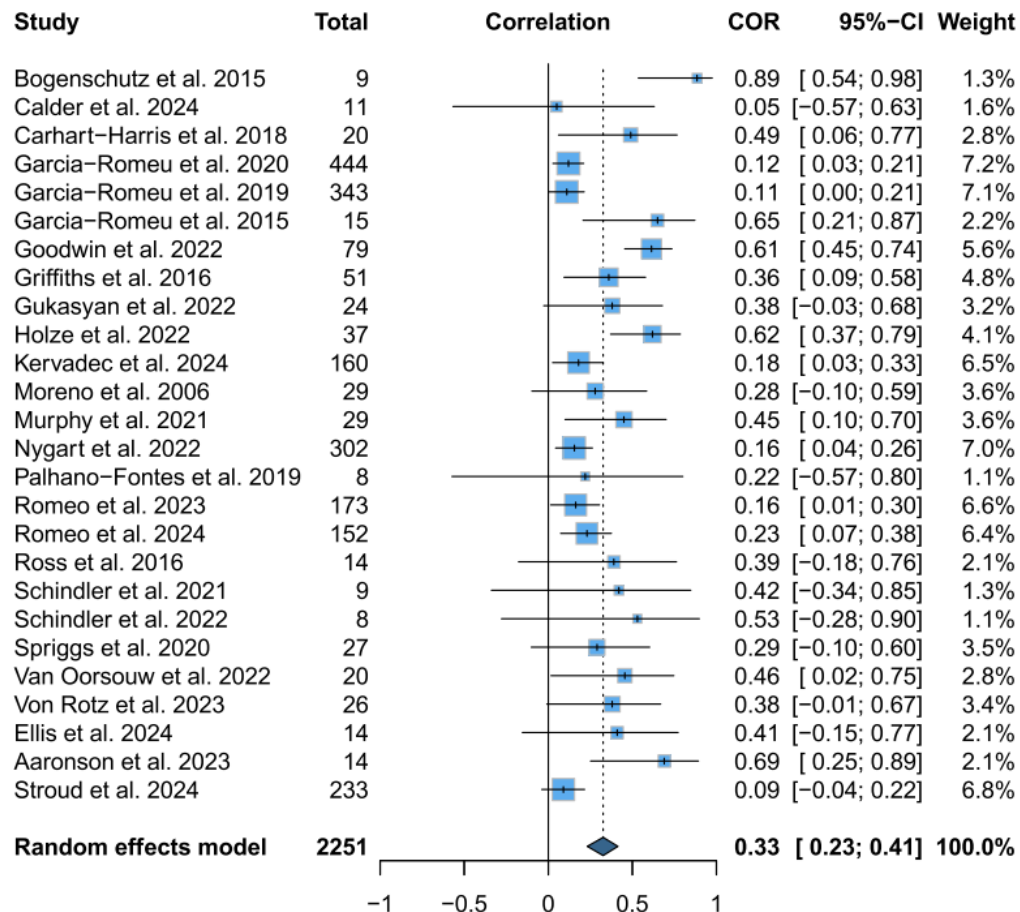
Key Findings

- Day 7 (primary endpoint): 23.0-point MADRS reduction (30mg) vs. 17.2-point (1.5mg control); difference 5.80 pts, $p=0.0094$
- Day 7 response/remission: 77.1% response vs. 61.6% (30mg vs. 1.5mg); 71.4% remission vs. 41.0%
- Day 28: ~70% of 30mg patients remained in remission — essentially unchanged from Day 7, indicating a durable rather than fading effect
- HAM-A (anxiety) response 65.7% (30mg) vs. 52.6% (1.5mg) at Day 7, maintained through Day 28
- FDA Breakthrough Therapy Designation granted (Feb 2026); single Phase 3 trial could support registration

PPD = postpartum depression

Clayton AH, Hoffman MC, Hendricks PS, et al. RE104: A novel serotonergic psychedelic 4-OH-DiPT prodrug for the treatment of postpartum depression. Poster presented at: ACNP Annual Meeting; Jan 12-15, 2026. [ClinicalTrials.gov NCT06342310](https://clinicaltrials.gov/NCT06342310).

Meta-Analysis Links Acute Psychedelic Experience to Longer-Term Therapeutic Benefit



Heterogeneity: $I^2 = 63\%$, $\tau^2 = 0.0336$, $p < 0.01$
 Test for overall effect: $t_{25} = 6.81$ ($p < 0.001$)

- **Overall correlation** between psychedelic experience intensity (predominantly measured via mystical-experience scales, alongside broader ASC dimensions) and clinical improvement: **$r=.33$, $p<.0001$**
- **Stronger for mood disorders ($r=.41$) than for addictions ($r=.19$)** — the intensity-outcome relationship is not uniform across psychiatric indications, and appears most robust specifically for depression/mood-related outcomes
- **Stronger in protocol-based clinical settings ($r=.50$) than in naturalistic/recreational use ($r=.14$)** — supervised, structured therapeutic contexts show a substantially tighter link between experience intensity and outcome than unsupervised use
- **Stronger in prospective study designs ($r=.43$) than retrospective designs ($r=.14$)** — addressing a common methodological critique of this literature (recall bias inflating retrospective correlations); the relationship holds up, and is actually stronger, when measured prospectively

Key Learning Points



- **Most investigational serotonergic psychedelics for MDD are thought to work primarily through 5-HT_{2A} receptor agonism**, distinguishing them from both traditional serotonergic and novel glutamatergic antidepressants
- Investigational formulations of psilocybin, psilocybin analogs, DMT/5-MeO-DMT, and LSD-related compounds are being evaluated for MDD and TRD, with early clinical studies suggesting potentially rapid and sustained antidepressant effects
 - **Example:** brexisiloin produced significantly greater reductions in MADRS scores at Day 14 with a 10-mg dose vs a 1-mg active comparator in a Phase 2a MDD trial
- Serotonergic psychedelics may combine neuroplastic effects with acute psychoplastic experiences
 - Although the intensity of the psychedelic experience has been associated with longer-term clinical benefit, its causal contribution remains uncertain

Development of Psychedelic-Assisted Psychotherapies (PAPs) in MDD

Andrew Penn

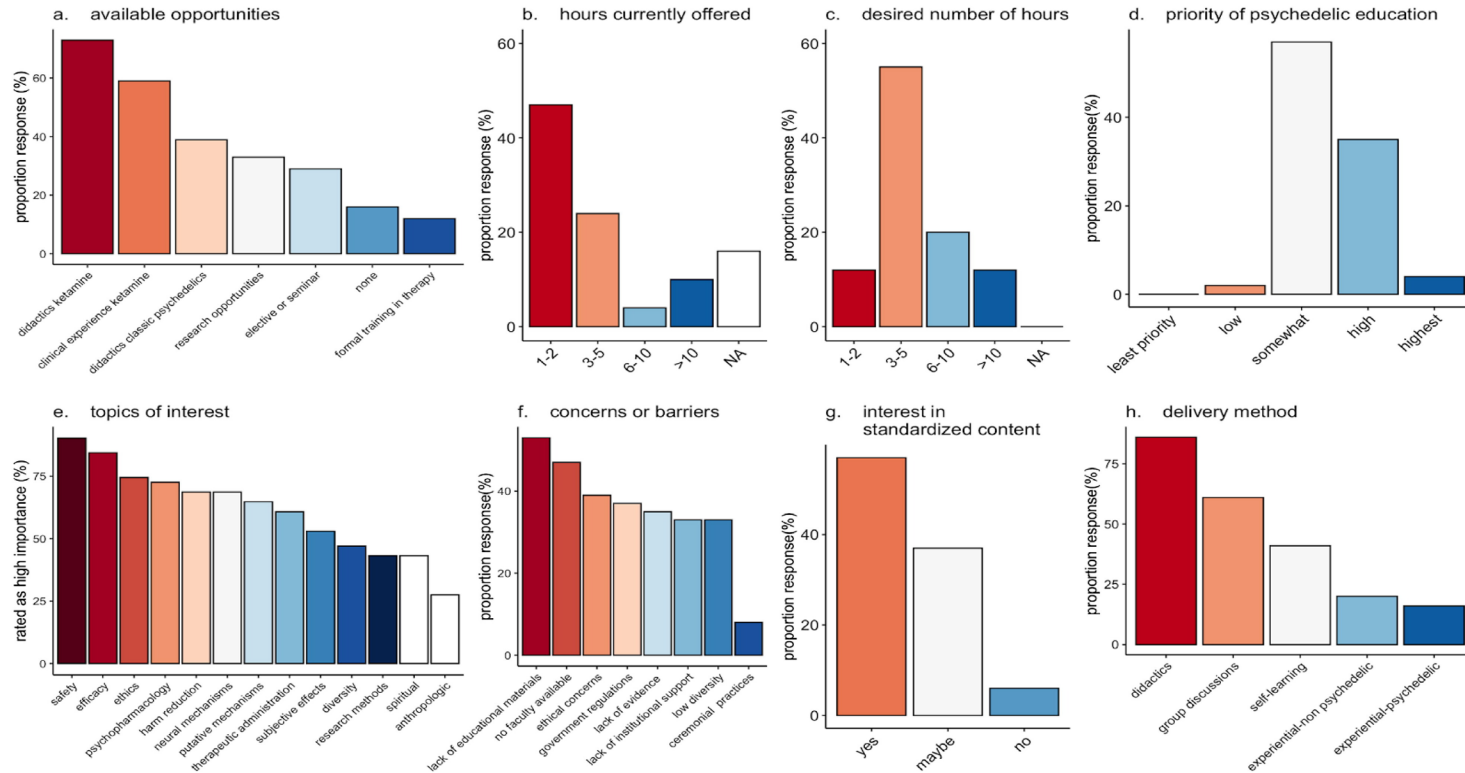
What's the rationale for combining therapy + psychedelic?



Leveraging synergy for better outcomes?



Current Psychiatry Residency Training Offers Little Content on Psychedelics

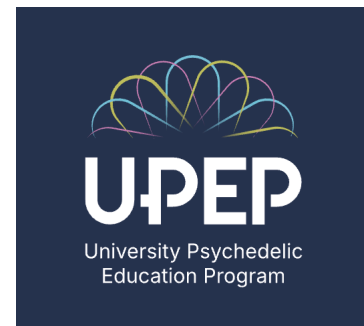


1-2 hours currently offered

Safety, efficacy, ethics, pharmacology are of greatest interest

Lack of materials and faculty are the largest barriers

Figure 1. (a) Psychedelic medicine education opportunities currently available. (b) Number of hours of psychedelic medicine education currently available. (c) Number of desired hours of psychedelic medicine education. (d) Priority of psychedelic medicine education. (e) Topics of high importance in psychedelic medicine education. (f) Concerns about or barriers to implementing psychedelic medicine education. (g) Interest in standardized content for psychedelic medicine education. (h) Preferred method(s) of delivering psychedelic medicine education in respondents' programmes.



Professional Practice Guidelines Emerged

PROFESSIONAL PRACTICE GUIDELINES FOR PSYCHEDELIC- ASSISTED THERAPY AUGUST 2023

PRESENTED BY
 AMERICAN
PSYCHEDELIC
PRACTITIONERS
ASSOCIATION


GUIDELINE STATEMENT SUMMARY

GUIDELINE STATEMENT SUMMARY

GUIDELINE 1

Psychedelic-assisted therapy practitioners are in good standing with the healthcare licensure and/or certification body of their professional discipline.

GUIDELINE 2

Psychedelic-assisted therapy practitioners have specialized training in psychedelic-assisted therapy appropriate to their scope of practice and strive to ensure their knowledge of the potential physical, psychological, and spiritual effects of psychedelics and core principles of psychedelic-assisted therapy.

GUIDELINE 3

Psychedelic-assisted therapy practitioners are committed to ongoing development in fundamental therapeutic competencies, including building and maintaining therapeutic rapport, maintaining emotional and physical presence, treating patients with dignity and respect, being welcoming and compassionate, and meeting the highest levels of ethical integrity.

GUIDELINE 4

Psychedelic-assisted therapy practitioners obtain and document informed consent before commencing treatment, respect the patient's right to withdraw consent, and approach consent as an ongoing

process to be addressed at multiple points over the course of therapy.

GUIDELINE 5

Psychedelic-assisted therapy practitioners specifically address the potential applications of touch in the informed consent process. Such consent includes the patient's right to refuse touch except in situations where touch is required to prevent serious injury, damage, or harm.

GUIDELINE 6

Psychedelic-assisted therapy practitioners ensure that patients have been comprehensively screened in accordance with existing evidence, guidelines, and clinical judgment.

GUIDELINE 7

Psychedelic-assisted therapy practitioners aim to build rapport and trust with patients during the preparatory period.

GUIDELINE 8

Psychedelic-assisted therapy practitioners prepare patients for a medication administration session by inviting them to share their personal histories, explaining medication administration session logistics, reviewing the range of possible experiences during the medication administration session, discussing potential therapeutic approaches that may be used, providing guidance for navigating challenging experiences that could arise, and answering patient questions.

GUIDELINE STATEMENT SUMMARY

GUIDELINE 9

Psychedelic-assisted therapy practitioners aim to facilitate a safe and therapeutic medication administration session conducted in a comfortable and confidential setting.

GUIDELINE 10

Psychedelic-assisted therapy practitioners monitor patients for adverse events both during and following the medication administration session, and ensure that complications are addressed.

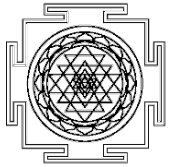
GUIDELINE 11

Psychedelic-assisted therapy practitioners support patients in understanding and making meaning of their psychedelic medication experience and incorporating desired changes into their lives.

GUIDELINE 12

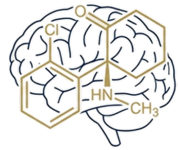
Psychedelic-assisted therapy practitioners communicate and coordinate with other relevant providers to ensure continuity of care.

Many programs popped up to train clinicians in both psychedelics (and ketamine)



California Institute
of Integral Studies

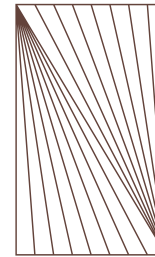
Fluence



KRI Ketamine
Research
Institute
Advancing ketamine therapy through
clinical care, education, and research



SYNTHESIS



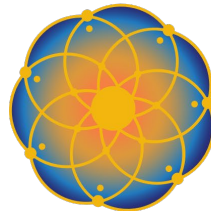
NUMINUS



MAPS
MULTIDISCIPLINARY ASSOCIATION FOR PSYCHEDELIC STUDIES



POLARIS INSIGHT CENTER



ketamine
training center



INTEGRATIVE
PSYCHIATRY
INSTITUTE



HEROIC
HEARTS
PROJECT

BCSP

UC Berkeley
Center for the
Science of
Psychedelics

Psychedelic Training Programs Vary Considerably

Table 1. State guidelines for psychedelic facilitation training in Oregon and Colorado.

Oregon	Hours	Colorado	Hours
Historical, Traditional, and Contemporary Practices and Applications	12		
Cultural Equity in Relation to Psilocybin Services	12	Indigenous Social, and Cultural Considerations	10
Safety, Ethics, and Responsibilities	12	Ethics and Colorado Natural Medicine Rules and Regulations	25
		Physical and Mental Health and State	25
		Facilitator Development and Self-Care	
Psilocybin Pharmacology, Neuroscience, and Clinical Research	12	Drug Effects, Contraindications, and Interactions	5
Core Facilitation Skills	16	Facilitator Best Practices	5
		Relation Boundaries and Introduction to Physical Touch	10
		Introduction to Trauma Informed Care	10
		Introduction to Suicide Risk	5
Preparation and Orientation	16	Screening	5
		Preparation	10
Administration	20	Administration	10
Integration	12	Integration	10
Group Facilitation	16	Group Facilitation	10
Total hours	128		150

Note: Content areas required for psychedelic facilitation training programs to be eligible for Oregon and Colorado certification are presented underneath column headers for each state, respectively. The number of hours required to be dedicated to each content area are listed to the right of each area. Content areas for each state are organized according to similarity. For example, requirements from each state pertaining to culture are located alongside one another. Where requirements from one state did not have counterparts in the other state, or when a single topic in one state corresponded to multiple topic in another state, fields in the table were left empty. When one state included multiple areas that all corresponded with a requirement for the other state, fields were left empty as well (e.g., OR's "core facilitation skills" corresponded with multiple requirements in CO guidelines).

128-150 hours for state regulated programs in OR and CO

CO: must also have a professional license (NP, MD, PA, LCSW, etc)

What are key skills for a psychedelic facilitator to have?

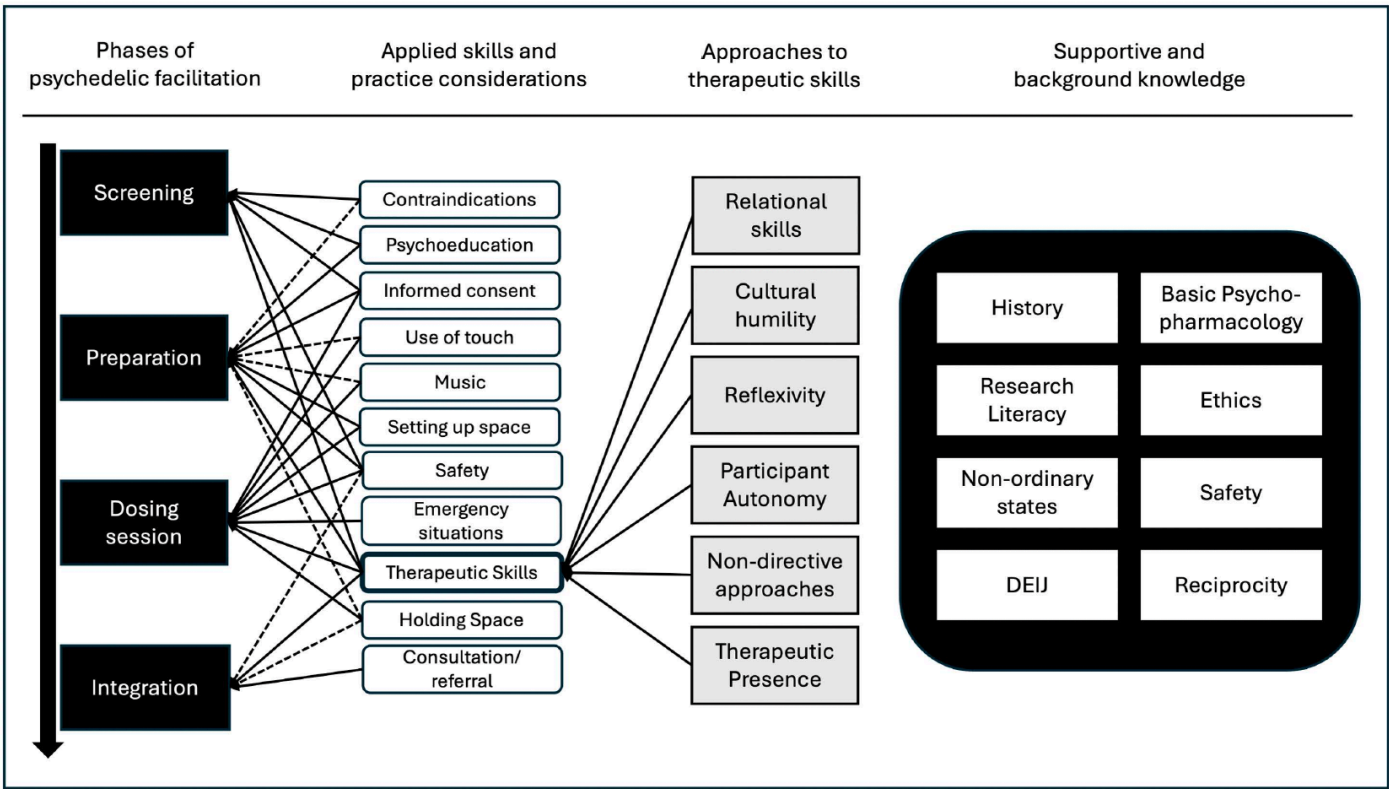


Fig 1. Content Emphases in Instruction. *Note:* This figure represents content emphases described by psychedelic facilitation training programs. Headings at the top of the figure refer to the content below each heading: The first, phases of psychedelic facilitation, represents in chronological order the phases of screening, preparation, dosing, and integration. Applied skills are illustrated in relation to the facilitation phases, with solid lines representing common, explicit references of a given skill to a given facilitation phase, while dashed lines represent only occasional mentions. Approaches to therapeutic skills are all included within “therapeutic skills”, which are an applied skill in facilitation, but which were discussed with depth and emphasis that warranted expansion as a discrete topic. Supportive and background knowledge includes aspects of instruction that were not explicitly tied to any given procedure but were taught due to their generalized importance for psychedelic care.

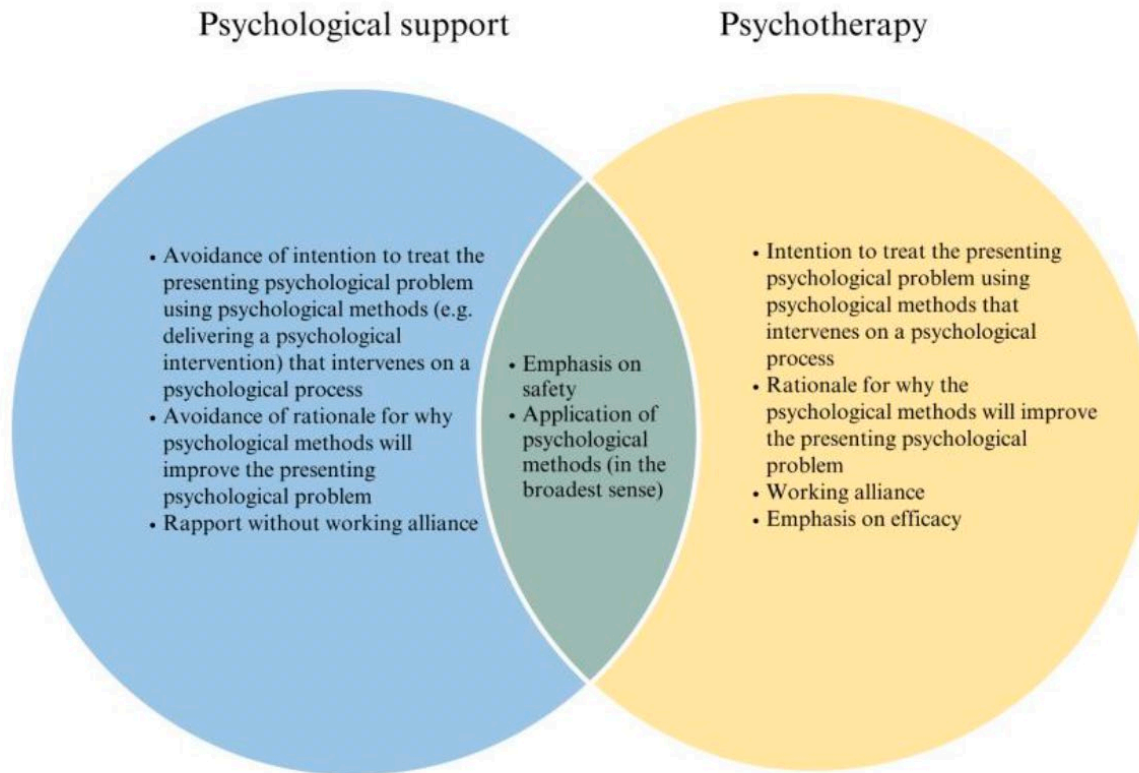
Qualities of a psychedelic therapist

1. Empathic abiding presence
2. Trust enhancement
3. Spiritual intelligence
4. Knowledge of the physical and psychological effects of psychedelics
5. Therapist self awareness and ethical integrity
6. Proficiency in complementary techniques

A trickier question: Do facilitators need their own experience with psychedelics to treat patients with psychedelics?

- Delphi process 17/18 experts felt it was important for psychedelic facilitators to have their own psilocybin experience
- It's thought to improve understanding of the patient's psychedelic experience
- Akin to psychotherapy training, where personal psychotherapy is often expected
- Parallel to indigenous praxis around psychedelics, where experiential knowledge is as important as declarative knowledge

Pharmaceutical trials have moved more towards “psychological support” and less towards “psychotherapy” *But what does that mean?*



Common factors are included in both

- Ritual
- Rapport
- Role
- Container

Psychotherapy uses psychology theory-based intervention, whereas psychological support avoids these

And is it an either/or? And does the FDA care?

An unclear question: what is the ideal “dose” of therapy?

1 block = 1 hour of therapist labor

MAPS	48 hours	2 Clinicians	=96 hours				
		USONA	24 hours	2 clinicians	=48 hours		
						Definium =	8 hours
							monitoring
							(not
							therapy)

Nonpsychedelic psychoplastogens

(take home)

What kind of psychotherapy are we pairing with psychedelics?

Existing studies have explored:

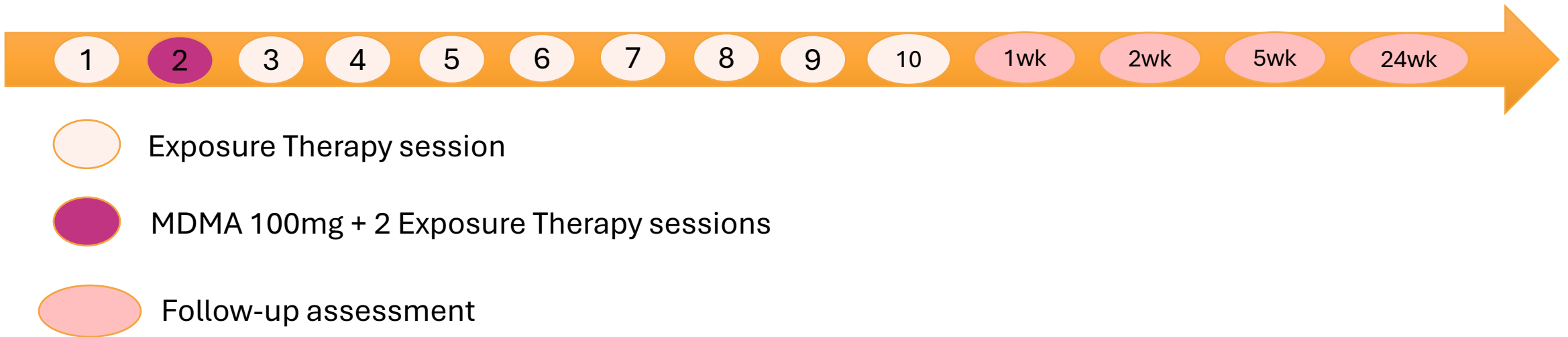
- Supportive presence
- Inner directed “inner healing intelligence”/ nondirective therapy
- CBT
- ACT (Acceptance and Commitment Therapy), other 3rd wave CBT
- Mindfulness Based Relapse Prevention/Motivation Enhancement Therapy
- Exposure with response prevention
- MDMA assisted therapy – trauma based therapy + experiential/humanistic therapy
- Transpersonal psychotherapy
- Internal Family Systems (“parts work”)
- Existential/transpersonal therapy (esp for end of life care)
- Family Based Treatment (Anorexia)
- Music is a common background in most therapies (but not music therapy)
- Art therapy is sometimes used in integration

33 studies analyzed

- 33% did not report the number of sessions
- 45% did not report the duration of sessions
- 42% did not report provider credentials
- 52% did not report whether their intervention used a therapy manual
- 64% did not reference a manual that was available to readers
- 82% did not report that they assessed treatment fidelity

Should we combine psychedelics with an evidence-based therapy?

MDMA Massed exposure for PTSD trial at Emory - recruiting

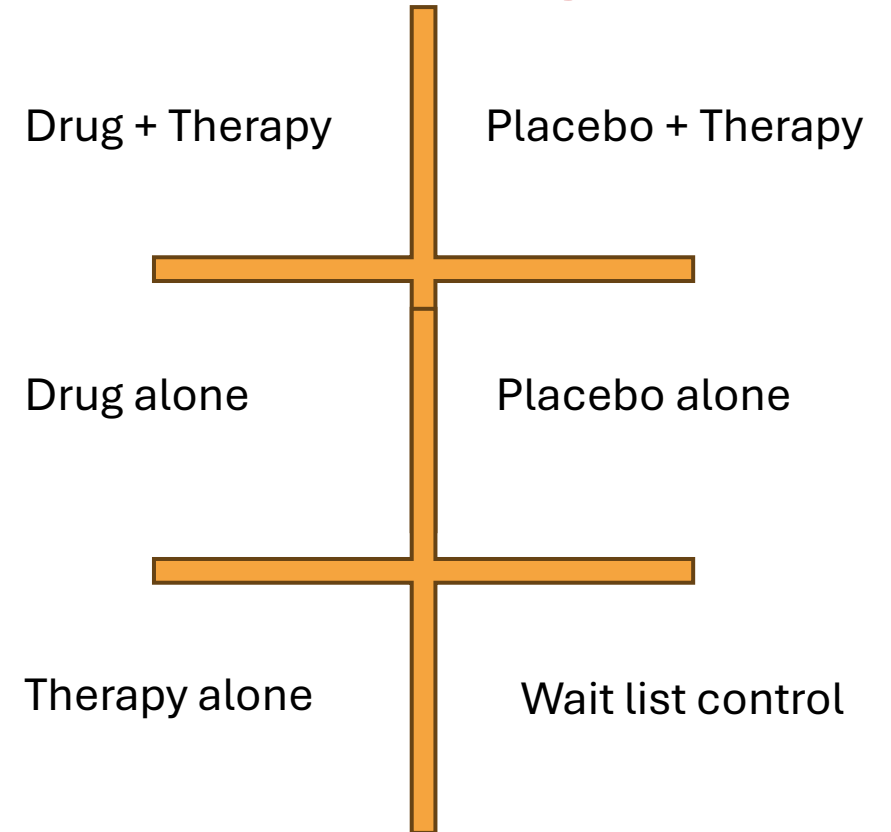


- Prolonged exposure is considered gold standard treatment for PTSD
- Outcomes: CAPS-5, PCL-5

The therapeutic effects of psychedelics are challenging to isolate from the context in which they are given

“Observations include a general lack of consistency in psychotherapy type and implementation employed across trials, an inability to disentangle the psychotherapeutic effect as distinct from or in interaction with the drug effect, and no clear optimal psychotherapeutic treatment or framework to complement psychedelic administration.”

- Leone, et al (2024)



Key Learning Points

- Psychedelics were historically paired with psychotherapy, but more recent trials have reduced this to monitoring and support and/or eliminated psychotherapy entirely
- Psychotherapies paired with psychedelics have been eclectic
- Many health care professional trainings historically have not included content on psychedelic treatments, and there is not an agreed upon curriculum for learning these skills

Implementation of Psychedelics in the Care of Patients with MDD

Andrew Penn and Chuck Raison

What will therapy look like post-approval?



FDA

Standard of Care (SOC):
REMS + How treatment is commonly done, based on best practices consensus, and edges defined by malpractice (Many Spravato clinics have a recliner in a room with neutral colors – this is SOC)



REMS: Time, storage, monitoring (absolute minimum requirements)
(The Spravato REMS doesn't care about the color of your treatment room)

REMS = Risk Evaluation and Mitigation Strategy.

BrainFutures. Professional Practice Guidelines for Psychedelic-Assisted Therapy. August 2023. Accessed January 25, 2026.

<https://www.brainfutures.org/mental-health-treatment/professional-practice-guidelines/>. Spravato

Rems <https://www.spravatorems.com/pdfs/REMSProgramOverview> Accessed 2/18/26

What will that REMS look like?

Psychedelic Drugs: Considerations for Clinical Investigations Guidance for Industry

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

July 2026
Clinical/Medical

“Observation by two monitors for the duration of the treatment session.

– A health care provider with **graduate-level professional training and clinical experience in psychotherapy, licensed to practice independently**, serving as the lead monitor.

– An **assistant monitor with a nursing or bachelor’s degree** and at least **1 year of clinical experience** in a licensed mental health care setting.

• If the lead monitor is not a physician, **availability of a licensed on-call physician able to reach the clinical site within 15 minutes** in the event of a medical emergency

How many patients can we treat in an 8-hour day?

Esketamine (2 hours per pt)



Can be tech



On Site



Graduate level
HCP



RN or
BS trained



On Site



DT120 – average time to d/c 5.8 hours, 100% at 8 hours

COMP360 – d/c time not reported

Usona – d/c time not reported

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?



Future Short-Acting Drug Candidates:

Subjectively Psychedelic

BPL003 (5MEO-DMT) – 2 hrs

CYB003 (Deuterated DMT) – 2-3 hours

Bretsilocin (novel 5HT2A agonist/monoamine releaser) – 2 hours

RE104 (4-HO-DiPT) – 3-4 hours



Subjectively nonpsychedelic

DLX-001 (isotryptamine neuroplastogen) – take-home

DLX-159 (tryptamine neuroplastogen) – take-home

Others under development

2hr REMS = 8 patients/day

4hr REMS = 2 patients/day

2 hours/ Existing REMS/ Existing CPT codes

CPT = Current Procedural Terminology.

WHEN TO USE WHICH CODES:		
If You Buy and Bill for SPRAVATO®		
Use Combination Drug and Service G Codes for		Use Drug HCPCS and Consider Using Service CPT*
■ Medicare (required)		■ Non-Medicare payers that do not require or accept the G Codes
■ Non-Medicare payers that require G Codes		
56-mg dose 2 devices	G2082	1 unit
84-mg dose 3 devices	G2083	1 unit
56-mg dose 2 devices	S0013*	56 units
84-mg dose 3 devices	S0013*	84 units
		Evaluation & Management (E/M) codes
If You Acquire SPRAVATO® Through a REMS-certified Pharmacy		
Consider Using Service CPT* Codes for:		
■ Medicare and non-Medicare payers		
Service: Evaluation & Management (E/M) codes		
■ 99415 – Prolonged clinical staff service (the service beyond the highest time in the range of total time of the service) during an evaluation and management service in the office or outpatient setting, direct patient contact with physician supervision; first hour (list separately in addition to code for outpatient E/M service)*		
■ 99416 – Each additional 30 minutes (list separately in addition to code for outpatient E/M service)		
■ 99417 – Prolonged office or other outpatient E/M service(s) beyond the minimum required time of the primary procedure that has been selected using total time, requiring total time with or without direct patient contact beyond the usual service, on the date of the primary service, each 15 minutes of total time (list separately in addition to codes 99205 or 99215 for office or other outpatient E/M service(s))		
■ G2212 – When billing Medicare for Prolonged Service(s), report G2212 instead of CPT 99417 and apply only after the maximum time required to report 99205 or 99215 has been exceeded by 15 minutes		
■ Bundled G codes may only be billed when the product is acquired by an office through a specialty distributor. They may not be used if product is acquired from a specialty pharmacy.		

The Monitor-Clinician Continuum (MCC) Model

- Establishing relationship/trust
- Psychological safety
- Stabilization during session
- Timely escalation if needed

- Team based care
- Functions, not titles
- Interdependent functions
- Could be 3,2, or 1 people
- No hierarchy is implied

**Monitoring
and
support**

**Psychotherapeutic
Intervention**

Patient

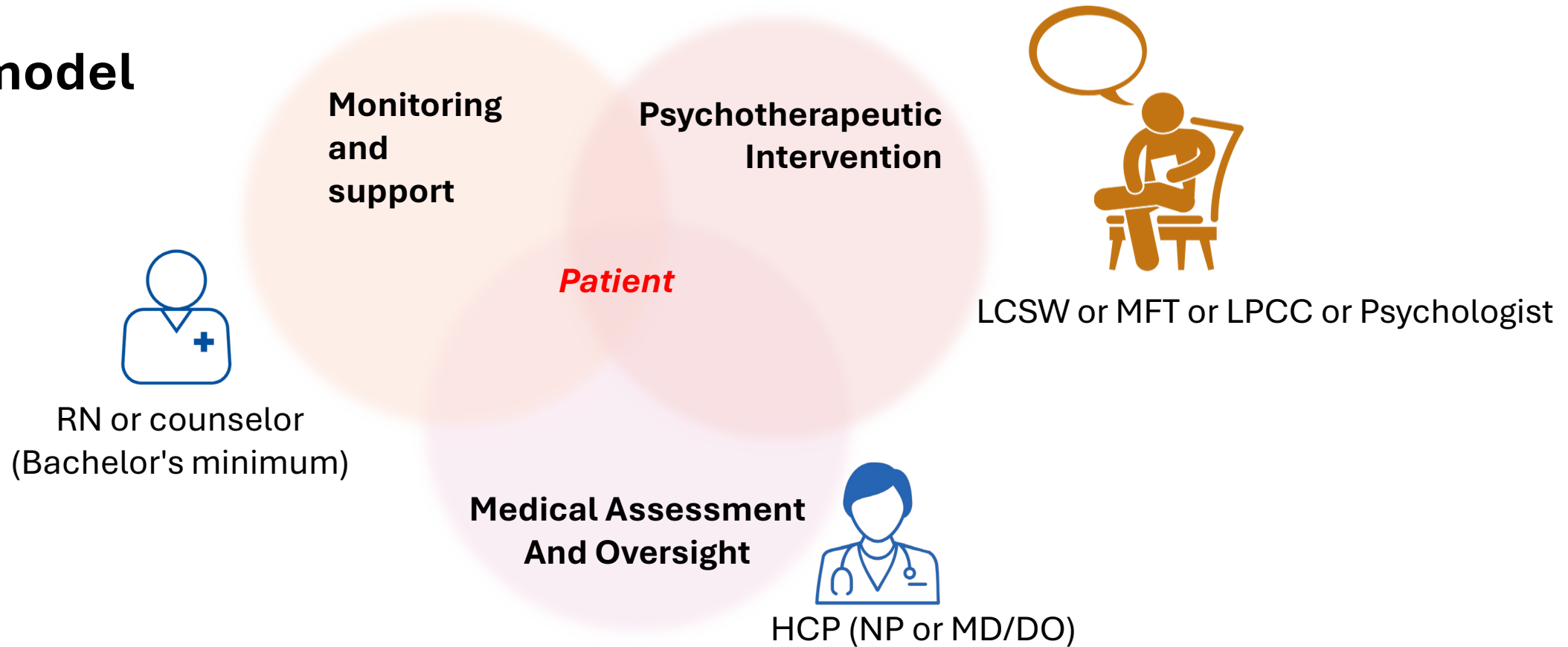
**Medical Assessment
And Oversight**

- Modality (drug) informed
- Treatment Formulation
- Treatment goals
- Intentional intervention
- Psychotherapeutic accountability

- Medical Eligibility
- Risk assessment
- Pharmacological Intervention
- Escalation
- Accountability

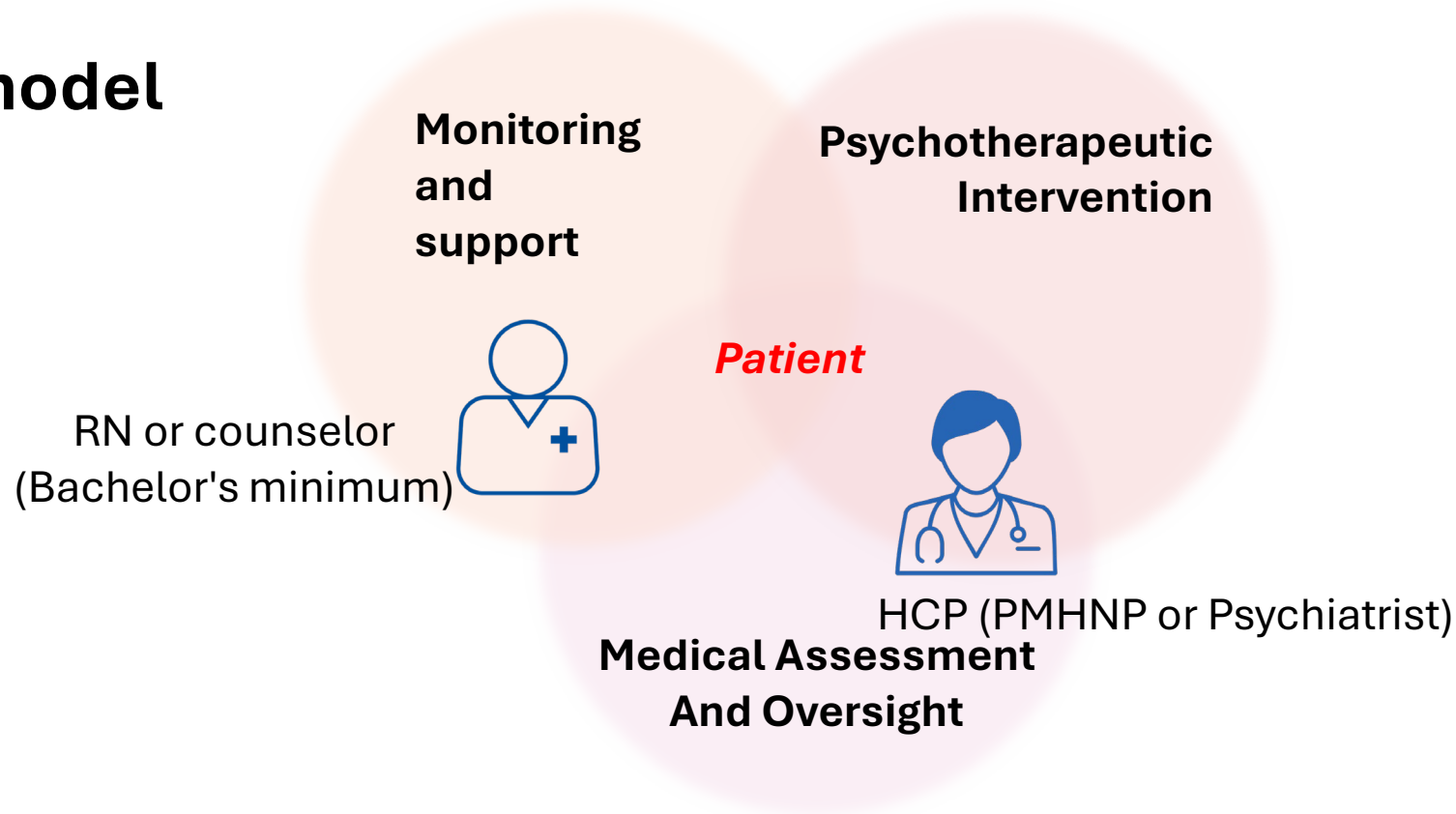
How might this look?

3 Person model



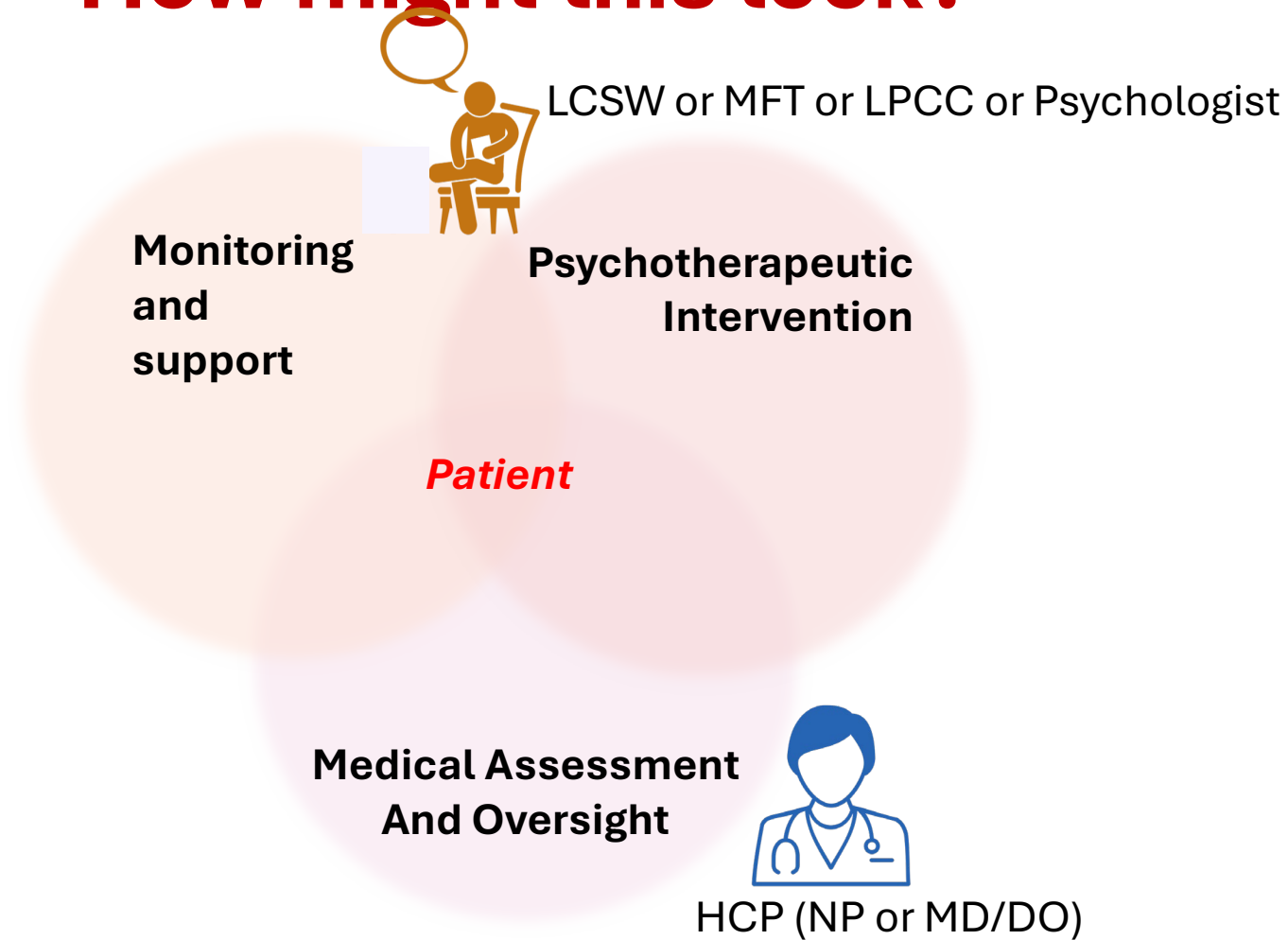
How might this look?

2 Person model



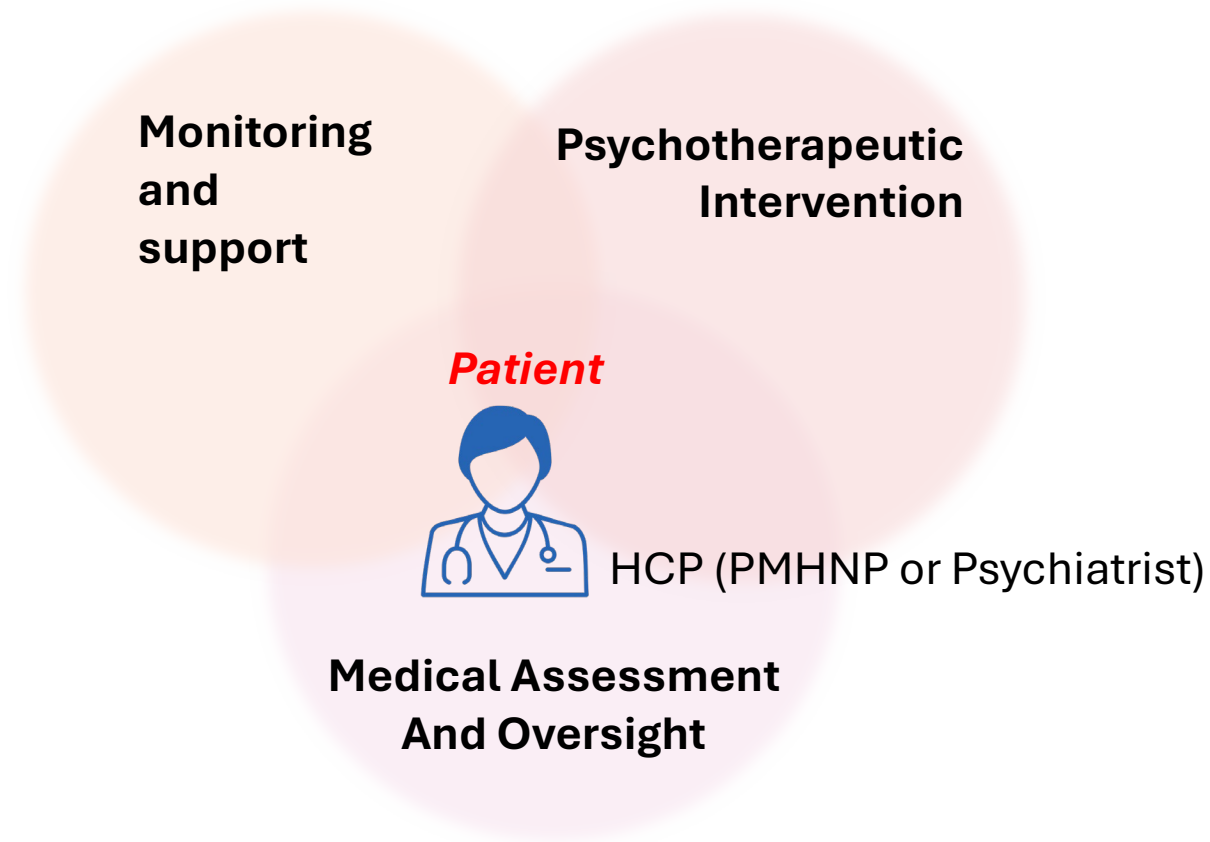
How might this look?

2 Person model



How might this look?

1 Person model



Key Learning Points

- Much of psychedelic treatment implementation will be dependent on the REMS, which will be decided upon post-approval and the standard of care that has been developing over many years
- The economics of psychedelic treatment implementation will depend significantly upon reimbursement, and the costs of personnel needed to deliver the treatments, and the cost of the drug
- Future models will likely involve treatment teams where different personnel can serve different functions in the treatment

Faculty Discussion: Hot Topics in the Future of Psychedelics in Psychiatry and MDD

Regulatory Complexities in Clinical Research and Real-World Practice

Multidisciplinary Cross-Training and Scope-of-Practice Concerns

Risk/Benefit Evaluations and Ethical Considerations in the Context of MDD



Q&A