Neuroscience Education Institute

From Breakthrough to Scrutiny: Promise, Proof, and the Path to Practice for Psychedelic Therapeutics

Roger S. McIntyre, MD, FRCPC



Disclosure

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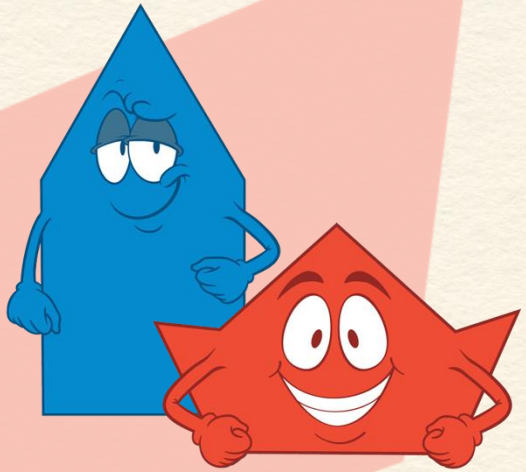
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Consultant/Advisor: AbbVie, Adhere Tech, Alkermes, Atai Life Sciences, Autobahn Therapeutics, Axsome, Bausch Health, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Definium, Eisai, Eli Lilly, GH Research, Intra-Cellular Therapies, Janssen, Johnson & Johnson, Kris, Lundbeck, Mitsubishi Tanabe Pharma, Neumora Therapeutics, NeuraWell, Neurocrine, NewBridge Pharmaceuticals, Novo Nordisk, Otsuka, Pfizer, Sanofi, Takeda, Teva, Torrent and Viatris

Speakers Bureau: AbbVie, Adhere Tech, Alkermes, Atai Life Sciences, Autobahn Therapeutics, Axsome, Bausch Health, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Definium, Eisai, Eli Lilly, GH Research, Intra-Cellular Therapies, Janssen, Johnson & Johnson, Kris, Lundbeck, Mitsubishi Tanabe Pharma, Neumora Therapeutics, NeuraWell, Neurocrine, NewBridge Pharmaceuticals, Novo Nordisk, Otsuka, Pfizer, Sanofi, Takeda, Teva, Torrent and Viatris

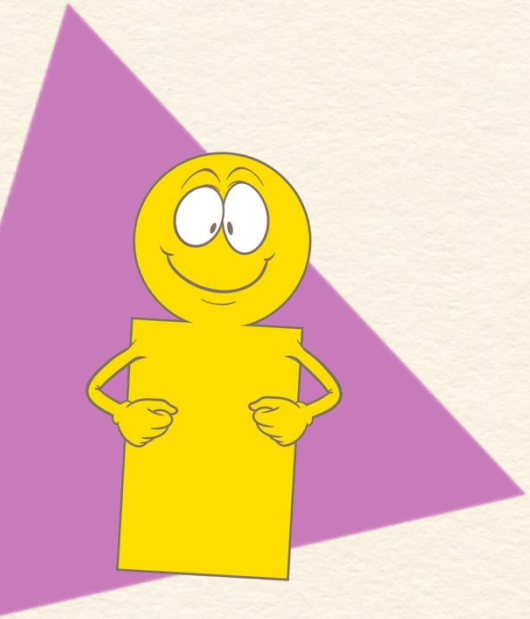
Research Support: CIHR/GACD/National Natural Science Foundation of China (NSFC) and the Milken Institute

Learning Objectives



- Describe the emerging role and current limitations of psychedelic-based therapies across psychiatric disorders
- Evaluate contemporary evidence on their neurobiology, efficacy, durability, and regulatory status
- Apply evidence-based principles for patient selection, risk assessment, monitoring, and clinical implementation

What We Will Cover



- Interpreting psychedelic trials: treatment models, comparators, blinding, and durability
- Psilocybin: depression, treatment-resistant depression, substance use disorders, and the phase 3 program
- MDMA: clinical trials in PTSD and the FDA regulatory outcome
- Lysergide (LSD), DMT, and 5-MeO-DMT: late-stage programs and shorter-acting approaches
- Clinical readiness: safety, patient selection, medication interactions, monitoring, and implementation

Psychedelic Landscape in 2026



Regulatory Status: Development Milestones Are Not Approvals

Program	Lead indication	Evidence stage	U.S. status as of Sept 16, 2026
Psilocybin (COMP360)	TRD	Two phase 3 topline readouts	Rolling NDA submission/review underway; not approved
Lysergide (DT120 ODT)	MDD / GAD	Three positive phase 3 topline readouts	Pre-NDA meeting planned; not approved
MDMA (Midomafetamine)	PTSD	Two published phase 3 trials	2024 complete-response letter; new trial requested
5-MeO-DMT (BPL-003, GH001)	TRD	Phase 3 initiated / published phase 2b	Investigational; not approved

NOTE → Breakthrough Therapy designation, a rolling NDA, a priority voucher, and state-regulated access do not establish FDA approval, labeling, or a standard of psychiatric care.

Current Treatment Model Extends Beyond Drug Administration

01 SCREEN

- Confirm diagnosis
- Medical and psychiatric risk
- Medication review
- Consent capacity

02 PREPARE

- Set expectations
- Explain boundaries
- Plan transportation
- Define support model

03 DOSE + MONITOR

- Standardized product
- Trained session monitors
- Vitals and mental status
- Emergency access

04 FOLLOW UP

- Discharge criteria
- AE and suicide checks
- Protocol-defined integration
- Durability / retreatment

WHAT VARIES BY PROGRAM?

Psychological support • formal psychotherapy • integration • number of sessions • retreatment rules

> Psychological support, psychotherapy, and integration are not interchangeable. Their active contribution to efficacy has not been characterized and may affect both labeling and scalability.

FDA. Psychedelic Drugs: Considerations for Clinical Investigations, 2026.

The Evidence Base Now Spans Phase 2 Through Pivotal Phase 3 Programs

Study / program	Agent / indication	Evidence stage
Raison	Psilocybin / MDD	Phase 2, n=104; peer reviewed
COMP360	Psilocybin / TRD	Phase 2b, n=233; peer reviewed
PsiDeR	Psilocybin / TRD	RCT, n=60; peer reviewed
EPISODE	Psilocybin / MDD	RCT, n=144; peer reviewed
COMP005 / COMP006	Psilocybin / TRD	Phase 3, n=839; sponsor reported
IV DMT phase 2a	DMT / MDD	Phase 2a, n=34; peer reviewed
MAPP2	MDMA-assisted therapy / PTSD	Phase 3, n=104; peer reviewed
MM120	Lysergide / GAD	Phase 2b, n=198; peer reviewed
Bogenschutz	Psilocybin / AUD	RCT, n=95; peer reviewed

NOTE: Trial populations, comparators, endpoints, and follow-up periods differ.

Trial Design Governs How Much Confidence a Positive Signal Deserves

Comparator

Inactive placebo?
Low dose?
Psychoactive control?

Active treatment creates different expectancy and assay-sensitivity conditions.

Blinding

Distinct subjective effects often reveal assignment. Participant and therapist guesses can influence ratings and behavior.

Care model

Preparation, monitored dosing, psychological support, and integration vary across programs. Their contribution remains uncertain.

Durability

Short primary endpoints may establish acute efficacy but provide limited guidance for relapse, retreatment, and long-term safety.

FDA. Psychedelic Drugs: Considerations for Clinical Investigations, 2026.

Psychedelics for the Treatment of Psychiatric Disorders: Interpreting and Translating Available Evidence and Guidance for Future Research

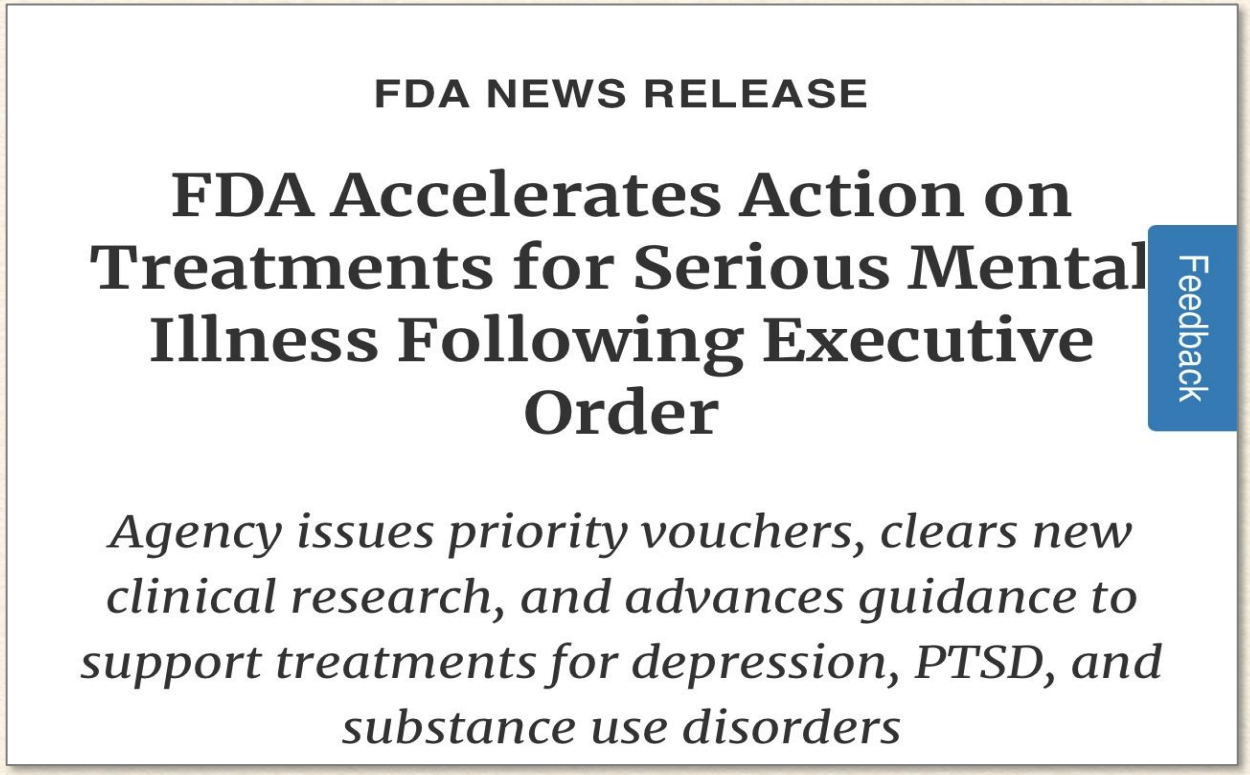
Roger S. McIntyre, M.D., F.R.C.P.C., Angela T. H. Kwan, M.Sc., Rodrigo B. Mansur, M.D., Ph.D., Albino J. Oliveira-Maia, M.D., Ph.D., Kayla M. Teopiz, H.B.Sc., Vladimir Maletic, M.D., Trisha Suppes, M.D., Ph.D., Stephen M. Stahl, M.D., Ph.D., Joshua D. Rosenblat, M.D., F.R.C.P.C.

McIntyre RS et al. Am J Psychiatry 182:1.

FDA Accelerates Action on Treatments for Serious Mental Illness Following Executive Order

"The FDA is issuing national priority vouchers to three companies studying:

- **Psilocybin** for treatment-resistant depression
- **Psilocybin** for major depressive disorder
- **Methylone** for post-traumatic stress disorder (PTSD)



FDA NEWS RELEASE

FDA Accelerates Action on Treatments for Serious Mental Illness Following Executive Order

Agency issues priority vouchers, clears new clinical research, and advances guidance to support treatments for depression, PTSD, and substance use disorders

Feedback

https://www.fda.gov/news-events/press-announcements/fda-accelerates-action-treatments-serious-mental-illness-following-executive-order

Psychedelics in Psychiatry: Comparative Effectiveness, Implementation, Commercialization, and Safety Lessons Learned From Intranasal Esketamine



EXPERT OPINION ON DRUG SAFETY
https://doi.org/10.1080/14740338.2026.2726227

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EDITORIAL

Check for updates

Psychedelics in psychiatry: comparative effectiveness, implementation, commercialization and safety lessons learned from intranasal esketamine

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ARTICLE HISTORY Received 14 July 2026; Accepted 26 August 2026

KEYWORDS Serotonergic psychedelics; intranasal esketamine; treatment resistant depression; major depressive disorder; GH001; COMP360; DT120-ODT; atypical antipsychotics

McIntyre RS. Expert Opin Drug Saf 2026;1–3. Advance online publication.

Is the Psychedelic Experience an Essential Aspect of the Therapeutic Effect of Serotonergic Psychedelics? Conceptual, Discovery, Development and Implementation Implications for Psilocybin and Related Agents



EXPERT OPINION ON DRUG SAFETY
2023, VOL. 22, NO. 10, 885–889
https://doi.org/10.1080/14740338.2023.2253144

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EDITORIAL

Check for updates

Is the psychedelic experience an essential aspect of the therapeutic effect of serotonergic psychedelics? Conceptual, discovery, development and implementation implications for psilocybin and related agents

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ARTICLE HISTORY Received 22 June 2023; Accepted 25 August 2023

KEYWORDS Psychedelic; psilocybin; lysergic acid diethylamide; mood disorders; antidepressants; discovery; pharmacology; FDA

McIntyre RS. Expert Opin Drug Saf 2023;22(10):885-9.

Hallucinogen Persisting Perceptual Disorder: A Scoping Review Covering Frequency, Risk Factors, Prevention, and Treatment



EXPERT OPINION ON DRUG SAFETY
EPUB OL. 21, NO. 6, 733-743
https://doi-org.myaccess.library.utoronto.ca/10.1080/14740338.2022.2063273

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Hallucinogen persisting perceptual disorder: a scoping review covering frequency, risk factors, prevention, and treatment

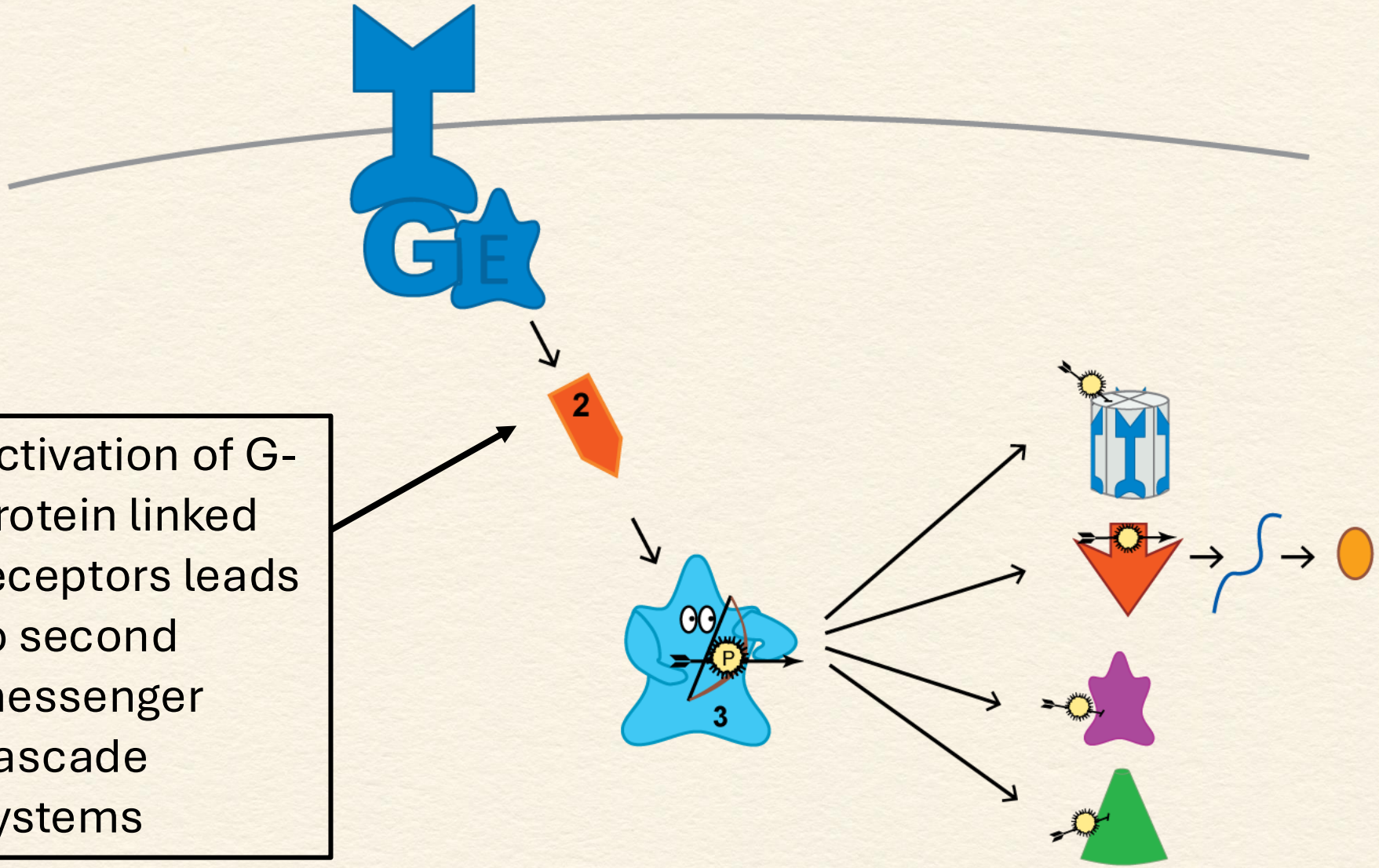
Marcus A. Doyle[a,b], Susan Ling[a,c], Leanna M.W. Lui[a,d], Paul Fragnelli[a], Kayla M. Teopiz[a], Roger Ho[e,f], Joshua D. Di Vincenzo[a,c,g], Joshua D. Rosenblat[a,e,g,h], Emily S. Gillissie[a], Danica Nogo[a], Felicia Ceban[a,i], Muhammad Youshay Jawad[a], and Roger S. McIntyre[a,c,d,g,h,i]

Doyle MA et al. Expert Opin Drug Saf 2022;21(6):733-43.

Classic Psychedelic Mechanism of Action



5HT2A Receptors Are G-Protein Linked



Activation of G-protein linked receptors leads to second messenger cascade systems

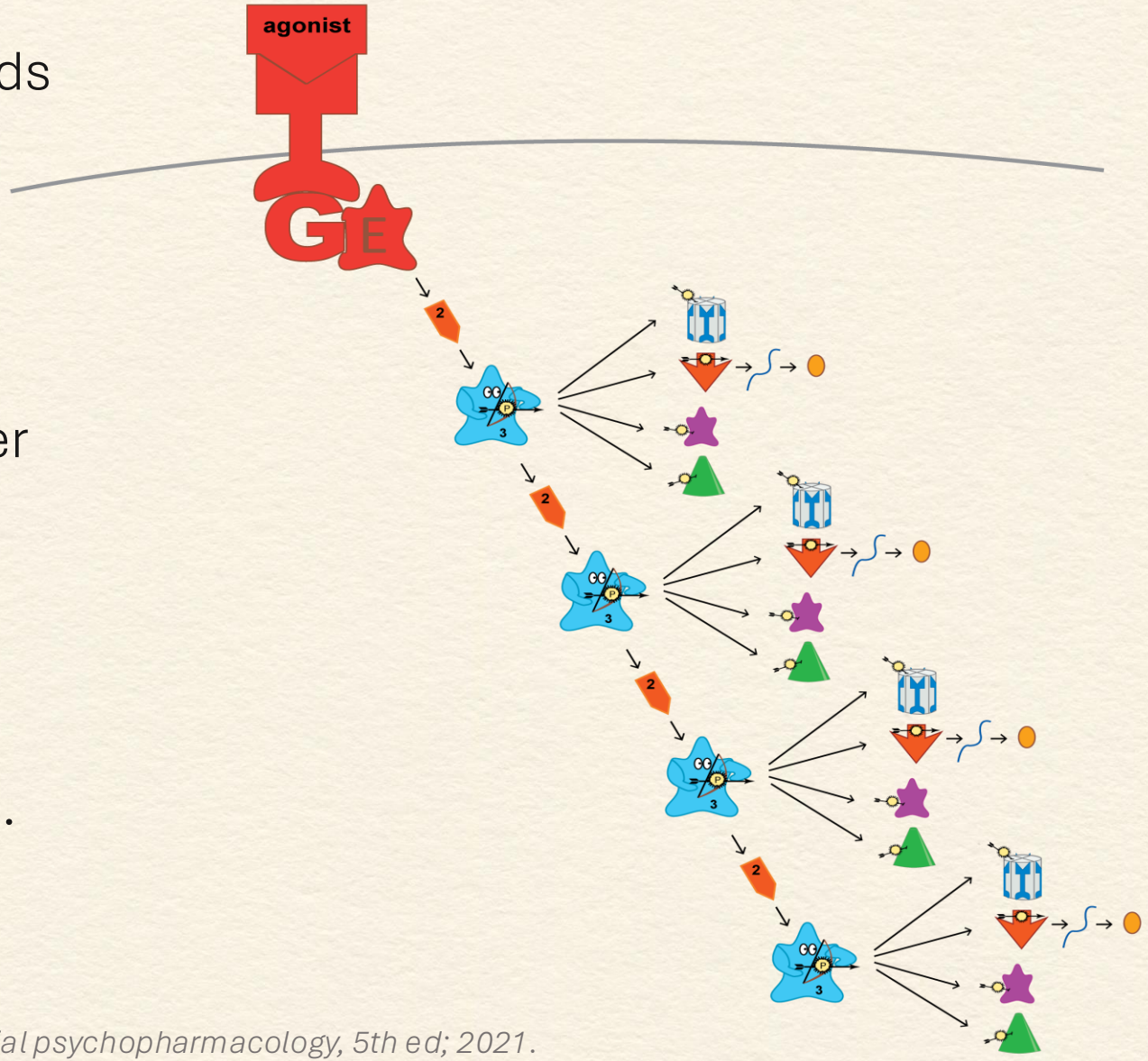
Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

5HT2A Agonism

5HT when bound to its 2A receptor tends to stimulate intracellular activity

Classic psychedelics drive 2A activity which leads to more second messenger activity

Overall, leads to an increase in neurocircuitry firing in various regions…



Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

Mechanistic Evidence Must Be Taught as a Hierarchy—Not a Single Causal Story

1 ESTABLISHED PHARMACOLOGY

Classic psychedelics act principally through 5-HT2A agonism; MDMA has a monoaminergic release/transporter profile; ketamine/esketamine are NMDA antagonists.

2 HUMAN BIOMARKER EVIDENCE

Psilocybin acutely desynchronizes large-scale networks, reduces network segregation, and can produce persistent hippocampal–default-mode connectivity changes.

3 PRECLINICAL PLASTICITY HYPOTHESES

Dendritic growth, synaptogenesis, extracellular-matrix remodeling, and reopened critical periods are biologically plausible—largely from cell and animal studies.

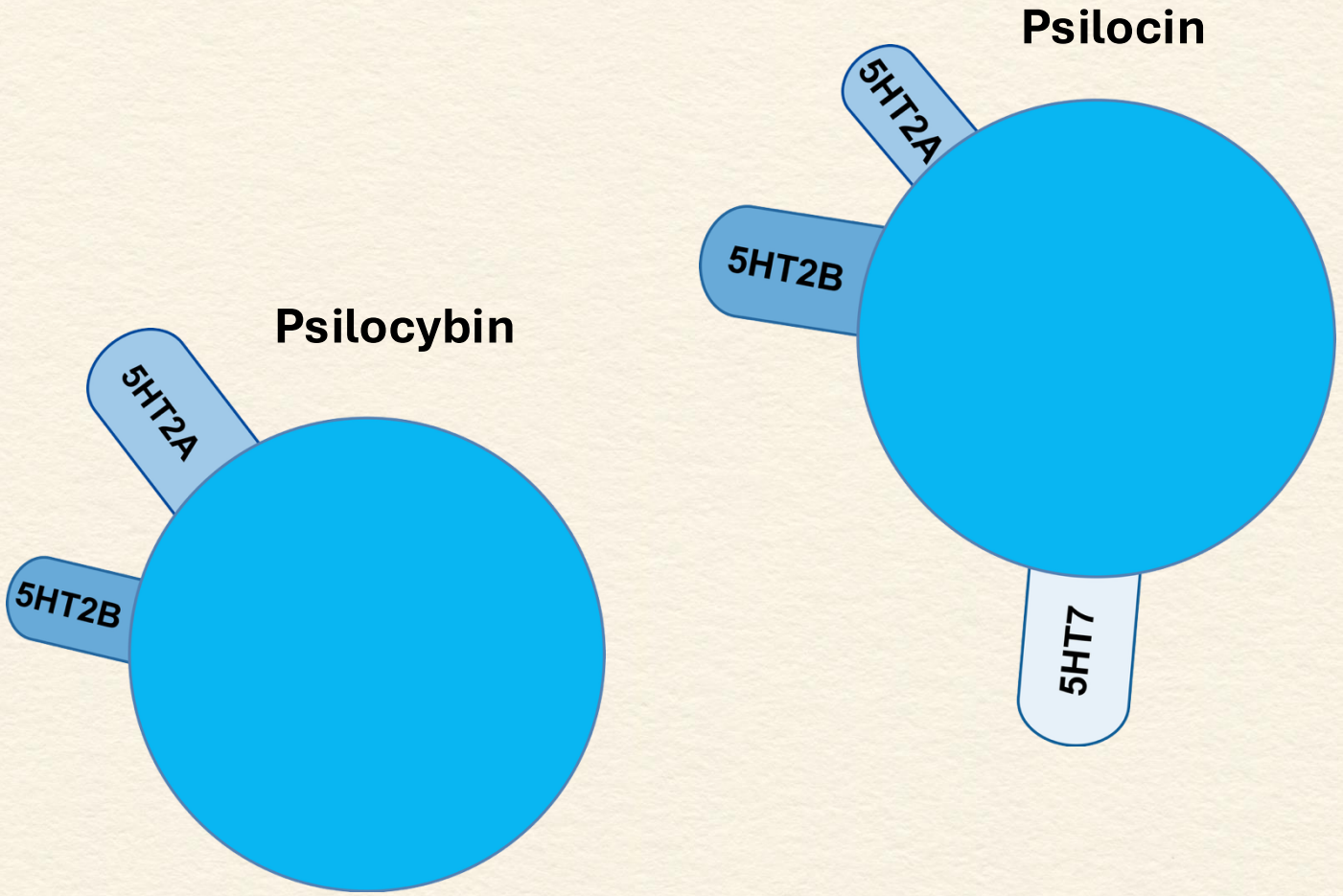
Siegel JS et al. Nature 2024; Dölen lab critical-period study. Nature 2023; FDA. Psychedelic Drugs: Considerations for Clinical Investigations. Final Guidance. July 2026.

Psilocybin



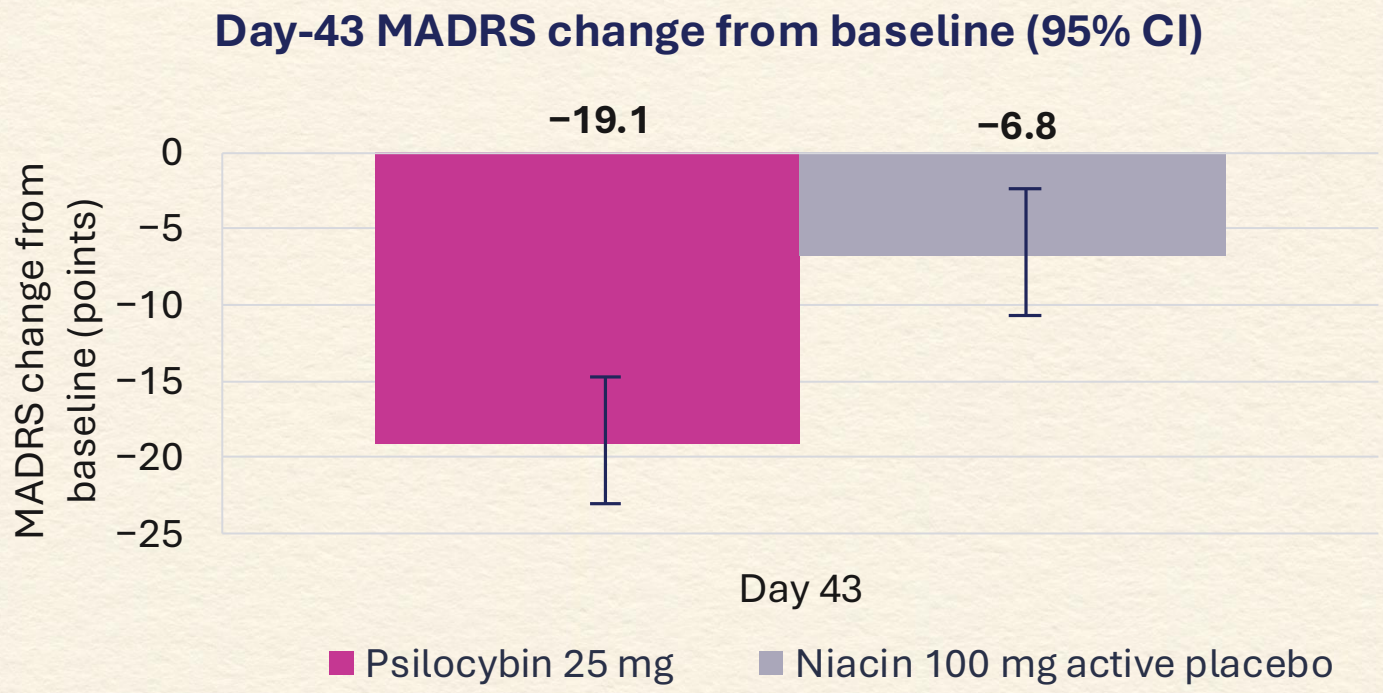
Psilocybin Background

- Contemporary clinical programs generally use standardized synthetic psilocybin; 25 mg is the most frequently studied therapeutic dose in MDD/TRD trials
- Targets serotonin 5HT2A and 5HT2B receptors



Psilocybin Produced a Rapid Antidepressant Effect Sustained Through Day 43

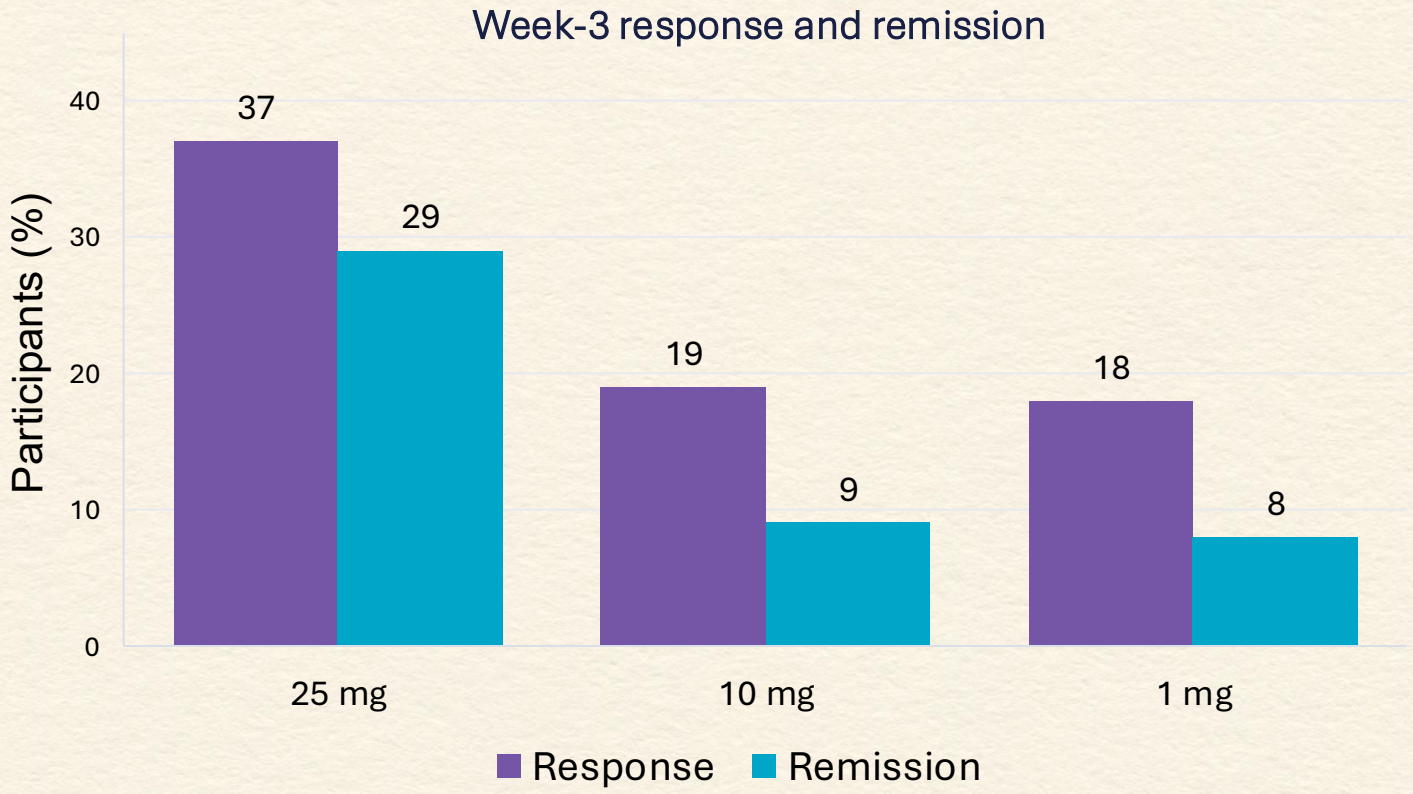
Trial characteristic	Study details
Design	Randomized, double-blind, active-placebo controlled
Population	Major depressive disorder; n=104
Intervention	Psilocybin 25 mg plus psychological support
Comparator	Niacin 100 mg plus psychological support
Primary endpoint	Change in MADRS total score from baseline to day 43



Raison CL et al. JAMA 2023;330:843-53.

Only COMP360 25 mg Separated From 1 mg at Week 3

Trial characteristic	Study details
Design	Randomized, double-blind, dose-ranging trial
Population	Treatment-resistant depression; n=233
Treatment arms	COMP360 psilocybin 25 mg, 10 mg, or 1 mg
Primary endpoint	Change in MADRS total score from baseline to week 3
Primary comparison	25 mg versus 1 mg: −6.6 MADRS points

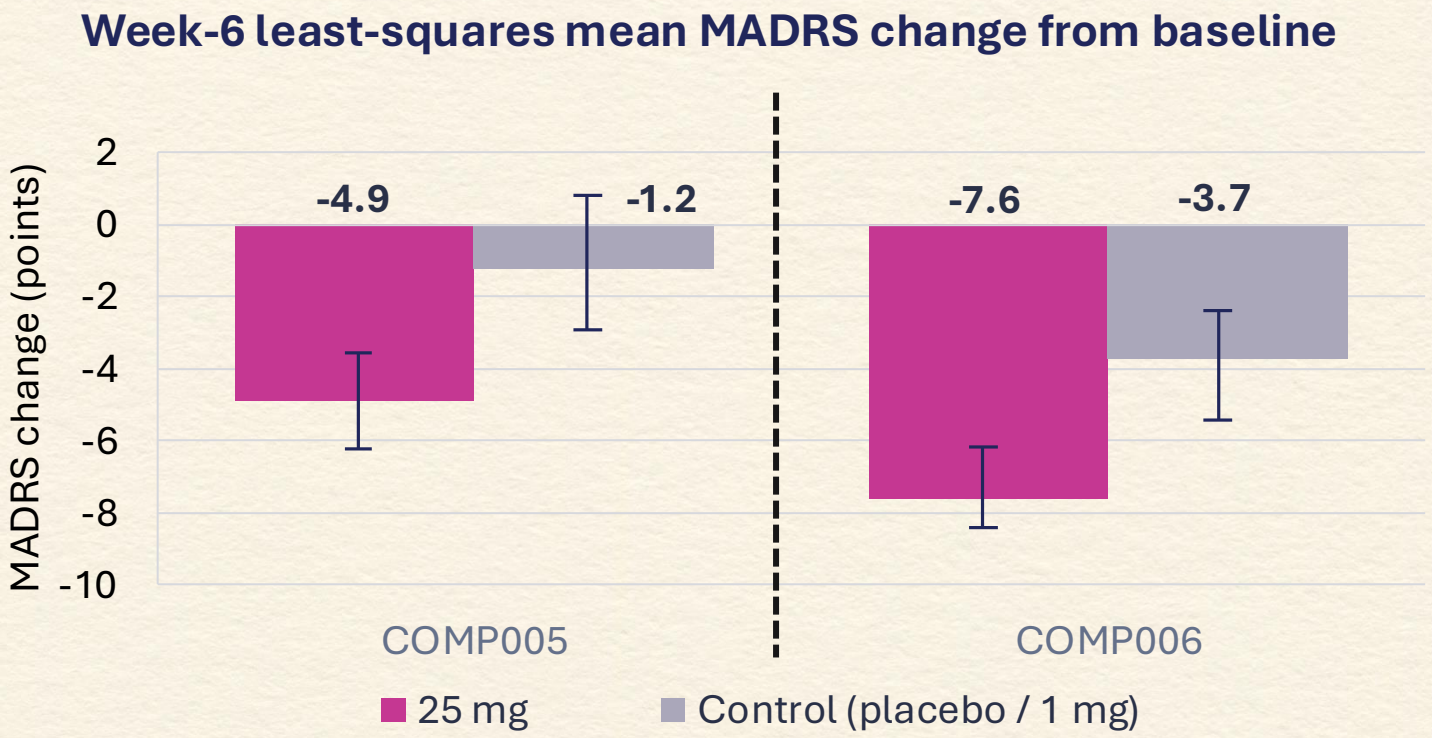


The 25-mg dose produced the clearest acute signal. Hierarchical testing **did not** establish a sustained response at week 12, and suicidality or self-injury findings require careful monitoring in later trials.

Goodwin GM et al. N Engl J Med 2022;387:1637-48.

Two COMP360 Phase 3 Trials Met Their Week-6 Endpoints

Trial	Study details
COMP005	Single COMP360 25-mg dose versus placebo; n=258
COMP006	Two COMP360 25-mg doses, 3 weeks apart, versus 10 mg or 1 mg; n=581
Primary endpoint	Between-group difference in MADRS change from baseline at week 6
Development status	Rolling NDA submission and review underway; not FDA approved



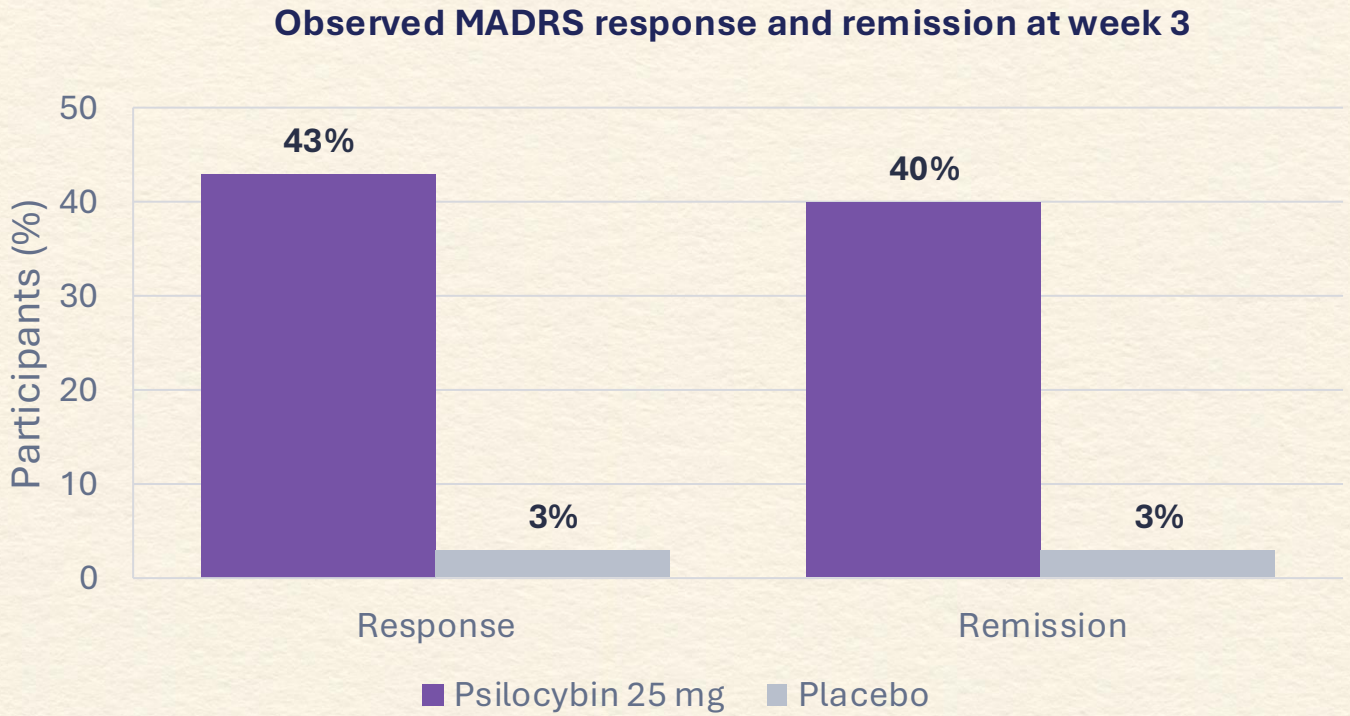
COMP005: −3.6 points
95% CI, −5.7 to −1.5

COMP006: −3.8 points
95% CI, −5.8 to −1.8

Compass Pathways topline presentation, Feb 17, 2026.

PsiDeR Found a Large 6-Week Signal in a Public Healthcare Setting

Trial characteristic	Study details
Design	Phase 2 feasibility trial with a randomized, double-blind, placebo-controlled design
Population	Treatment-resistant depression, n=60 randomized 1:1
Intervention	Single psilocybin 25-mg dose plus preparation, dosing support, and integration
Comparator	Matching placebo plus equivalent psychological support
Primary outcomes	Feasibility: recruitment, retention, and estimation of MADRS variance
Clinical estimate	Week 3 adjusted MADRS difference: −10.41 points (95% CI −14.86 to −5.95)



Observed counts

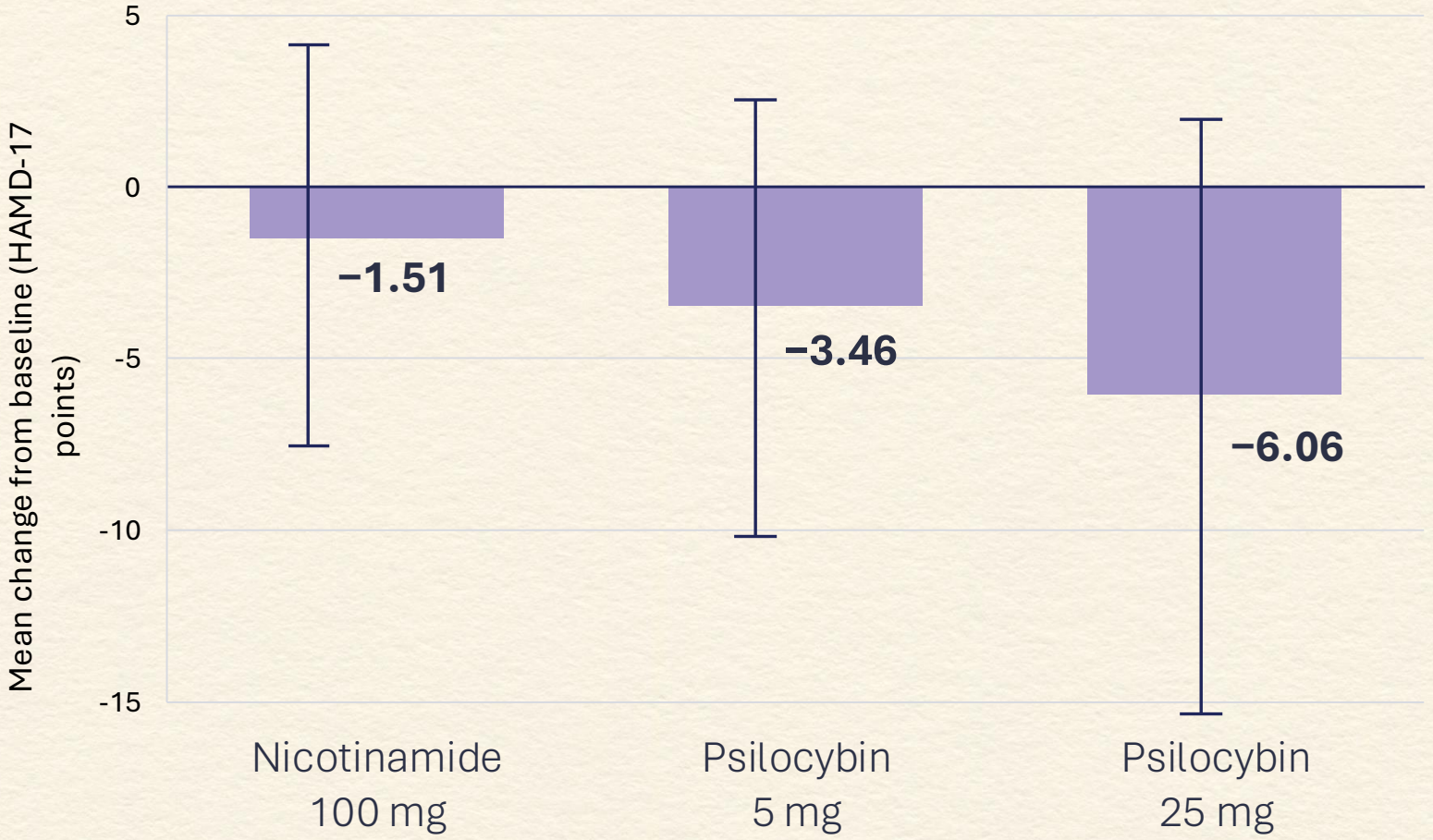
Response: 13/30 vs 1/29 Remission: 12/30 vs 1/29

The independently funded NHS feasibility trial found a large adjusted MADRS difference that persisted through week 6. The small sample, inactive placebo, and functional unblinding limit efficacy inference. A larger confirmatory trial is needed.

Rucker JJ et al. Nat Med 2026;32:3430-7.

EPISODE Did Not Meet Its Primary Week-6 Response Endpoint

Trial characteristic	Study details
Design	Phase 2 randomized, double-blind, 3-arm, 2-center trial
Population	Treatment-resistant major depression; n=144 randomized, n=142 in the primary analysis
Arms	Psilocybin 25 mg, psilocybin 5 mg, or nicotinamide 100 mg, each with psychotherapy
Primary endpoint	HAMD-17 response at week 6 after dose 1, defined as at least 50% improvement
Primary result	25 mg vs nicotinamide: OR 1.73 (95% CI 0.53–6.23), P=.19

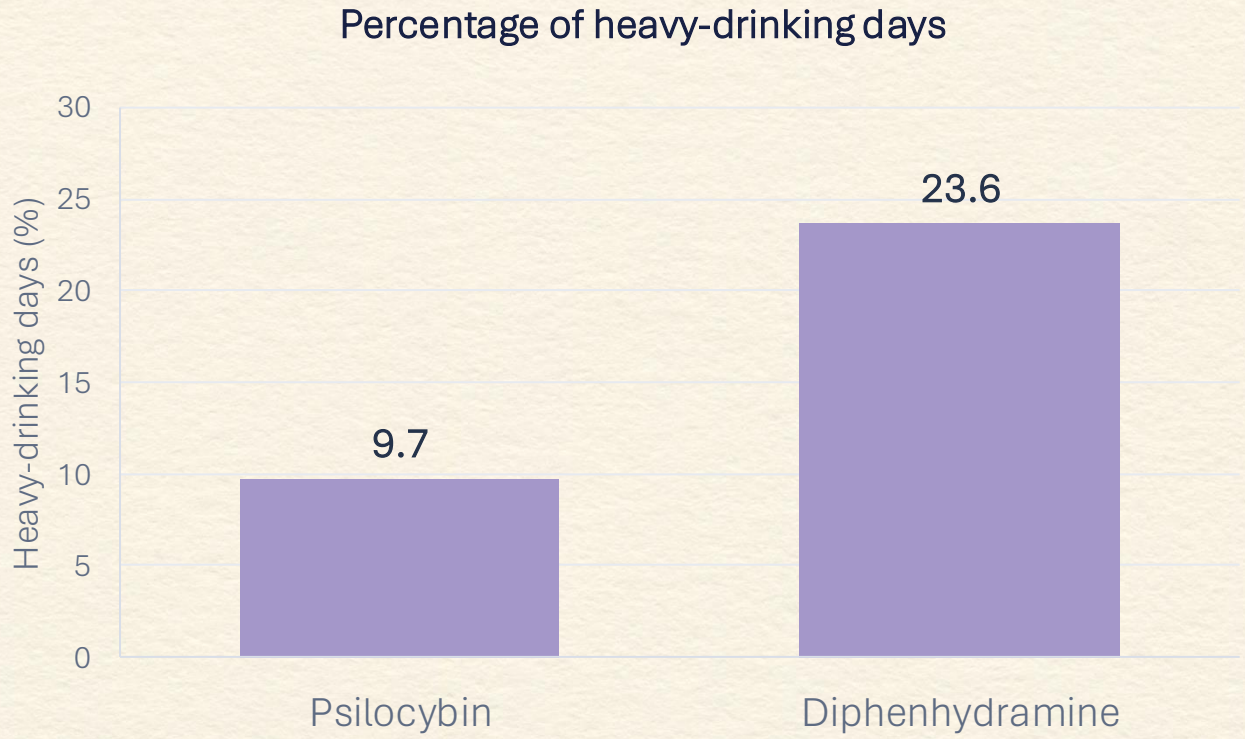


Secondary continuous measures favored 25 mg, but they do not replace the negative primary endpoint. Most participants receiving 25 mg identified their assignment, and placebo response was unusually low.

Schramm E et al. JAMA Psychiatry 2026.

Psilocybin Reduced Heavy-Drinking Days When Added to Structured Psychotherapy

Trial characteristic	Study details
Design	Randomized, double-blind, active-placebo–controlled, 2-site trial
Population	Adults with alcohol dependence; n=95 randomized, n=93 in the primary analysis
Intervention	Two psilocybin sessions (25–40 mg/70 kg) plus 12 sessions of manualized psychotherapy
Comparator	Two diphenhydramine sessions (50–100 mg) plus the same psychotherapy
Primary outcome	Percentage of heavy-drinking days during weeks 5–32
Treatment difference	13.9 percentage points (95% CI 3.0–24.7), P=.01



This trial provides the strongest current substance-use signal, but both groups received psychotherapy. The study cannot isolate the drug effect from the combined treatment model or establish a scalable standard of care.

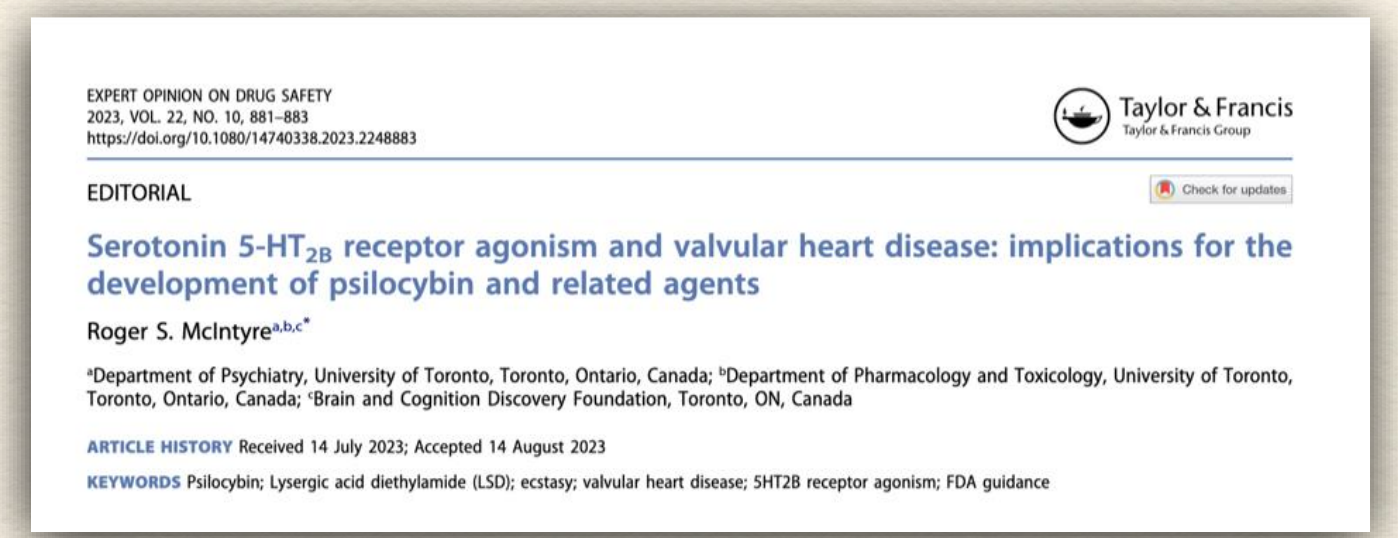
Bogenschutz MP et al. JAMA Psychiatry 2022;79:953-62.

Psilocybin Depression Trials Point in the Same Direction, but Not With the Same Certainty

Study	Comparator	Primary result	What strengthens confidence	What limits confidence
Raison	Niacin	Positive at day 43	Randomized multisite design	Short follow-up and imperfect blinding
Goodwin	1-mg psilocybin	25 mg positive at week 3	Large phase 2b dose-ranging study	Week-12 hierarchy and safety signals
PsiDeR	Placebo	Positive at week 3	Independent public-sector setting	Small feasibility trial and unblinding
EPISODE	5 mg and nicotinamide	Primary outcome negative	Blinding assessment and 3-arm design	Low comparator response and limited power
COMP005 / 006	Placebo or 1 mg	Positive at week 6	Two large pivotal trials	Top-line sponsor reports only

The direction of effect is generally favorable, yet comparator choice, endpoint definition, blinding integrity, and publication status explain much of the variation in apparent effect size.

Serotonin 5-Ht2B Receptor Agonism and Valvular Heart Disease: Implications for Development of Psilocybin and Related Agents



EXPERT OPINION ON DRUG SAFETY
2023, VOL. 22, NO. 10, 881–883
https://doi.org/10.1080/14740338.2023.2248883

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EDITORIAL

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Serotonin 5-HT_{2B} receptor agonism and valvular heart disease: implications for the development of psilocybin and related agents

Roger S. McIntyre[a,b,c*]

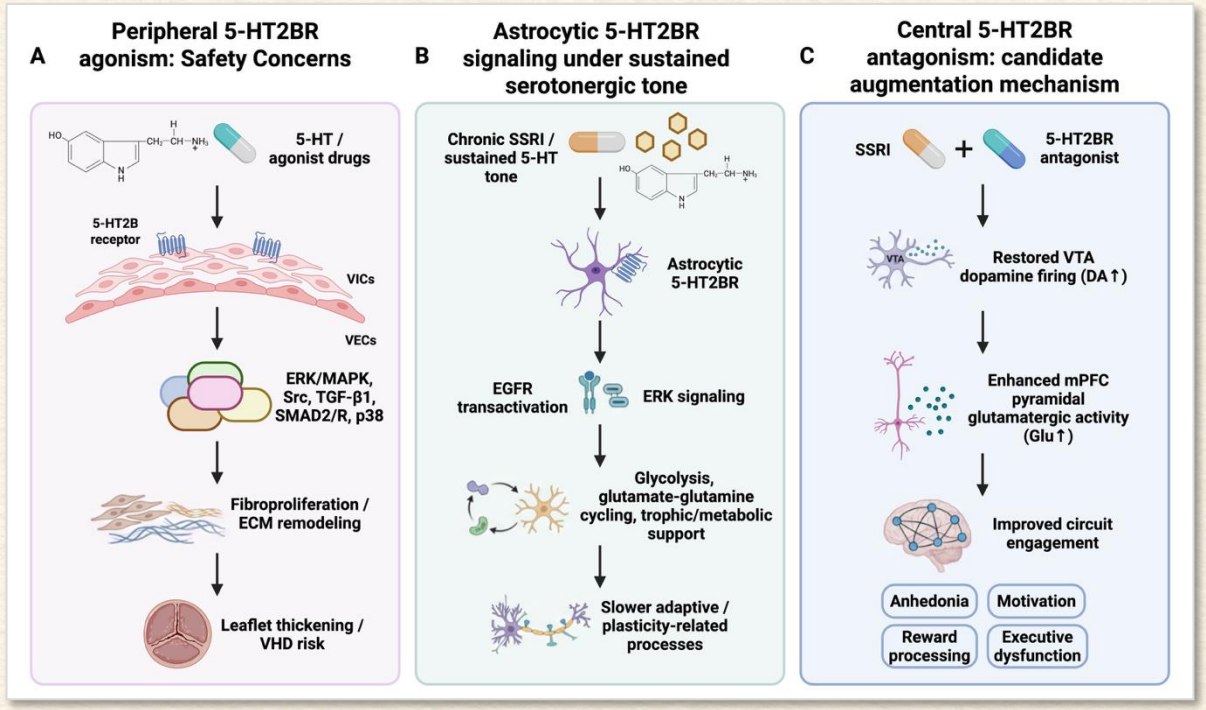
[a]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada; [b]Department of Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada; [c]Brain and Cognition Discovery Foundation, Toronto, ON, Canada

ARTICLE HISTORY Received 14 July 2023; Accepted 14 August 2023

KEYWORDS Psilocybin; Lysergic acid diethylamide (LSD); ecstasy; valvular heart disease; 5HT2B receptor agonism; FDA guidance

McIntyre RS. Expert Opin Drug Saf 2023;22(10):881-3.

The Serotonin 2B (5-HT2B) Receptor: A Narrative Review of Preclinical and Clinical Evidence on the Safety Considerations and Therapeutic Potential for the Treatment of Depression



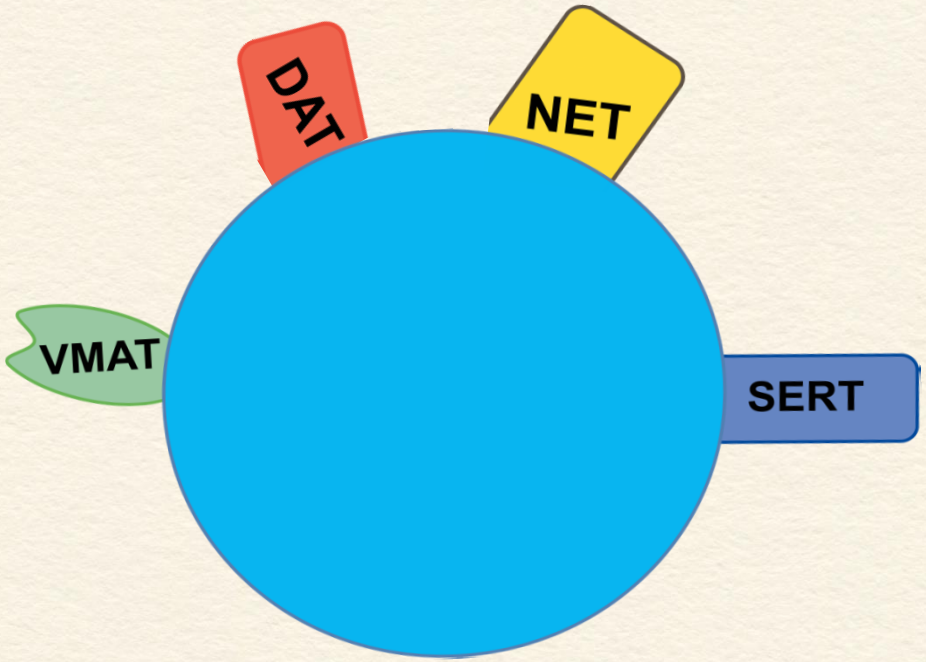
Le GH et al. Clin Pharmacol Ther 2026;120(2):345-56.

MDMA



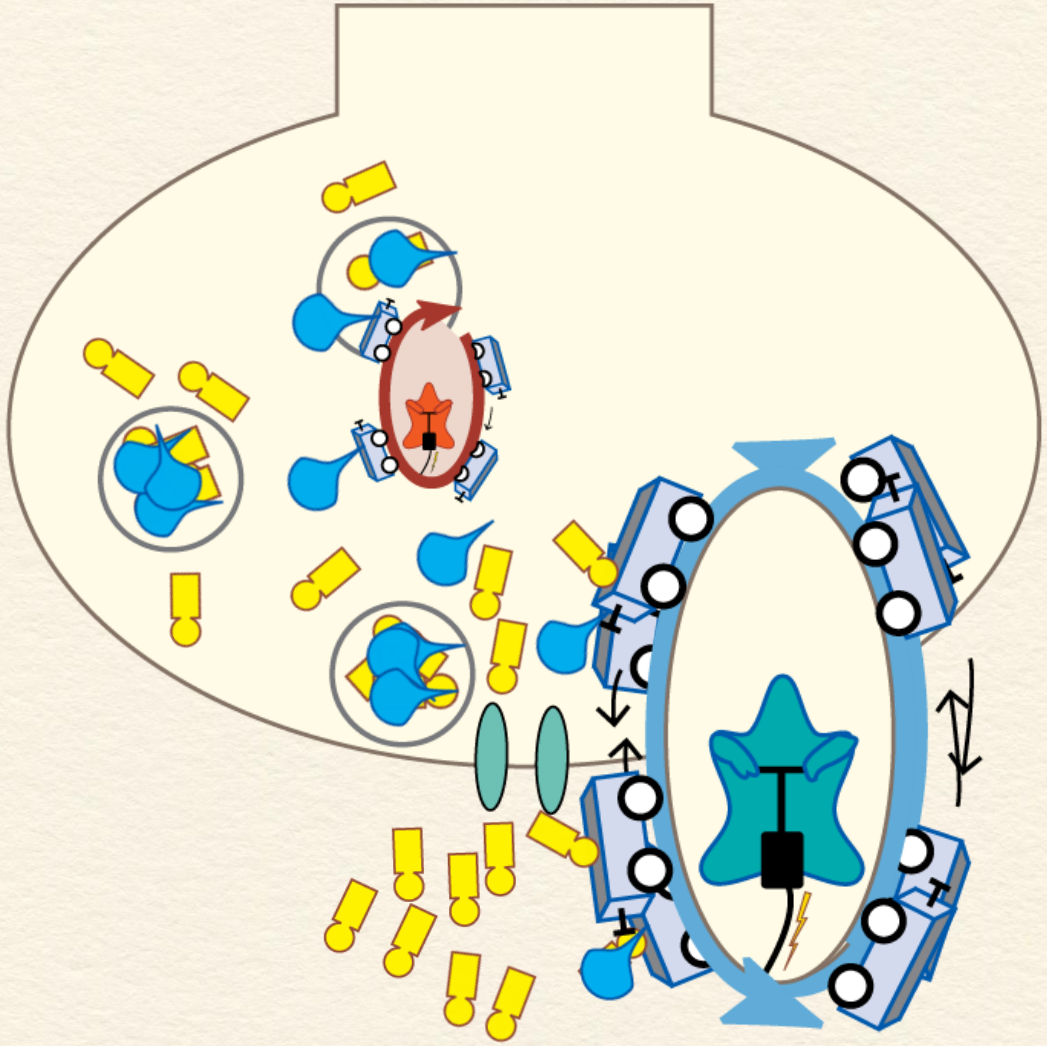
MDMA Background

- Street name: Ecstasy
- Typical dose between 50–200 mg
- Targets serotonin, norepinephrine, and dopamine neurotransmission
- FDA granted Breakthrough Therapy designation for PTSD in 2017 after phase 2 trials; since then, two phase 3 trials reported positive efficacy findings, but the FDA declined approval in 2024 and requested an additional trial to better establish efficacy, durability, and safety



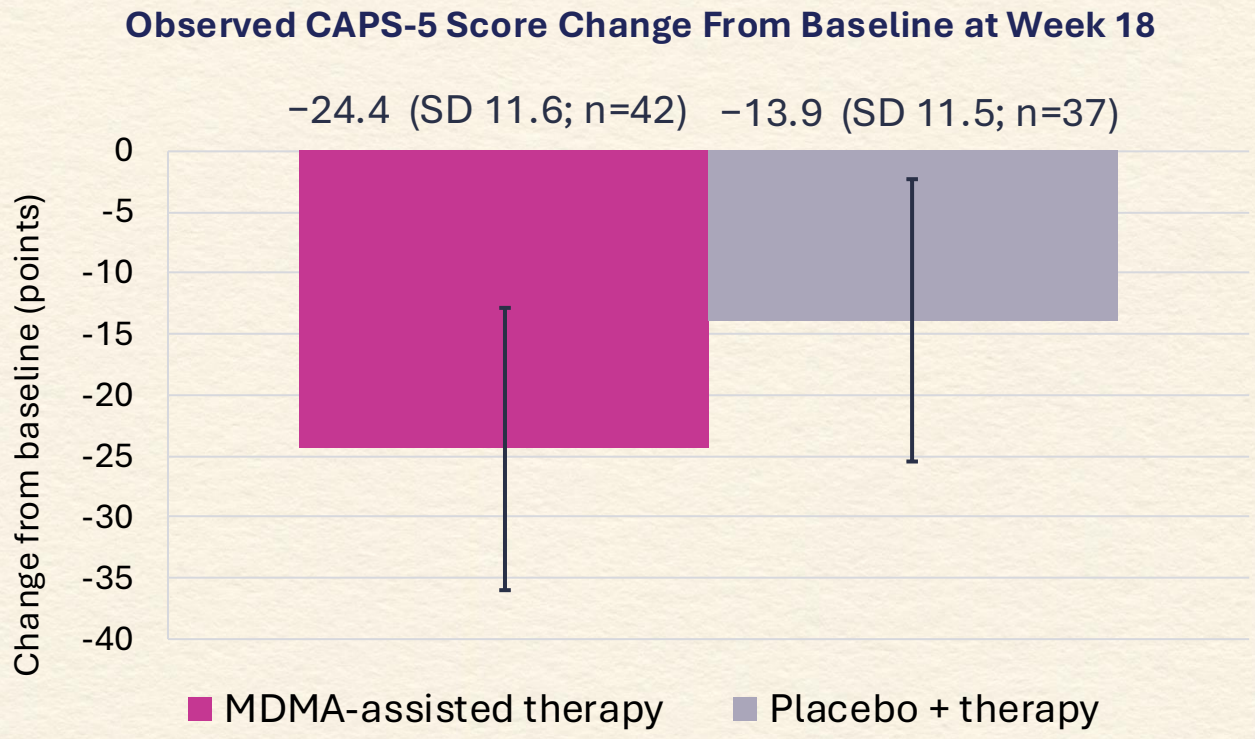
Mechanism of MDMA at Serotonin Synapses

1. MDMA acts as a competitive inhibitor to displace serotonin from the reuptake transporter
2. SERT transports MDMA into the synaptic terminal
3. MDMA is transported into synaptic vesicles by VMAT
4. Transport of MDMA into vesicles displaces serotonin into the terminal
5. Once enough serotonin has built up in the terminal, SERT transport reverses and transports serotonin out of the terminal…
6. And causes channels to open allowing serotonin to leak from these channels



MAPP1 Established the First Pivotal MDMA Efficacy Signal in Severe PTSD

Trial characteristic	Study details
Design	Randomized, double-blind, inactive-placebo–controlled, multisite phase 3 trial
Population	Severe PTSD; n=90 mITT, with n=89 in the primary analysis
Intervention	Three MDMA sessions (80–180 mg divided dose) plus 3 preparation and 9 integration sessions
Comparator	Inactive placebo plus the same manualized therapy schedule
Primary endpoint	CAPS-5 change from baseline to week 18
Analysis shown	Per-protocol completers: MDMA n=42; placebo n=37
Primary result	MMRM difference 11.9 points (95% CI 6.3–17.4), P<.0001



d = 0.91

Between-group effect size

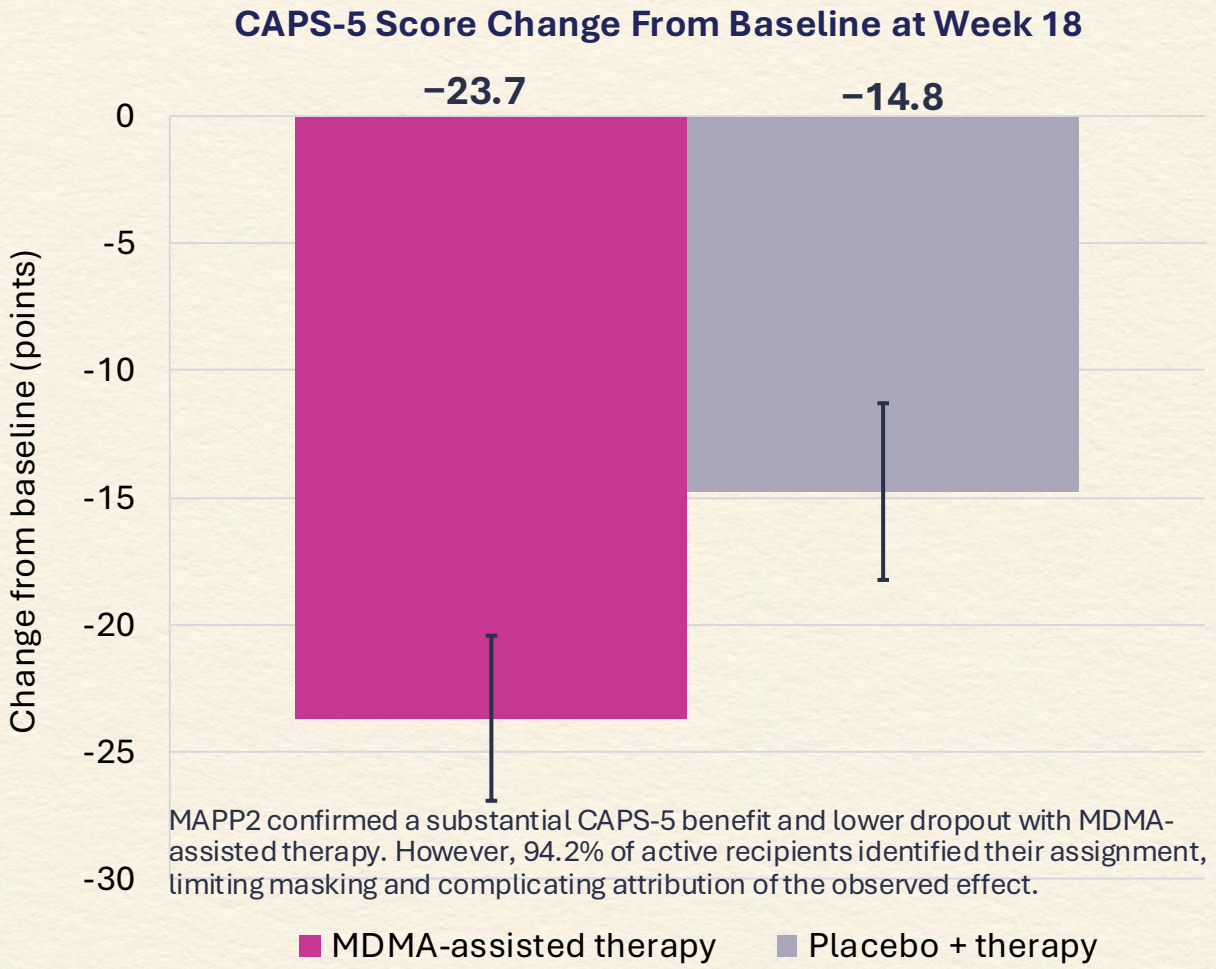
67% vs 32%

No longer met PTSD criteria

Mitchell JM et al. Nat Med 2021;27:1025-33.

MAPP2 Replicated a Clinically Meaningful PTSD Signal, but Functional Unblinding Was Pronounced

Trial characteristic	Study details
Design	Randomized, double-blind, inactive-placebo–controlled, confirmatory phase 3 trial
Population	Moderate-to-severe PTSD; n=104 randomized, n=103 in the primary analysis
Intervention	Three MDMA sessions (120–180 mg split dose) plus 3 preparation and 9 integration sessions
Comparator	Inactive placebo plus the same manualized therapy schedule
Primary endpoint	CAPS-5 change from baseline to week 18
Analysis shown	MMRM de jure estimand: MDMA n=53; placebo n=50
Primary result	Difference −8.9 points (95% CI −13.70 to −4.12), P<.001; d=0.7



Mitchell JM et al. Nat Med 2023;29:2473-80.

FDA Review of MDMA

Did the data show effectiveness?

2 yes 9 no

Did benefits outweigh risks with the proposed REMS?

1 yes 10 no

Why did the FDA request another trial?

Efficacy integrity: functional unblinding, expectancy, and selection bias limited interpretability

Durability: follow-up did not establish how long benefit persists or when retreatment is needed

Safety capture: adverse-event collection did not fully characterize impairment or abuse-related experiences

Treatment model: the contribution and generalizability of the psychotherapy regimen remained uncertain

Medical monitoring: cardiac, laboratory, electrolyte, and discharge data remained incomplete

Statistical significance alone cannot support approval when trial integrity, safety characterization, durability, and delivery requirements remain unresolved.

FDA advisory committee minutes and complete-response letter, 2024.

LSD, DMT, and 5-MeO-DMT



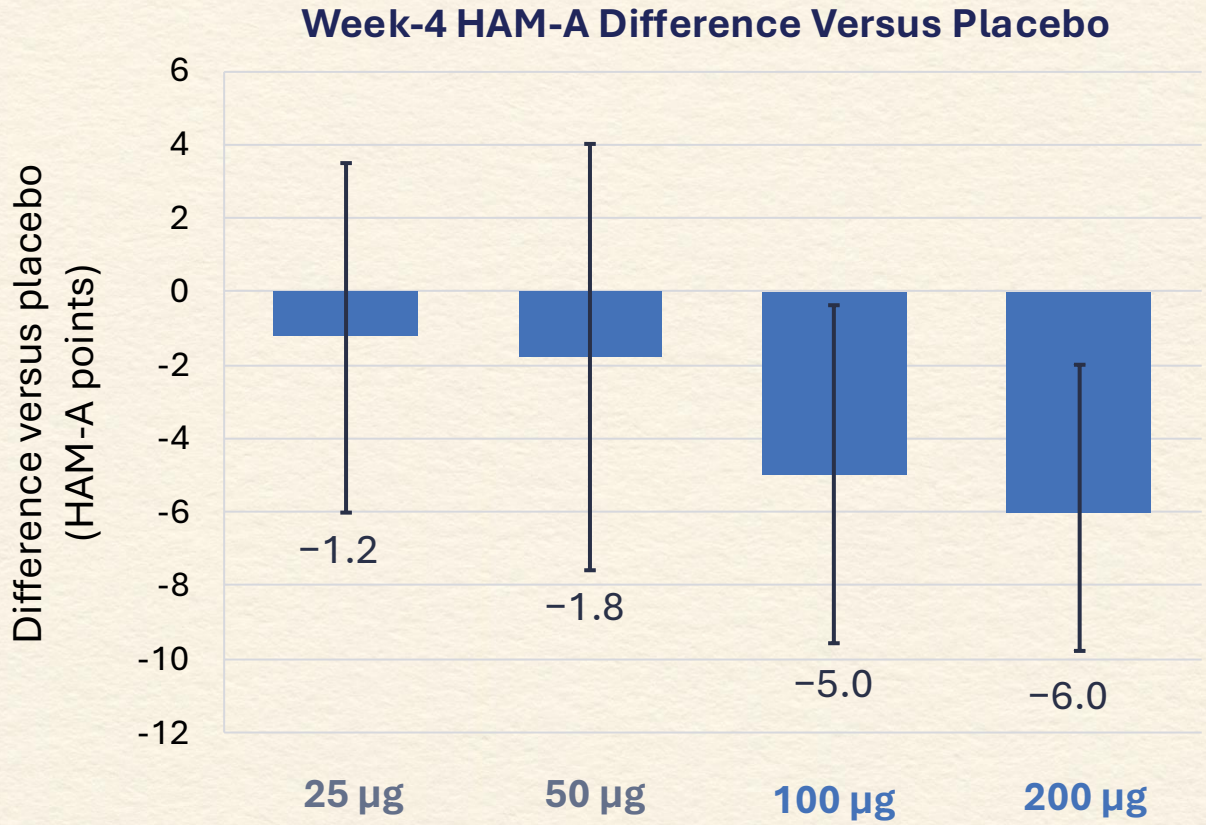
DT120 ODT (Previously MM120) Now Has Three Positive Phase 3 Topline Readouts

Trial	Population	Design / dose	Primary endpoint	Placebo-adjusted result
Emerge	MDD, n=149	Single 100 µg dose	Week-6 MADRS	−8.1 points; p<0.0001
Voyage	GAD, n=214	Single 100 µg dose	Week-12 HAM-A	−5.4 points; d=0.81
Panorama	GAD, n=245	100 µg vs 50 µg vs placebo	Week-12 HAM-A	−5.1 points; d=0.64

Definium Therapeutics sponsor-reported topline results, June–September 2026.

Single-Dose DT120 ODT Showed a Dose-Response Signal in GAD Without Protocol-Delivered Psychotherapy

Trial characteristic	Study details
Design	Multicenter, randomized, double-blind, placebo-controlled phase 2b trial
Population	Moderate-to-severe GAD; n=198 randomized, n=194 in the full analysis set
Intervention	Single MM120 (lysergide D-tartrate) dose: 25, 50, 100, or 200 µg
Comparator	Placebo
Primary endpoint	Dose-response for HAM-A change at week 4 using MCP-Mod
Care model	Two safety monitors; psychotherapy prohibited during dosing; existing therapy continued unchanged
Primary result	Dose-response positive; 100-µg and 200-µg differences versus placebo were significant



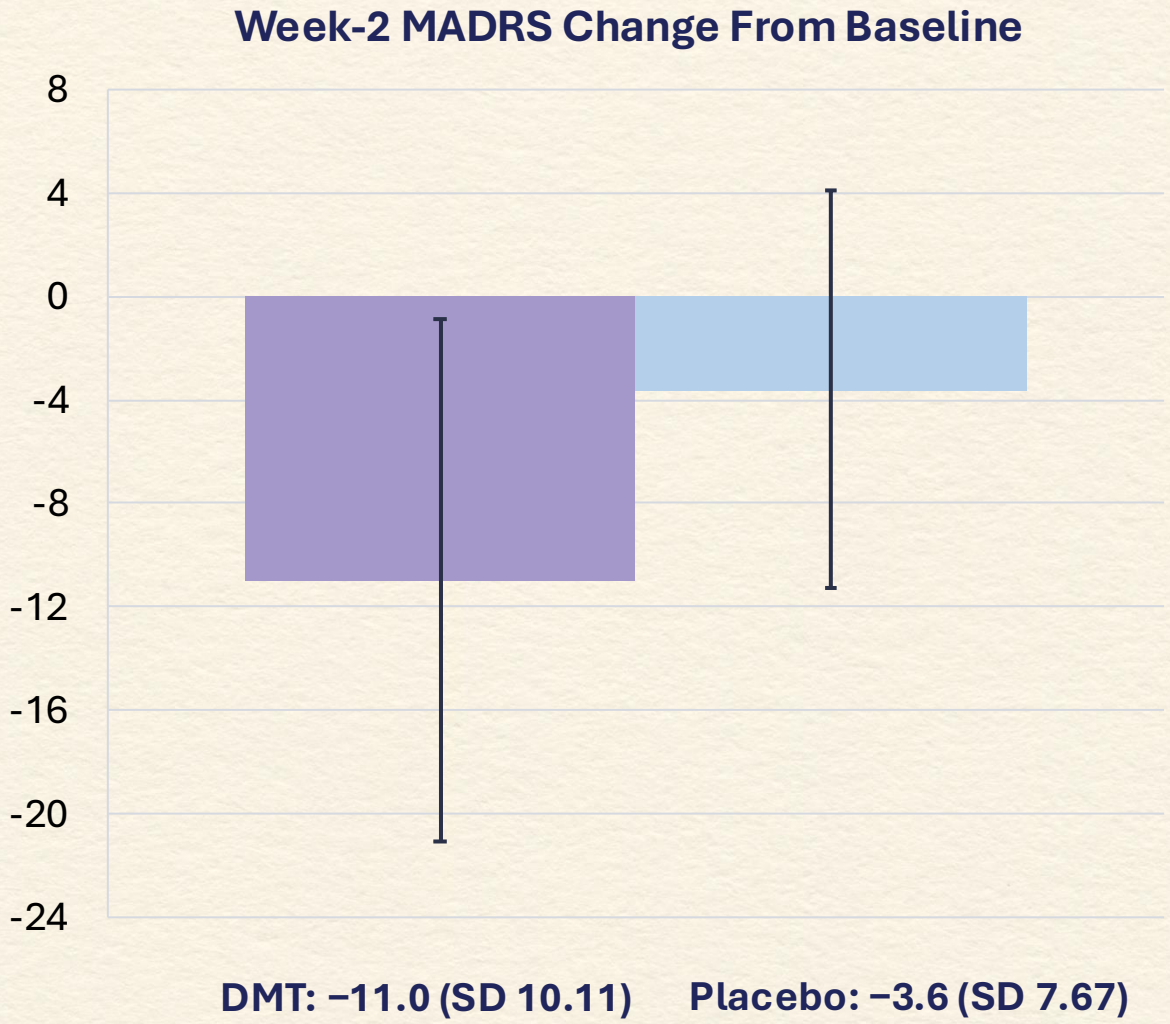
The 100-µg and 200-µg doses separated from placebo, whereas the lower-dose confidence intervals crossed zero. The trial isolated drug plus structured monitoring, but medication tapering and functional unblinding remain important limitations.

Robison R et al. JAMA 2025;334:1358-72.

A Single IV DMT Dose Reduced MADRS Scores at Weeks 1 and 2

SHORT-ACTING PSYCHEDELIC MODEL

Trial feature	Study details
Design	Randomized, double-blind, placebo-controlled phase 2a trial
Population	Moderate-to-severe MDD; n=34, with 17 participants per arm
Arms	DMT fumarate 21.5 mg IV over 10 minutes versus IV placebo; both with supportive psychotherapy
Primary endpoint	MADRS change from baseline at week 2



Erritzoe D et al. Nat Med 2026;32:591–8.

Shorter-Acting 5-MeO-DMT Programs in TRD

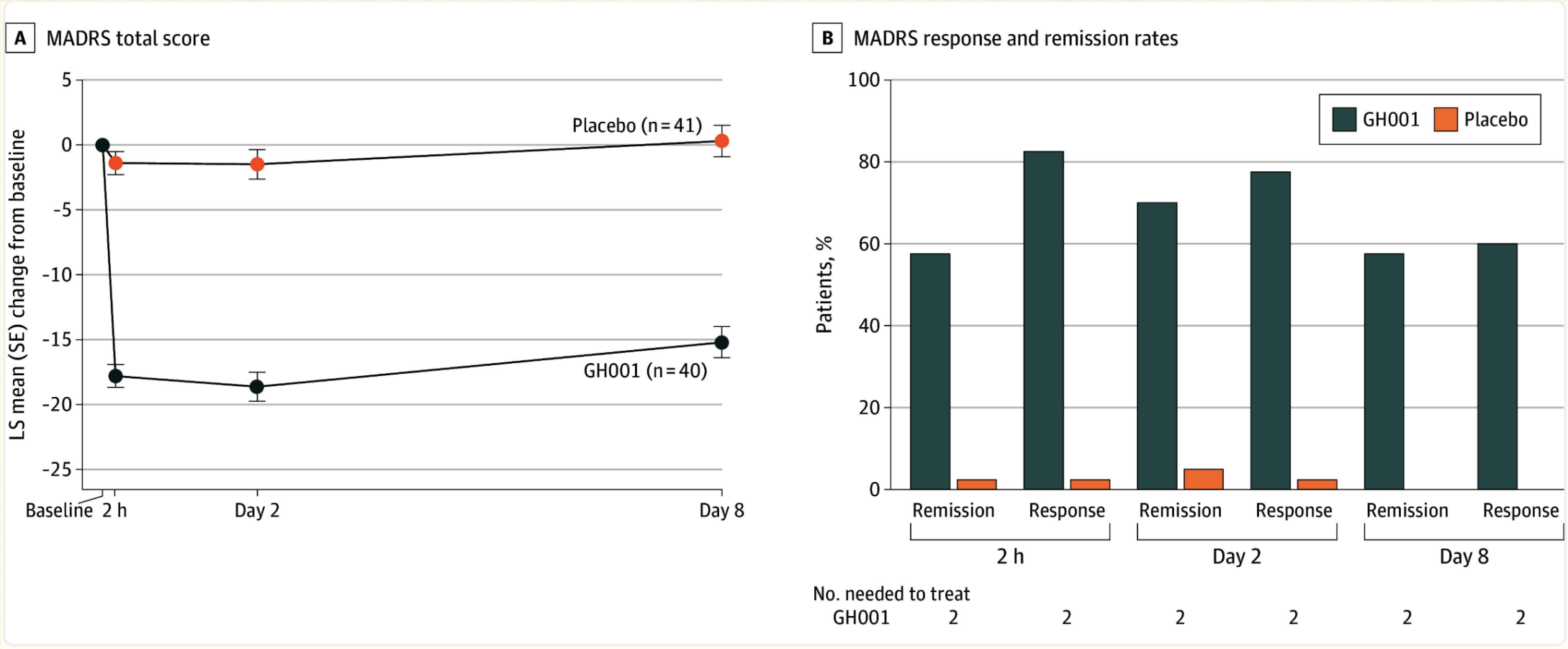
PROGRAM	GH001	BPL-003
Molecule and route	Inhaled mebufotenin	Intranasal mebufotenin benzoate
Evidence and status	Phase 2b; 81 patients with TRD Investigational	**Phase 2b completed; phase 3 initiated** **Breakthrough Therapy; investigational**
Key evidence	**Day 8: −15.5 MADRS points vs placebo** **57.5% remission vs 0%**	Phase 3 efficacy and safety confirmation pending
Delivery and safety	Single-day individualized regimen up to 18 mg No planned psychotherapy; no severe or serious adverse events in the blinded period	Phase 2b program averaged approximately 2 hours in clinic Phase 3 confirmation remains pending

GH001 provides phase 2b efficacy data. BPL-003 has entered phase 3 development.

Cubała WJ et al. JAMA Psychiatry 2026; Eli Lilly press release. July 16, 2026.

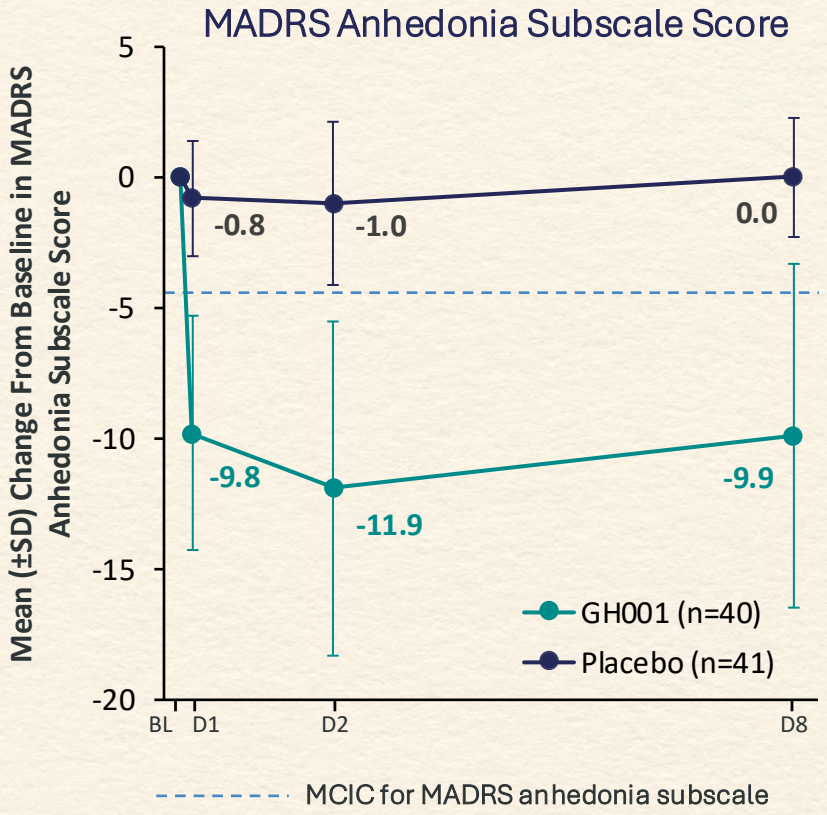
GH001 vs Placebo in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial

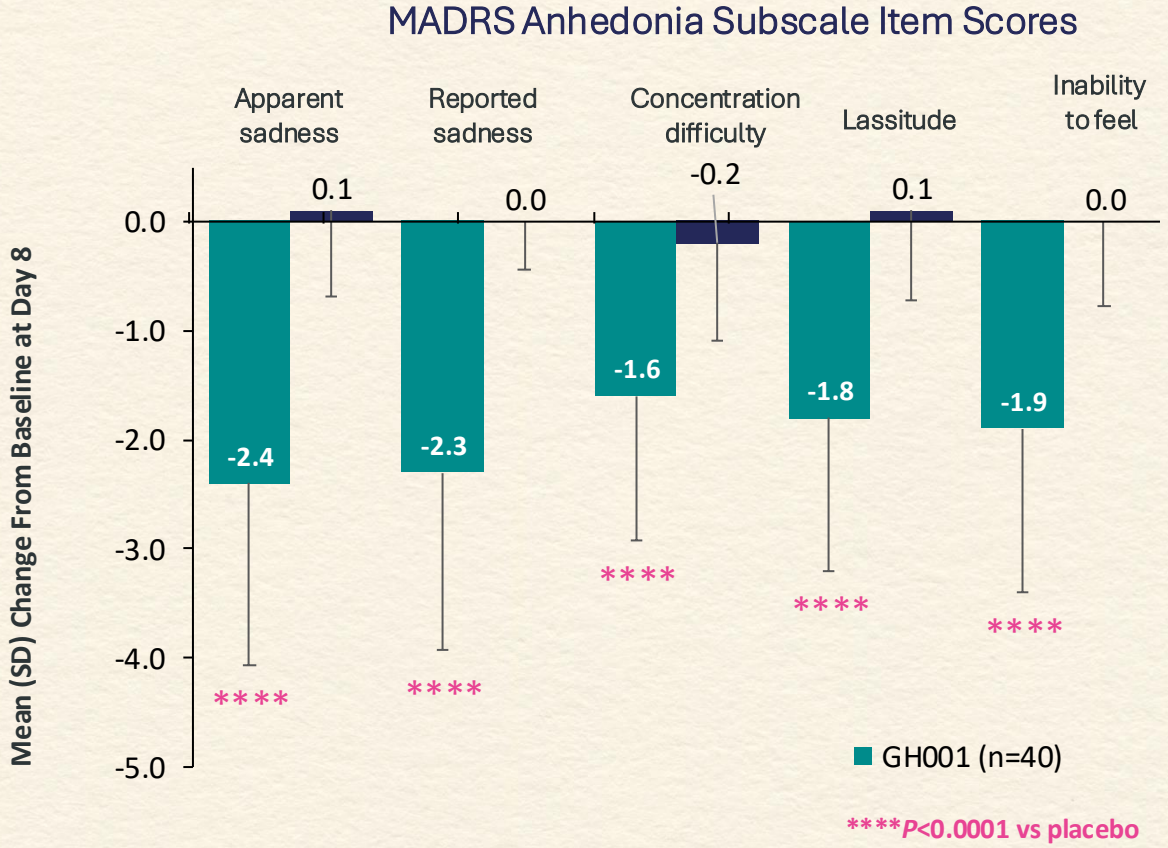
MADRS Score Change, Response, and Remission During Part 1



Cubala WJ et al. JAMA Psychiatry;83(6):561-9.

GH001 Led to Rapid and Clinically Meaningful Improvements in MADRS Anhedonia Scores in the Double-Blind Part of the TRD Study





[a]Clinically meaningful improvement in anhedonia has been reported as an MCIC of –4.6 to –5.5 points based on an analysis of patients with MDD.[1]
Abbreviations: BL = Baseline; D = Day; MADRS = Montgomery–Åsberg Depression Rating Scale; MCIC = Minimal clinically important change; MDD = Major depressive disorder; SD = Standard deviation; TRD = Treatment-resistant depression.

McIntyre RS. J Affect Disord 2024;363:430-5.

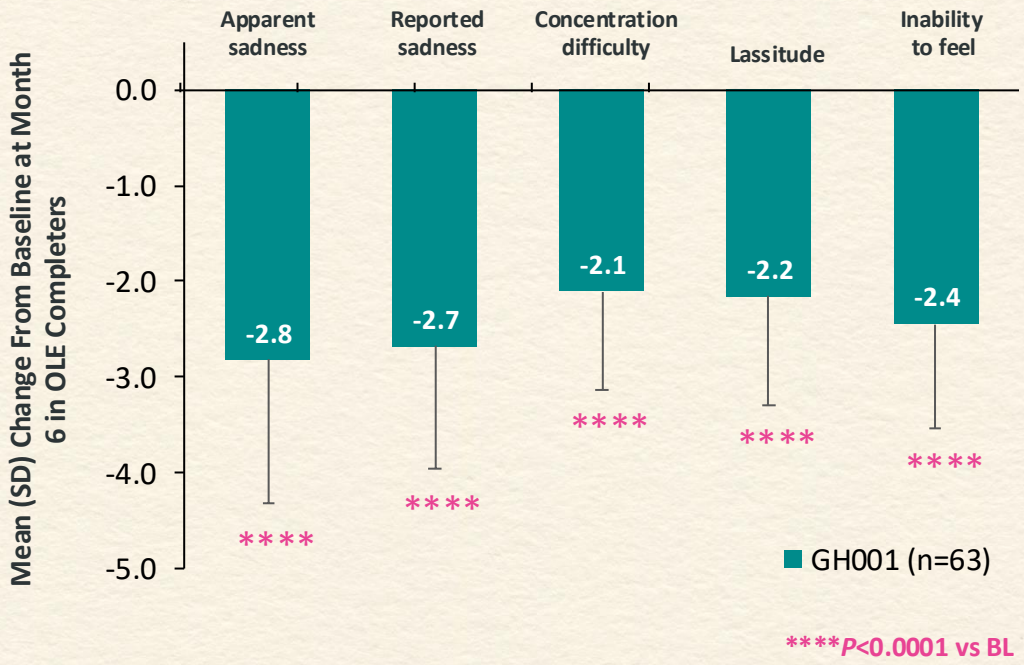
MADRS Anhedonia Improvements Were Maintained Through Month 6 in TRD OLE Completers

Among Patients Who Completed the TRD Study OLE (n=63), Clinically Meaningful[a] Improvement in MADRS Anhedonia Score Was Maintained at Month 6

MADRS Anhedonia Subscale Score

In OLE completers (n=63), mean (SD) change from baseline in MADRS anhedonia subscale score was **−12.2 (4.9) at Month 6 (*P*<0.0001)**

MADRS Anhedonia Subscale Item Scores



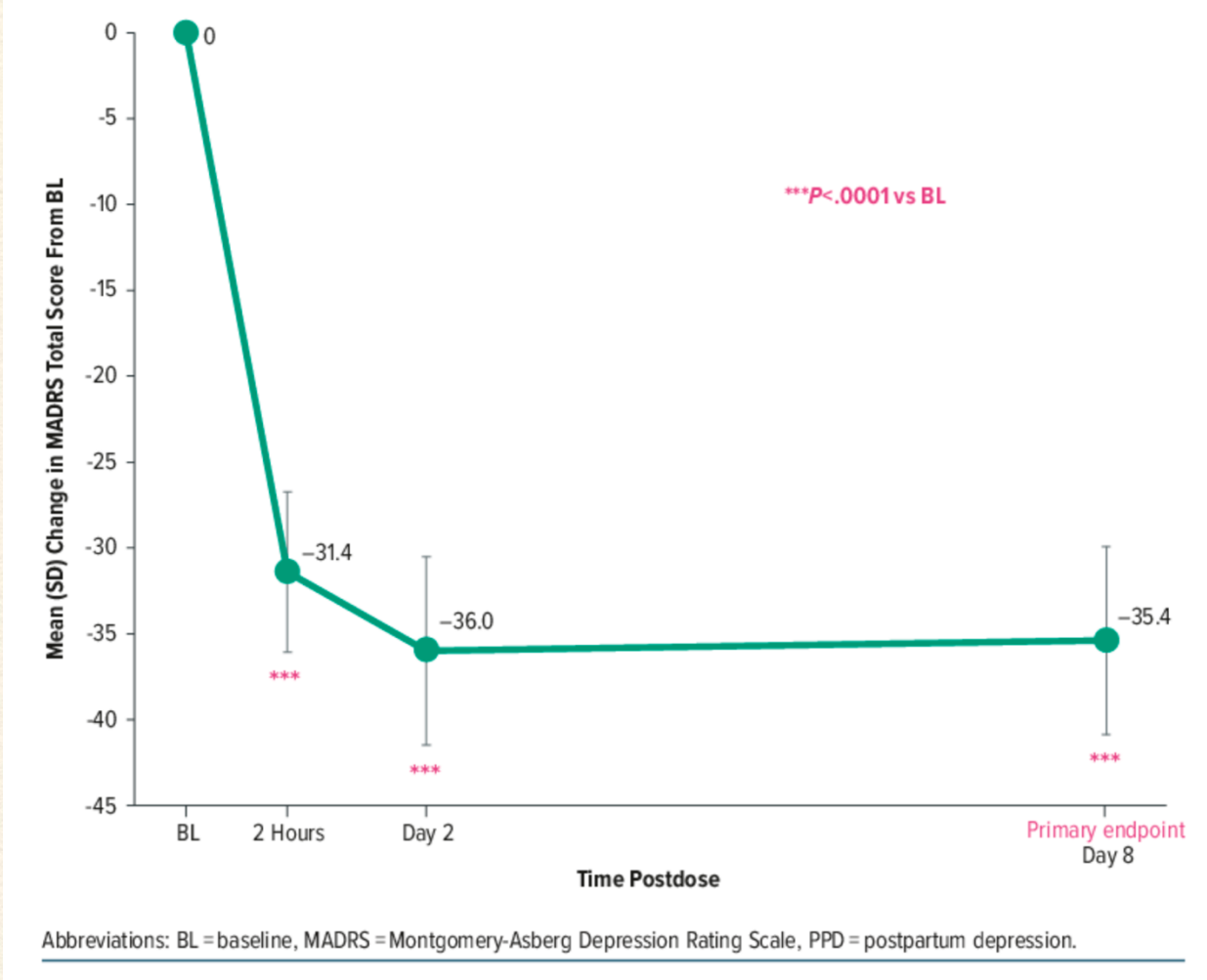
[a]Clinically meaningful improvement in anhedonia has been reported as an MCIC of –4.6 to –5.5 points based on an analysis of patients with MDD.

Abbreviations: BL = Baseline; MADRS = Montgomery–Åsberg Depression Rating Scale; MCIC = Minimal clinically important change; MDD = Major depressive disorder; OLE = Open-label extension; SD = Standard deviation; TRD = Treatment-resistant depression.

McIntyre RS. J Affect Disord 2024;363:430-5.

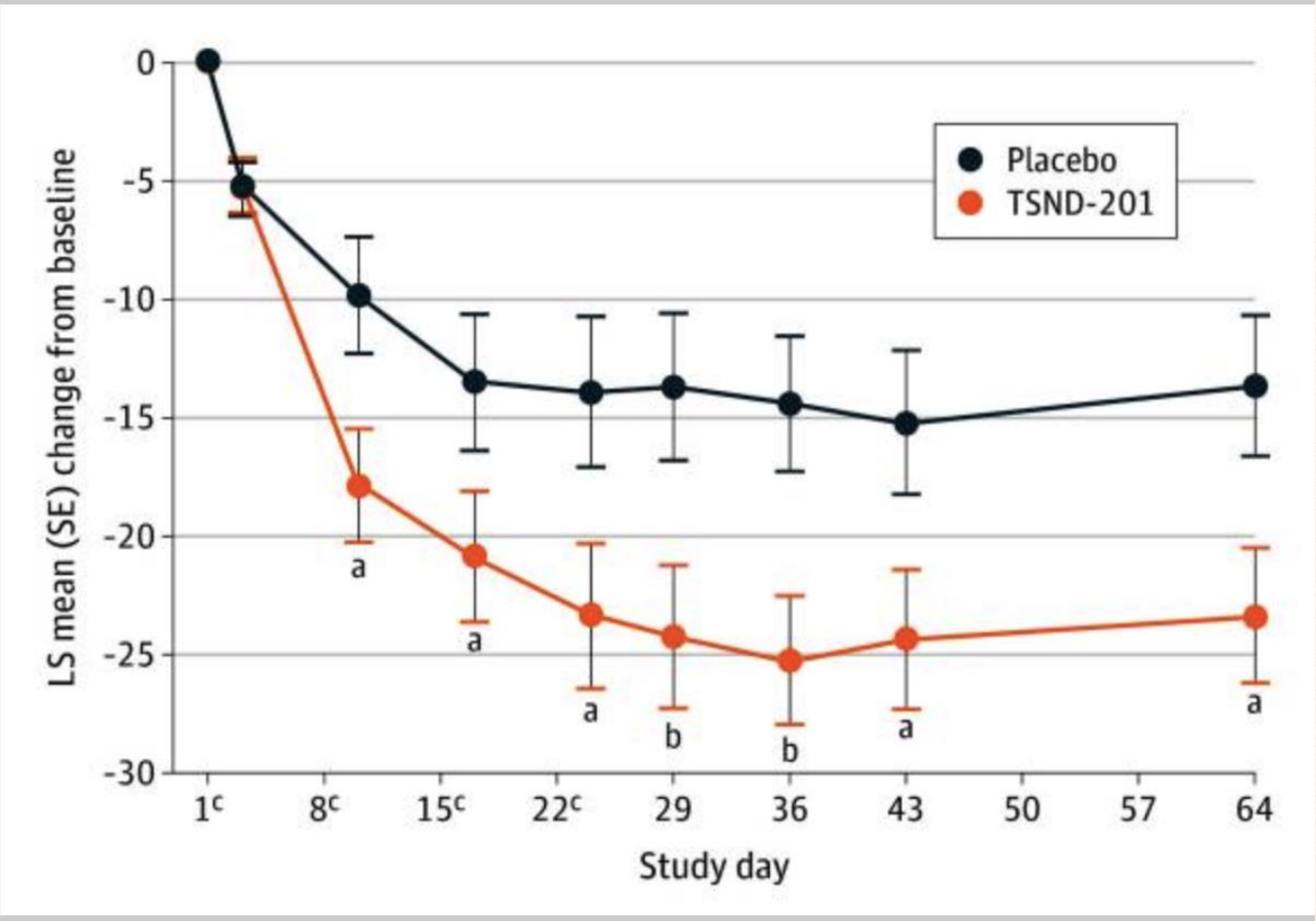
Inhaled Mebufotenin (GH001) for Adult Patients With Postpartum Depression: A Phase 2a Open-Label Clinical Trial

Trial feature	Study details
Design	Phase 2a, single-arm, open-label, proof-of-concept trial
Population	Adult women ages 18–45 with MDD with peripartum onset; n=10
Treatment	Individualized inhaled GH001 regimen: up to 3 escalating doses (6, 12, and 18 mg) on Day 1, 1 hour apart
Primary endpoint	MADRS change from baseline to Day 8



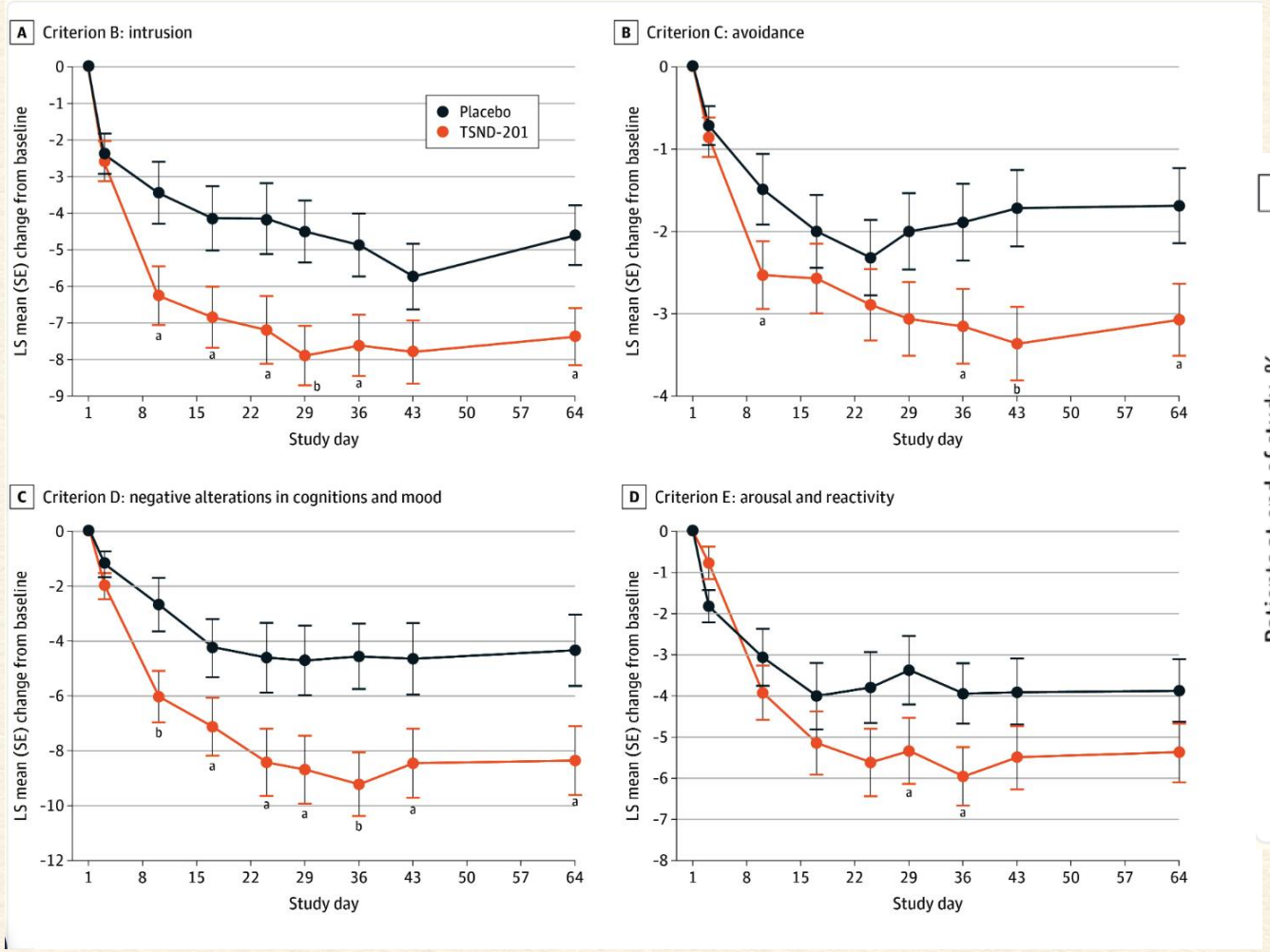
Johnson M et al. J Clin Psychiatry 2026;87(3):25m16284.

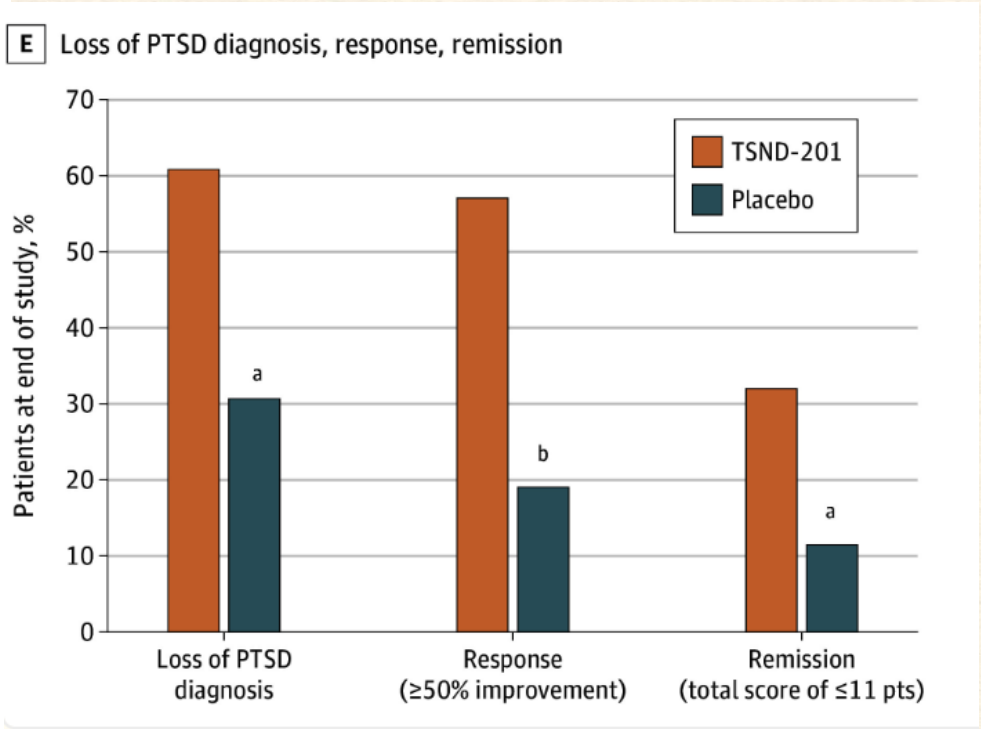
Efficacy and Safety of the Neuroplastogen TSND-201 for the Treatment of PTSD—A Randomized Clinical Trial



Jones A et al. JAMA Psychiatry 2026;83(5):469-77.

Efficacy and Safety of the Neuroplastogen TSND-201 for the Treatment of PTSD—A Randomized Clinical Trial





Jones A et al. JAMA Psychiatry 2026;83(5):469-77.

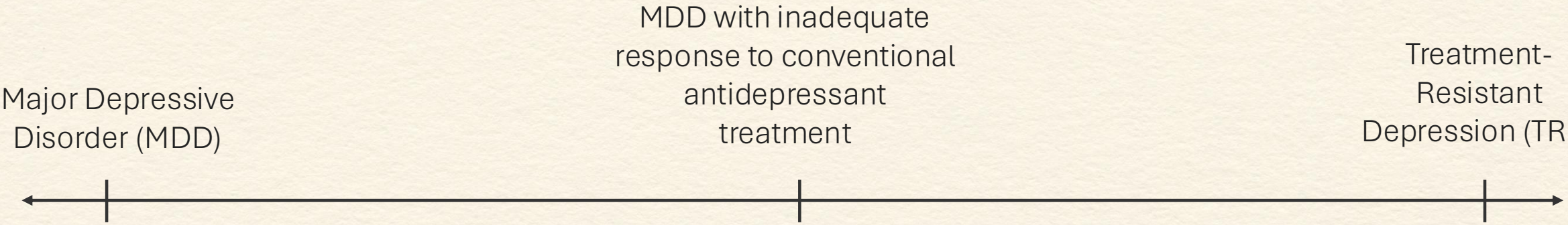
Clinical Readiness Remains Uneven



Compound / Development Name	Indications Under Development	Anticipated Observation Duration
Usona Psilocybin/COMP360	TRD, MDD, PTSD	6 to 8 hours
Deuterated psilocin/ HLP003 / CYB003	MDD	4 to 8 hours
Bretisilocin GM-2505 / ABBV-2505	TRD, MDD, PTSD	Approximately 2 hours
Intranasal 5-MeO-DMT/BPL-003	TRD	Approximately 2 hours
Inhaled 5-MeO-DMT/GH001	TRD, postpartum depression (PPD)	1 to hours, depending on whether 1 to 3 doses are received
Buccal DMT/VLS-01	TRD; MDD planned	Approximately 2 hours
Deuterated DMT HLP004 / CYB004	GAD	Approximately 3 hours
LSD / lysergide DT120ODT / MM120	GAD, MDD; PTSD planned	8 hours
MDMA / Midomafetamine	PTSD	Approximately 8 hours
Methylone / TSND-201	PTSD	At least 8 hours
Subcutaneous 4-HO-DiPT / Luvesilocin	PPD, GAD, Adjustment Disorder	Approximately 8 hours

McIntyre RS et al. Am J Psych. Publication Pending.

Emerging Serotonergic Psychedelics and AMPA Modulators for Major Depressive Disorder (MDD): Across the Treatment Continuum From MDD to Treatment-Resistant Depression



Serotonergic Psychedelics and Neuroplastogens:

- ayahuasca
- LSD (DT120 ODT)
- psilocybin (ELE-101, PEX010)
- bretisilocin
- DMT
- zalsupindole

AMPA Modulators:

- DT101

Serotonergic Psychedelics and Neuroplastogens:

- HLP003
- DMT
- psilocybin (PEX010)
- bretisilocin

AMPA Modulators:

- osavampator
- DT101

Serotonergic Psychedelics and Neuroplastogens:

- ayahuasca
- mebufotenin (BPL003, GH001)
- psilocybin (COMP360)
- DMT (VLS-01)

Xiao K, Mattingly G, Jain R, McIntyre RS. Manuscript under review at Journal of Affective Disorders. 2026.

Domain	Minimum requirement	Recommended practice	Evidence gaps / unresolved issues
Infrastructure and treatment environment	Dedicated administration/ recovery space ensuring privacy, safety, and medical monitoring	Individual treatment/recovery environment; lavatory access; infrastructure matched to psychoactive-effect duration and monitoring needs	Safety/feasibility of shared recovery spaces; optimal "set and setting"
Personnel and scope of practice	Professionals trained in mental-disorder assessment, interventional psychiatry, safety monitoring, and emergency management	Competence in psychological support, boundaries, and agent-/route-specific administration; medical support readily accessible	Optimal staffing and staff-to-patient ratio; need for manualized psychotherapy training
Patient selection	Approved indication; psychiatric/medical eligibility; capacity for informed consent	Structured review of diagnosis, treatment history, comorbidities, substance use, medications, and psychosocial factors	Predictors of response/adverse outcomes; populations underrepresented in pivotal trials
Psychedelic agent selection	Approved agent for approved indication, considering route, duration, and safety requirements	Shared decision making based on clinical presentation, prior treatments, preference, burden, and infrastructure	Comparative effectiveness, tolerability, durability, and patient–treatment matching
Drug–drug interactions	Medication/substance reconciliation and identification of relevant contraindications/interactions	Agent-specific management of MAO inhibitors, serotonergic drugs, CYP interactions, and concomitant treatments	Clinical relevance of theoretical interactions; management of concomitant antidepressants



McIntyre RS et al. Am J Psych. Publication Pending.

Domain	Minimum requirement	Recommended practice	Evidence gaps / unresolved issues
Safety monitoring and emergency preparedness/	Monitoring of vital signs, mental status, psychedelic effects, and adverse events; capacity to manage acute complications, REMS (where applicable)	Standardized monitoring/escalation tailored to agent, patient, route, and regulatory requirements	Optimal intensity and duration of monitoring across agents and populations
Suicide risk assessment and management	Assessment of current suicidal ideation/behavior and need for acute psychiatric stabilization	Reassessment when indicated and before discharge; predefined escalation pathway for emerging/ worsening suicidality	Safety, efficacy, and positioning in patients with acute suicidal ideation or behavior
Discharge readiness and continuity of care	Clinical stability, clear sensorium, attenuation of acute effects, and reliable transportation	Structured discharge assessment: vital signs, mental status, psychiatric safety, transport, instructions, follow-up, and clinical responsibility	Validated discharge criteria, observation duration, and continuity-of-care models
Algorithmic selection and sequencing of available treatments	Position treatment within evidence-based pathways for the approved indication	Shared decision making considering efficacy, safety, prior treatments, alternatives, preferences, burden, access, and cost	Optimal sequencing relative to esketamine/ketamine, neuromodulation, augmentation, and emerging treatments
Cost, reimbursement, and service sustainability	Defined pathways for drug acquisition, treatment delivery, monitoring, and reimbursement, staffing and consumables, payer coverage, and prior authorization, CPT codes and billing structure	Prospective consideration of staffing, room use, treatment frequency, payer requirements, coding, and unit economics	Sustainable reimbursement, scalability, equitable access, and comparative cost-effectiveness



McIntyre RS et al. Am J Psych. Publication Pending.

Previous Substance Misuse Requires Individualized Risk Assessment

CLINICAL HISTORY	PRACTICAL INTERPRETATION
Active use disorder involving the proposed drug	Generally defer dosing pending stabilization and addiction-focused assessment
Recent uncontrolled polysubstance use	Assess interactions, adherence, recovery supports, and risk of use outside the protocol
Previous disorder in sustained remission	Not an automatic exclusion; assess craving, stability, triggers, prior complications, and available supports
Prior exposure without impaired control	Exposure alone does not establish a use disorder, but it may increase expectancy and functional unblinding

ABUSE RISK IS NOT UNIFORM

Classic serotonergic psychedelics show fewer signals of compulsive repeated use than MDMA. Lower risk does not mean no risk.

Monitor craving, rapid redosing, self-directed acquisition, dose escalation, and continued use despite harm.

Studying a drug as a treatment for addiction does not establish that the drug cannot be misused.

Active or unstable use generally supports deferral. Remote misuse in sustained remission requires individualized assessment and stronger safeguards.

FDA final psychedelic-drug guidance, 2026; FDA midomafetamine review, 2024.

The Clinical Signal Is Real, but the Path to Practice Still Requires Stronger Proof

01	**Psilocybin has reached phase 3**	Depression data are generally favorable, but effect sizes vary with population, comparator, endpoint, and blinding.
02	**MDMA defines the regulatory challenge**	Positive efficacy trials could not overcome concerns about bias, durability, safety capture, therapist conduct, and treatment delivery.
03	**The pipeline now extends beyond psilocybin & MDMA**	Lysergide, IV DMT, and other candidates test different indications and shorter or simpler delivery models.
04	**Psychological support remains part of the intervention**	Most trials combine medication with preparation and monitored care. The necessary intensity and active contribution remain uncertain.
05	**Clinical readiness requires more than efficacy**	Long-term safety, retreatment, implementation, workforce needs, and equitable access will shape real-world value.

Safety Is Best Understood Across the Treatment Timeline

DURING THE SESSION

0h

- Blood pressure and heart rate increase
- Anxiety, panic, or agitation
- Nausea, headache, dizziness
- Perceptual and cognitive impairment

HOURS TO DAYS

24h

- Headache and fatigue
- Residual impairment
- Mood instability or anxiety
- Suicidality reassessment

DELAYED OR UNCOMMON

>1w

- Mania or hypomania
- Psychosis or prolonged destabilization
- Persistent perceptual symptoms
- Seizures in susceptible patients

MDMA-SPECIFIC GAPS

!

- Cardiovascular and QT effects
- Hyperthermia and electrolyte risk
- Hepatic assessment
- Abuse potential and impairment

Trial samples systematically exclude many high-risk patients; therefore, study safety cannot be generalized to unscreened or unsupervised use. Report severity, timing, resolution, and ascertainment—not only whether an event was serious. Expected or subjectively positive psychoactive effects still belong in safety data.

FDA guidance; pivotal psilocybin and MDMA trials.

Monitoring and Ethical Safeguards in Psychedelic Trials

FDA TRIAL-MONITORING EXPECTATIONS

STAFFING

Two monitors. Lead: independently licensed clinician with graduate psychotherapy training. Assistant: nursing or bachelor's degree plus at least 1 year in mental health care.

MEDICAL READINESS

If the lead is not a physician, an on-call physician must reach the site within 15 minutes. Use defined discharge criteria and address transportation and driving safety.

SAFETY DOCUMENTATION

Record the incidence, duration, and severity of all CNS effects, including experiences described as positive or neutral.

ETHICAL SAFEGUARDS

CONSENT AND VULNERABILITY

Discuss altered perception, cognition, judgment, vulnerability, suggestibility, and impairment that may persist for hours.

BOUNDARIES AND REPORTING

Predefine policies for physical contact, chaperoning, prohibited relationships, and recording. Provide an independent complaint and adverse-event escalation route.

AFTERCARE AND ROLE SEPARATION

Separate session monitoring from later psychotherapy. Confirm transportation, responsible support, emergency contacts, and follow-up.

FDA. Psychedelic Drugs: Considerations for Clinical Investigations. Final guidance. July 2026.

Clinical Takeaways

- Psychedelic therapies differ in mechanism, duration, and regulatory status
- Psilocybin shows promise for depression, but evidence remains mixed
- Positive efficacy trials do not guarantee regulatory approval
- Patient selection, medication interactions, and monitoring are essential
- Safe delivery requires preparation, supervision, and follow-up



Posttest Question 1 of 2

A 59-year-old patient with PTSD takes lisinopril for hypertension. At screening for an MDMA-assisted therapy trial, blood pressure is 168/102 mm Hg. What is the most appropriate response?

1. Continue screening because lisinopril prevents MDMA-associated cardiovascular effects
2. Defer participation because the patient's hypertension is not adequately controlled
3. Discontinue lisinopril before the MDMA dosing session
4. Proceed with a reduced MDMA dose if the electrocardiogram is normal



Posttest Question 2 of 2

Which staffing plan most closely follows FDA recommendations for an investigational psychedelic dosing session?

1. One physician monitor without an assistant
2. Two qualified monitors, with an on-call physician able to reach the site within 15 minutes when the lead monitor is not a physician
3. Two peer-support monitors with physician consultation available by telephone
4. Unsupervised dosing after written consent and baseline vital signs