PSYCHEDELICS: The Next Wave of Blockbuster Therapeutics in Neuroscience

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Significant Mental Health Burden Persists Despite Therapeutic Choice and Broad Accessibility

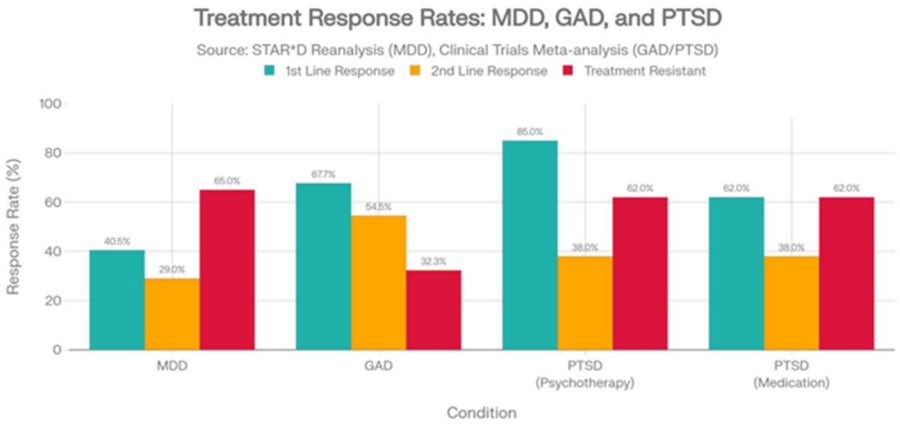
Major Depressive Disorder (MDD) continues to present significant clinical challenge and economic burden globally, affecting > 350 million people worldwide

A landmark publication in BMJ outlining results of the STAR*D Re-Analysis Trial (NIH-funded) indicates that only ~ 40.5% of MDD patients respond to 1st line therapy

Cumulative remission rate with 1st line therapy was ~ 35%, while 65% of patients remained treatment-resistant after 4 optimized treatment levels

The drop-out rate of ~53.7% underscores a highly frustrated patient population

Prevalence of treatment-resistance in Generalized Anxiety Disorder (GAD) and Post-Traumatic Stress Disorder (PTSD) is also remarkably high at 32% and 62% respectively



Why are Psychedelics capturing so much attention?

R&D in the psychedelic space has made substantial progress with reproducible, robust clinical efficacy, greater mechanistic precision and an improving regulatory environment that provides visibility into approvable pathways

Across major drug class categories (psilocybin, DMT, 5-MeO-DMT, LSD, dissociative anesthetics) evidence demonstrates rapid-onset and durable antidepressant effects

Forecast estimates suggest that the Psychedelic market may reach global sales of ~US$20B by 2035, from MDD and TRD indications alone

A compelling aspect about psychedelics is that they work across indications, providing meaningful symptom improvement in depression, anxiety and substance use disorders, explains Dr. David Olson, founding director of the UC Davis Institute of Psychedelics and Neurotherapeutics

Psilocybin, LSD, and DMT have all demonstrated therapeutic benefit for MDD and TRD:

- Psilocybin can enhance senses, perception and cognition at therapeutic doses, in contrast to SSRIs, which may have a blunting effect via serotonin reuptake inhibition

- Clinical evidence suggests psilocybin (psilocin) can improve synchronicity in areas of the brain responsible for introspective and internally focused thought processes, increasing connectivity more broadly

- In MDD, psilocybin appears to precisely target and rewire dysfunctional thought patterns within distinct neural networks

- A brief 30-minute exposure to DMT has been shown to result in significant symptom improvement in various depression indications, within 24hrs

- LSD has shown the ability to foster emotional insight and improve cognitive flexibility, both critical variables in alleviating depression symptoms and promoting MDD recovery

Innovation In Psychedelic Development Forges Two Paths

- Broadly speaking, the Psychedelic landscape could be described as bifurcating into two separate categories or "waves" of clinical innovation and advancement:

- "Wave 1" is comprised of long-acting, durable therapeutics that are paving the regulatory path in major markets

- "Wave 2" is comprised of short-acting therapeutics with favorable safety profiles, negligible hallucinatory experience, efficient out-patient scheduling and system scalability

- Managing the hallucinatory and dissociative side effects of classic psychedelics & ketamine have presented substantial burden on healthcare providers, limiting patient volume capacity and access

- Next generation, non-hallucinogenic psychedelics represent potential blockbuster commercial opportunities, given their notable efficacy, ease of administration and reduced healthcare system burden

Rapidly Expanding Landscape in MDD, TRD & other Indications

A wide array of psychedelic drug profiles in development indicates that physicians will have increasing ability to tailor therapeutic choice for distinct clinical profiles

The table below outlines details of the different classes of psychedelics in development, their respective mechanisms, target pathways, routes of administration and most advanced therapeutic areas of development.

Drug Class/Compound (Company Candidate Examples)	Hallucinogenic	Route of Administration	Mechanism of Action	Target Pathways	Therapeutic Areas
Classic Psychedelics - Psilocybin (Compass Tx - COMP360; Helus HLP003)	Yes	Oral (synthetic formulation)	5-HT2A receptor agonist (serotonergic)	5-HT2A receptor → BDNF release → mTOR pathway activation → synaptic plasticity	TRD (primary), PTSD, anxiety disorders, anorexia nervosa (in development)
Classic Psychedelics - LSD (Definium DT120)	Yes	Oral	5-HT2A receptor agonist (lysergamide)	5-HT2A, 5-HT1A, D2 receptors → BDNF → neuroplasticity	Anxiety associated with life-threatening illness, treatment-resistant depression, cluster headaches
Classic Psychedelics - DMT/5-MeO-DMT (Atai Beckley, Lusaris, GH Research, Reunion Tx, Helus, BioMind)	Yes	IV infusion, sublingual, inhalation	5-HT2A receptor agonist (tryptamine)	5-HT2A, 5-HT1A receptors → rapid neuroplasticity induction	MDD, anxiety, Alzheimer's-related anxiety/depression, substance use disorders; PPD
Atypical Psychedelics - MDMA (Lykos, Atai, Definium, Tactogen, Awaken Life Sciences)	No / Variable (entactogen, mild perceptual changes)	Oral capsules	(Entactogens) Serotonin-norepinephrine-dopamine releasing agent + oxytocin release	SERT, NET, DAT → massive serotonin release → oxytocin → enhanced emotional processing and fear extinction	PTSD (primary), social anxiety in autism (exploratory)
Dissociative Anesthetics - Ketamine Dizocilpine (racemic)	Mixed (dissociative)	IV infusion, IM injection	NMDA receptor antagonist	NMDA antagonism on GABA → glutamate burst → AMPA activation → BDNF release → mTOR activation → rapid synaptogenesis	TRD, suicidal ideation (acute), PTSD, substance use disorders
Dissociative Anesthetics - Esketamine (JNJ - Spravato)	Mixed (dissociative, less than racemic)	Intranasal spray	NMDA receptor antagonist (S-enantiomer with higher NMDA affinity)	NMDA antagonism → glutamate surge → AMPA activation → calcium influx → BDNF → mTOR → dendritic growth and synaptogenesis	TRD (with oral antidepressant), acute suicidal ideation/behavior in MDD
Atypical Psychedelics (Ibogaine - active chemical of parent compound)	Yes (intense dissociative/oneiric state)	Oral	Multi-target: NMDA antagonist, kappa-opioid receptor agonist, serotonin transporter inhibitor, sigma receptor modulation	NMDA, KOPR, SERT, sigma-2, nicotinic receptors → GDNF upregulation → neuroprotection and plasticity	Opioid use disorder (primary), alcohol use disorder, stimulant use disorder, depression comorbid with SUD
Atypical Psychedelics - Noribogaine (DemeRx NB)	Reduced/minimal	Oral	Active metabolite of ibogaine with similar multi-target profile but reduced hallucinogenic liability	NMDA, KOPR, opioid receptors, SERT, DAT → GDNF upregulation	Opioid use disorder, cocaine use disorder, alcohol use disorder
Non-Hallucinogenic Psychedelics - Tabernanthalog (TBG) (Delix Therapeutics - DLX007)	No	Oral (water-soluble)	Structural analog of ibogaine engineered to retain therapeutic effects without hallucinogenic properties (tryptamine)	5-HT2A antagonist (unlike ibogaine), reduced opioid activity → neuroplasticity via alternative pathways	Substance use disorders (alcohol, heroin), depression (preclinical evidence)
Non-Hallucinogenic "Ketalogs" Zalsupindole (Delix Tx DLX-001)	No (nondissociative)	Oral	Functionally mimics ketamine's downstream mechanisms without NMDA antagonism - different molecular scaffold	Alternative pathway to NMDA/AMPA cascade → neuroplasticity without dissociation	Depression
Non-Hallucinogenic Psychedelics **5-HT1A Biased Agonist** (Neurolixis NLX-204)	No	Oral	5-HT1A selective receptor biased agonist with preferential activation of ERK1/2 phosphorylation pathway	5-HT1A receptor → preferential pERK1/2 activation → pCREB → BDNF signaling → neuroplasticity without dissociation or hallucinogenic effects	Depression, Treatment-Resistant Depression (TRD), anxiety, cognitive deficits in depression; chronic pain
Non-Hallucinogenic Psychedelic Arketamine - Paused Programs Otsuka & Perception Neuro / Jiangsu Hengrui	Reduced dissociation vs racemic/esketamine	IV infusion	R-enantiomer of ketamine with different NMDA receptor binding profile	NMDA antagonism with potentially less dissociative liability → BDNF/mTOR pathway	TRD, potentially safer than S-ketamine

- MDD and TRD are leading indications pursued first by most developers, however clinical programs in GAD, PTSD and substance use disorders are now common across the industry pipeline

- Psilocybin has the broadest pipeline across indications

- Novel ketamine analogs are now in development by smaller biotech however JNJ maintains its market exclusivity with esketamine

- Atypical psychedelics belonging to the MDMA category have predominated for treatment of PTSD

- Multiple companies are progressing programs in depression across all the categories

- Drug developers emphasize neuroplasticity benefits, instilled through BDNF release, mTOR pathway activation, synaptic remodeling, and/or dendritic growth

Are hallucinogenic properties essential for neuroplasticity and long-term benefit from psychedelics?

In 2018, Olson & colleagues proposed the term “psychoplastogen” to describe small molecules capable of promoting structural and functional neuroplasticity, independent of subjective perceptual phenomenology

Often, a non-hallucinogenic psychedelic is thought of as a molecule that binds to the 5-HT2A receptor and triggers therapeutically beneficial neurobiological changes without inducing subjective effects such as hallucinations

Scientific consensus has now shifted towards a solidified view that neuroplasticity and robust clinical benefit can be fully achieved while being decoupled from hallucinogenic effects

Clinical evidence suggests that dissociative symptoms triggered by esketamine are not crucial for its antidepressant effects in TRD, MDD and BD, and clinical studies with parent compound ketamine have also shown that dissociative experiences are not necessary for ketamine to produce antidepressant effects

A wide body of preclinical literature demonstrates that it is possible to decouple the hallucinogenic effects of psychedelics from their beneficial effects on neuroplasticity. The non-hallucinogenic LSD analog, 2-Br-LSD reverses chronic stress behaviour and induces dendritogenesis and spinogenesis in rat cortical neurons

Low-dose LSD can substantially increase brain plasticity

Tabernanthalog (TBG) promotes cortical neuroplasticity and spinogenesis, resulting in sustained antidepressant-like behavioral effect. The absence of an immediate glutamate burst or IEG activation event eliminates the head twitch response in mice, which is typically thought of as a proxy for hallucinogenic effect in humans

Critically, psychedelics engage multiple serotonergic receptors and downstream effectors. As well as 5-HT2A receptors, they activate, to

different extents, 5-HT2B receptors (a known cardiac risk factor), 5-HT2C receptors and also 5-HT1A receptors, which are known to elicit anti-depressant and anxiolytic properties.

Psychoplastogens are known to impact BDNF/TrkB signaling rapidly after a single administration and have shown benefit in a range of indications beyond depression, such as PTSD and addiction.

Thus, the precise receptor mechanisms and cellular signaling pathways that elicit therapeutic activity of psychedelics remain a subject of investigation.

Reference terminology has become fuzzy over time….

From the 1960's onward, the term psychedelic referred to a compound that acted as full or partial agonist at the serotonin 2A receptor, meaning it would bind to the 5-HT2AR on the neuron and trigger a full or partial signaling cascade, and would also invariably produce profound alterations in perception, cognition, and self-experience

Contemporary drug development has diversified well beyond the 5HT2AR-centric mechanism, yet definitions of atypical and classic psychedelics are often blurred and overlapping

Atypical psychedelics, a class of drugs that bind to different receptors (other than 5HT2A), produce distinct neurobiological signaling cascades, elicit robust therapeutic outcomes but generally lack the canonical hallucinogenic signature characteristic of the classic psychedelics.

Research into ketamine, MDMA and ibogaine has provided greater understanding of diverse mechanisms that are capable of rapid antidepressant effect. Particularly compelling are those that provide rapid antidepressant effect without dissociative, nor hallucinogenic liability such as Neurolixis' NLX-204 and Delix Therapeutics' Tabernanthalog (TBG).

NLX-204 is a novel neuroplastogen, providing rapid antidepressant activity, by increasing pERK1/2 and pCREB in prefrontal cortex and hippocampus, similar to ketamine's signature.

NLX-204 represents a **distinct class** of compound, however, as its rapid-acting antidepressant activity is achieved through specific activation of **5-HT1A** receptors, propagating glutamatergic/NMDA neurotransmission and downstream engagement of the Akt-mTOR pathway.

In Summary, Current Evidence Strongly Supports:

- Neuroplasticity effects can be fully decoupled from hallucinogenic and dissociative experiences

- Non-hallucinogenic psychoplastogens show comparable or superior preclinical efficacy

- Clinical correlation between mystical experience and outcome is inconsistent and may reflect target engagement, not causal necessity

- Neuroplasticity may be elicited by a range of mechanisms and pathways, not restricted or anchored to 5HT2A agonism

Clinical Catalysts & Key Developments for 2026

2026 will be a transformative year for the psychedelic sector

- Multiple companies are planning for H2, 2026 pivotal trial readouts; Compass Pathways just announced results from their second positive phase 3 trial in TRD, with 26-week durability data anticipated in Q3, and a rolling NDA submission planned for Q4, 2026

- Definium Therapeutics (rebranded from MindMed) expects 3 phase 3 trial readouts in 2026 involving its orally disintegrating LSD tablet; two pivotal trial readouts are in GAD, one in MDD

- Reunion Neuroscience plans to initiate a phase 3 trial in post-partum depression as well as a phase 2 trial in GAD in 2026

- Atai Beckley will report results of its phase 2 trial, evaluating VLS-01 (DMT) in TRD in H2, '26, a short-acting psychedelic

- Cybin will report topline phase 3 results for 220 patients with MDD, involving its deuterated psilocin candidate, CYB003, in Q4, '26

Company	Date	Notes
Compass	Q1, 2026	**COMP360**: COMP-006 Part A, 9-week, **TRD trial** treating with two doses: Successfully achieves primary readout in second Phase 3 trial
AtaiBeckley	Q1, 2026	▪ Rolling NDA submission with FDA ▪ Initiation of Phase 2b/3 trial in PTSD **BPL-003/(5-MeO-DMT): TRD Trial** ▪ End-of-Phase 2 meeting with FDA will inform the Phase 3 trial design and other aspects of the development program
AtaiBeckley	Q2, 2026	**VLS-01 DMT**: Report top-line data from Phase 2 trial in TRD ▪ VLS-01 has potential as a disruptive short-acting psychedelic treatment for depression; could improve patient accessibility and reduce patient and clinical time commitment.
AtaiBeckley	Q1, 2026	**EMP-01 (R-MDMA)** ▪ Report top-line data from Phase 2 trial in Social Anxiety Disorder, enabling advancement to Phase 3 trial in SAD
Definium Therapeutics	Q1 & Q2, '26	**DLT120 (LSD)** ▪ Report topline 12-week Part A data from ▪ Phase 3 trial (VOYAGE) & Phase 3 trial (PANORAMA) in GAD, likely supportive for an NDA filing in GAD ▪ Report topline 12-week Part A data from