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Psychedelic therapies: Navigating setbacks and opportunities in a transforming landscape

A rapidly evolving field

Over the past several decades, research into the potential of psychedelic therapies has grown significantly, with several compounds, such as psilocybin, MDMA (3,4-methylenedioxymethamphetamine), DMT (dimethyltryptamine), and LSD (lysergic acid diethylamide), being explored in clinical trials.

Momentum for these investigational psychedelic therapies is supported by compelling clinical data, regulatory shifts, and growing patient demand for alternatives to traditional treatments. Psychiatric conditions, such as post-traumatic stress disorder (PTSD), major depressive disorder (MDD), treatment resistant depression (TRD), generalized anxiety (GAD), and substance use disorders, are the initial wave of indications targeted by psychedelic therapies. In these conditions, where pharmaceutical innovation has been limited in recent years, psychedelic therapies may bring a novel approach with superior outcomes compared with existing therapies.

In depressive disorders, traditional antidepressants require daily dosing and often take several weeks to show effect, while psychedelic therapies may offer rapid and long-lasting benefit from as little as a single session. Spravato (esketamine) monotherapy, for example, showed improvement in depressive symptoms as early as 24 hours in clinical trials.[1] Meanwhile, in a 2023 Phase 2 study, more than half of the patients (16 of 28) treated with a single dose of 25mg COMP360 psilocybin with psychological support remained in remission from their depression at 18 months post-administration.[2] The psychedelic mechanism in the brain may help “reset” neural circuits, allowing patients to process traumatic memories or break patterns of negative thought in a more effective manner.

Despite the growing momentum and promising clinical data, the path to regulatory and commercial success remains complex. The Food and Drug Administration’s (FDA) August 2024 rejection of Lykos Therapeutic’s application for MDMA-assisted therapy in PTSD serves as a reminder that while the potential is great, psychedelic therapies must meet the same rigorous standards as any other pharmaceutical treatment. This includes navigating unconventional challenges related to clinical trial design, such as functional unblinding and participant expectancy bias.

The FDA's 2024 rejection of Lykos's MDMA therapy: What went wrong?

In August 2024, the FDA declined to approve Lykos's new drug application for MDMA-assisted therapy for PTSD, a not entirely unexpected decision following the critical FDA advisory committee meeting.[3]

Key concerns cited by the FDA included:

- **Study design limitations**: There were questions whether the trial was sufficiently rigorous, particularly in terms of ensuring reliable blinding and controlling for potential expectancy bias.
    - Functional unblinding describes how trial participants may be able to unblind their treatment assignment based on the unmistakable psychoactive effect of the investigational drug.
    - Expectancy bias describes how outcomes of a psychedelic therapy trial may be influenced by participants' preexisting expectations of efficacy (especially in those with prior exposure to MDMA); this is exacerbated if participants also are able to unblind themselves due to experiencing psychoactive effects.
- **Data integrity issues**: Experts raised concerns that therapists' enthusiasm for the treatment may have influenced patient outcomes, potentially inflating efficacy results.
- **Safety concerns**: Regulators also expressed concerns about risks with MDMA-assisted therapy, including potential abuse liability and adverse psychological reactions, and did not consider the capture of safety events in the trial to be robust.

In addition to the above concerns, allegations of misconduct against Lykos were made during the Open public hearing of the psychopharmacologic drugs advisory committee meeting.[4] These allegations were not cited by the FDA as part of the rationale for the rejection, and later were reported to be driven by external advocacy groups campaigning against commercialization of psychedelics.[5]

The FDA requested that Lykos run an additional Phase 3 clinical trial to further assess the therapy's safety and efficacy. The journal *Psychopharmacology* also retracted three papers related to Lykos's MDMA therapy shortly after the FDA rejected Lykos's application. For Lykos, these setbacks resulted in leadership departures and a 75% reduction in headcount, but for the broader psychedelic therapy industry it resulted in valuable lessons.

Lessons for psychedelic therapy developers: Trial design is essential

With the issues of functional unblinding and expectancy bias raised prominently in the FDA advisory committee and eventual FDA rejection, there are some potential measures to take to minimize these risks in future trials.

- **Include a "psychoactive placebo" arm**: Using a three-arm approach (therapeutic dose, subtherapeutic dose, and placebo) is likely to minimize the risk of patients knowing they received the therapeutic dose based on psychoactive effects alone.
- **Utilize independent raters**: Potential biases on the part of trial investigators may be mitigated by blinded raters who are uninformed about the dose received or the patient's dosing experience and can thereby evaluate outcomes independently.

- **Enroll psychedelic-naïve patients**: Naïve participants are likely to have reduced preexisting expectancy bias for positive effects of psychedelic therapies and provide a more representative view of the broader real-world population that may ultimately be treated with these therapies.

- **Extend timelines**: Assessing longer-term efficacy outcomes increases the likelihood of outlasting expectancy biases and ensures all participants have completed the blinded phase of trials prior to data releases.

Some psychedelic therapy developers, such as Cybin and COMPASS Pathways, have already made immediate adjustments to their respective Phase 3 pivotal programs in light of Lykos's rejection, hoping to avoid similar pitfalls upon FDA submissions for their assets.[6,7]

Catalysts in psychedelic drug development are on the horizon

Interestingly, in both the US and Europe, there are a number of locally sanctioned organizations offering self-pay ketamine infusion clinicals for a range of (off-label) mental health conditions, including TRD, PTSD, pain, anxiety, and trauma. This suggests there is demand for novel approaches to treating psychiatric disorders and a willingness to provide for patients ahead of broader regulatory decisions, which often work on longer timescales.

While it remains to be seen how future psychedelic therapy submissions are viewed by regulators, there was a boost for the space in early 2025, with the FDA approving Spravato (esketamine) nasal spray as a monotherapy for TRD.[8] Spravato has been approved and marketed since March and October 2019 (by the FDA and EMA, respectively) in combination with SSRI (selective serotonin reuptake inhibitor) or SNRI (serotonin and norepinephrine reuptake inhibitors) antidepressants.[9,10]

With several Phase 3 programs underway (*Figure 1*), there are important catalysts on the horizon in 2025 that will have significant implications for the broader psychedelic space:

- **Early 2025 readouts** are focused on psilocybin in depression disorders, with Part A of COMPASS Pathways' COMP005 trial recently reading out statistically significant topline 6-week data.[11]

- **Trial recruitment is highly active** for several recently initiated Phase 3 trials (MindMed's Voyage and Panorama trials, Cybin's APPROACH trial, Solvonis Therapeutics' MORE-KARE trial, and Usona Institute's uAspire trial), with readouts anticipated in 2026 or 2027.[12,13,14,15,16]

- **Early or mid-2025 trial initiations** are in progress for additional Phase 3 trials (Cybin's EMBRACE trial and MindMed's Emerge trial), which round out these pivotal programs ahead of potential 2026 regulatory inflection points.[17,18]

Figure 1: Overview of Phase 3 trials in the psychedelic therapeutics space

Company	Asset	Indication	Trial name	Expected readout date
COMPASS Pathways	Psilocybin *COMP360*	Treatment-resistant depression	COMP005 – PART A	Readout June 2025 *Topline 6-week data*
			COMP006	2H 2026 *26-week data*
Usona Institute	Psilocybin	Major depressive disorder	uAspire	April 2026 – *Primary completion date* December 2026 – *Study completion date*
Cybin	Deuterated Psilocybin Analog *CYB003*	Major depressive disorder	APPROACH	2026 *Topline results*
			EMBRACE *Trial to be initiated mid-2025*	*n/a – not yet initiated*
MindMed	LSD *MM120 ODT*	Major depressive disorder	Emerge	2H 2026 *Topline 12-week data*
		Generalized anxiety disorder	Voyage	1H 2026 *Topline 12-week data*
			Panorama	2H 2026 *Topline 12-week data*
Solvonis	Ketamine *SVN-001*	Severe alcohol use disorder	MORE-KARE	2026-27 *Study completion date*

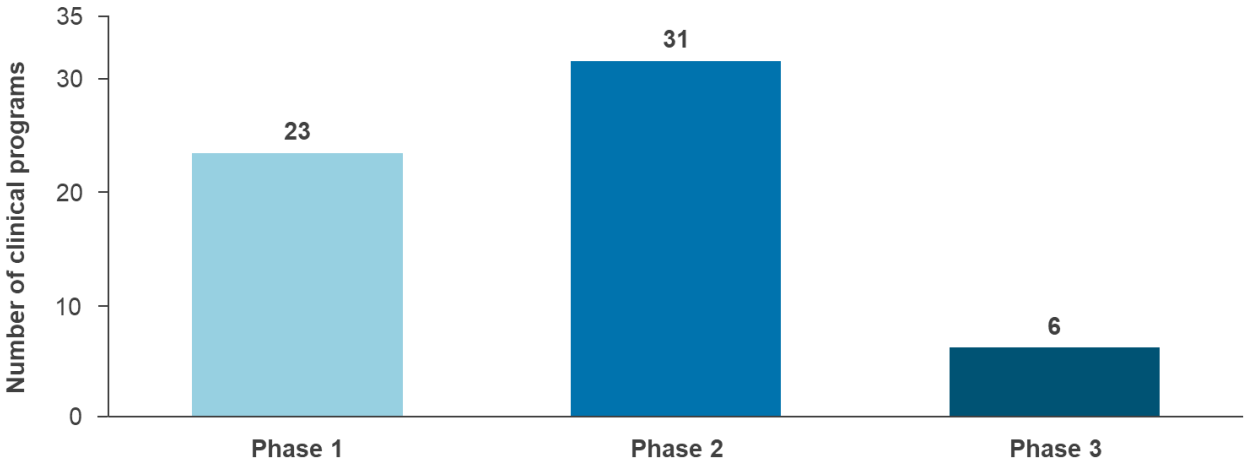
* Sourced from company press releases and clinicaltrials.gov (accessed July 2025)

Looking earlier in the pipeline, there are 54 trials in Phases 1 and 2, with the majority focused on psychiatric and central nervous system indications (*Figure 2*).[19] Interestingly, there are some early trials looking at metabolic diseases and data from these trials will shed light on the potential of psychedelic therapies across broader therapeutic areas:

- In late 2024, Relmada Therapeutics initiated dosing in a Phase 1 study investigating a low-dose, modified-release psilocybin formulation for metabolic disease. Positive PK/PD and safety data from this Phase 1 trial may pave the way for a Phase 2a proof-of-concept study to begin in the first half of 2025.[20]

- Also in 2024, Biomind announced its intention to advance a mescaline-based candidate into Phase 1 and 2 trials for obesity, following encouraging preclinical data showing anti-inflammatory properties.[21] However, detailed timelines around this study remain unclear. This study fits a growing trend to approach obesity not purely from the perspective of being a metabolic disorder but rather as a complex disease that may include a psychiatric element.

Figure 2: Investigational psychedelic therapies by clinical development stage, as of July 2025



* Sourced from Psychedelic Alpha's Drug Development Tracker (accessed July 2025)

The long road continues, but a promising future lies ahead

The psychedelic therapy landscape is at a pivotal juncture; while recent setbacks like the FDA's rejection of Lykos's MDMA-assisted therapy highlight the complexities of achieving regulatory approval, they also provide valuable lessons for drug developers in the space. Addressing trial design challenges such as expectancy bias and adopting innovative approaches to blinding are critical as more companies move toward pivotal data readouts and potential regulatory submissions.

Recently (mid-2025), there were two promising trial readouts involving psychedelic derived drugs:

- **Gilgamesh Pharmaceuticals** reported positive topline results from its Phase 2a MDD study of GM-2505 (a short acting psilocybin derived compound), which showed rapid onset as early as Day 14, with 94% of patients achieving remission with sustained effects observed up to 74 days.[22]

- **Beckley Psytech** also announced positive topline results from its Phase 2a TRD study of BPL-003 (an intranasal DMT derived compound) in combination with SSRIs; BPL-003 was associated with an average reduction on the Montgomery-Asberg Depression Rating Scale (MADRS) of 18 points from baseline observed the day after dosing, which was maintained at 19 points after a month and 18 points at three months.[23]

The busy late-stage pipeline and continued investment into psychedelic therapies ensure there will be continued "shots on goal" to ultimately bring such therapies to market. The high degree of unmet need in the targeted indications, such as TRD, MDD, and PTSD, means there is an opportunity for successful psychedelic therapies to potentially become standard of care in the future.

While opportunities exist for psychedelics, these may take some time to materialize, given that several uncertainties and potential hurdles remain. Beyond clinical and regulatory challenges, there is a need to focus on developing go-to-market strategies to support successful commercialization. Given the nature of psychedelic therapies and the frequent need for accompanying supervision (or trained specialist support), manufacturers will need to navigate complex reimbursement and funding flows for

such therapy protocols and support appropriate training for therapists. Furthermore, in some markets, there is a need to shift societal stigma around the use of psychedelics, which will require engagement with policymakers and the general public.

We believe innovative psychedelic treatments present a great opportunity to meet significant unmet patient need while also being commercially viable products. CRA can help you work through the challenges of commercializing these therapies through supporting activities across unconventional channels in the health care ecosystem.

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