Psychedelics - A Trip to a Brighter Future

January 2025

The promise of transformational efficacy and improved safety of psychedelic agents in the pipeline, plus the commercial success of Spravato, signal a brighter future for psychedelics

Bright Spots Emerging in the Psychedelics Field

Current Climate The FDA's rejection of Lykos Therapeutics' MDMA in August 2024 marked a period of upheaval for drug developers and investors in the psychedelic space. However, the field should remain optimistic with a rich pipeline of 80+ agents, including several demonstrating positive clinical data and impending trial readouts

Efficacy Potential

Enthusiasm for psychedelics is largely driven by the onset of efficacy, durability, and remission rates that are superior to conventional treatments, including the first approved psychedelic, esketamine (Spravato)

- 15+ agents in Ph 2 or Ph 3 have demonstrated one or more of these benefits in clinical trials
- Such agents could lower resource burden for clinics administering Spravato, especially with the potential for one-time administration

Safety Considerations

Heightened concerns about the cardiovascular risks, psychoactive side effects, and abuse potential exist—these are predominantly linked to the serotoninergic activity

- To improve safety, non-serotoninergic mechanisms and alternative analogs are being explored
- While a REMS program will likely still be required, these benefits may minimize monitoring time post administration and/or improve drug scheduling

Commercial Outlook Spravato is a trailblazer for future psychedelics; it set up the infrastructure of target clinics, established a precedent for reimbursement, and brought greater acceptance of the drug class in general

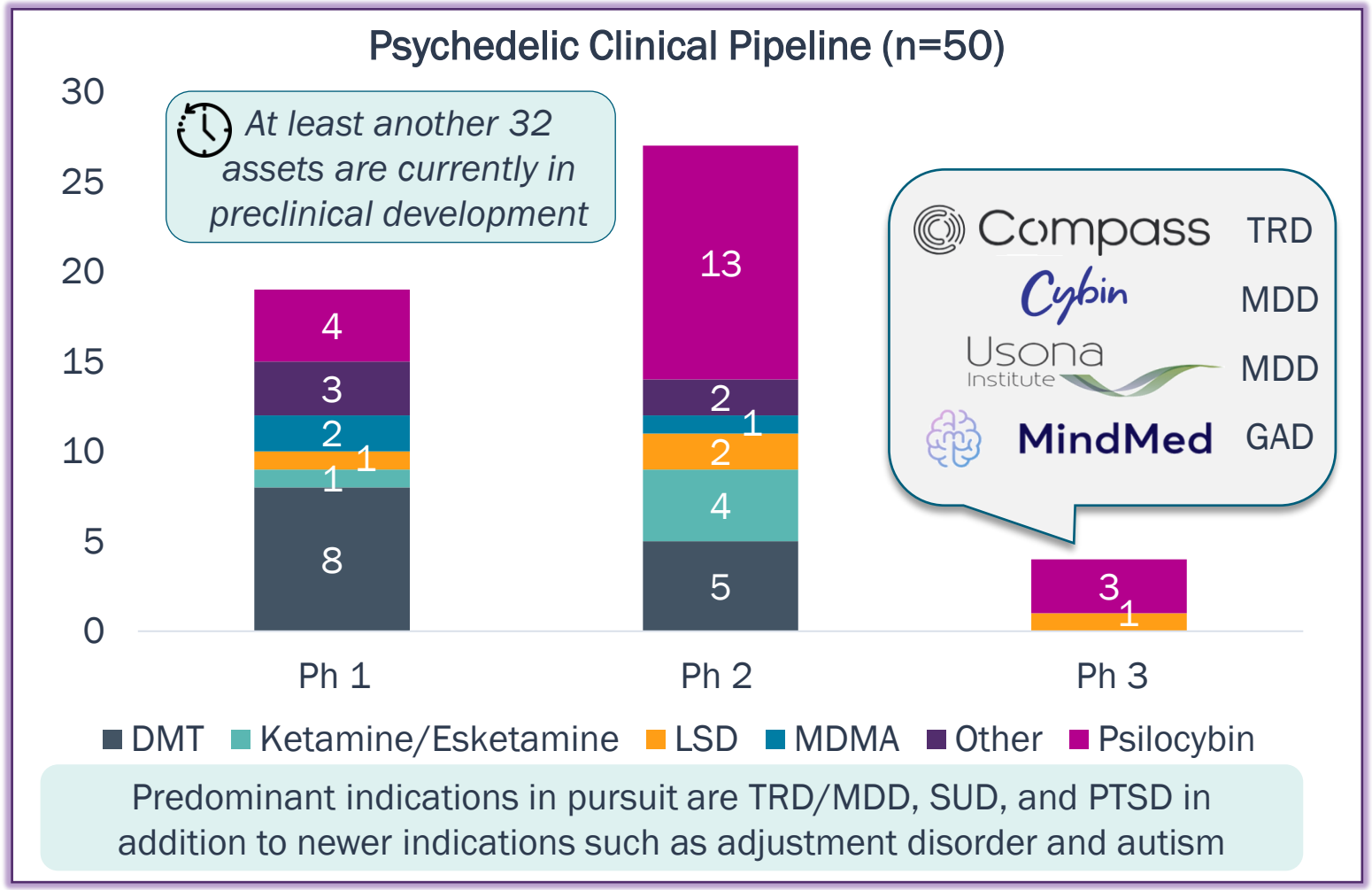
REMS = Risk Evaluation and Mitigation Strategies. A REMS program is required by the FDA for certain drugs with serious safety concerns and may entail multiple requirements including extra training by providers, monitoring post-administration, and AE reporting

Despite the high-profile failure of Lykos that has sobered the field on the prospect of psychedelics, the field is still ripe with promising agents, including assets in Phase 3 trials

Psychedelic Pipeline

As Lykos developed MDMA-assisted therapy for PTSD, challenges emerged that sparked FDA's request for an additional Phase 3 study, taking into account:

- *Confounding concerns on efficacy*
  - Functional unblinding due to the psychoactive nature of the drug
  - Concerns about a lack of standardization and impact of psychotherapy
- *An incomplete view of safety*
  - Questions about the drug abuse potential and lack of data surrounding euphoria with treatment
  - The need for comprehensive data on cardiovascular risks, hepatotoxicity, and a plan for a REMS program



Sources: PharmaProjects; company websites

TRD = treatment-resistant depression; MDD = major depressive disorder; GAD = generalized anxiety disorder; SUD = substance use disorder, PTSD = post-traumatic stress disorder; other includes mescaline and proprietary unspecified molecules

Psychedelics are psychoplastogens with a greater efficacy potential than traditional treatments, largely due to rapid onset of efficacy, effect size and sustained duration of effect

Relative Efficacy of Psychedelics Compared to Conventional Treatments

Relative Efficacy Onset, Effect Size, and Duration
(higher number of green shaded boxes = more favorable efficacy)

	Classic psychedelics (Psilocybin)	Current Non-Classic psychedelics (Esketamine)	Conventional Drug Options (SSRIs, TCAs)
1 Degree of Induced Plasticity	■■■■	■■■□	■□□□
2 Efficacy onset	■■■■	■■■■	■□□□
3 Efficacy Duration	■■■■	■■□□	■□□□
4 Degree of Subjective Effects	■■■■	■■□□	□□□□

Key Trends Regarding Relative Efficacy

1. As "psychoplastogens," (plasticity-promoting neurotherapeutics) in contrast to conventional options, psychedelics induce a fast, durable promotion of structural and functional neural plasticity. Notably, "classical" psychedelics directly target the 5-HT_{2A} pathway, whereas "non-classic" psychedelics target other receptors, e.g. NMDA
2. Esketamine and psilocybin have efficacy onset within a few hours, while SSRIs may require a few weeks
3. Esketamine and psilocybin are expected to have a longer efficacy duration than SSRIs, with psilocybin being more durable than esketamine. Psilocybin has the potential for a single dose to last for six months, whereas esketamine may require 20+ doses in the same period
4. Subjective effects, i.e., an intense disassociation or perception of altered reality, are a signature feature of psychedelics – one major remaining question is whether the effects of a "trip" are required for therapeutic benefit

SSRI = Serotonin Selective Reuptake Inhibitor; TCA = Tricyclic Antidepressant

Source: (1) Vargas et al. (2021). Frontiers in psychiatry, 12, 727117. (2) George et al., StatPearls, https://www.ncbi.nlm.nih.gov/books/NBK538165/
(3) Psiuk et al., (2022). *International Journal of Molecular Sciences*, *23*(19), 11450. (4) company websites (5) ICER 2019

Faith in the efficacy potential of psychedelics drives development; ~50% of assets in Ph 2 or later have positive POC data with notable remission rates, efficacy onset, and durability

Efficacy Advantages of Psychedelics

- All four Phase 3 assets have FDA breakthrough designation, given early efficacy shown and high unmet need remaining in the indications pursued
- 18 of 31 assets in Phase 2 or later have positive POC data in their respective indications

Key efficacy improvements in comparison to SOC include:

- Improved remission rates
- Faster efficacy onset
- Durable efficacy and potential for intermittent or single administration

Multiple companies have assets in development that aim to limit psychedelic activity to under 2 hours

Cybin · atai LIFE SCIENCES · reunion NEUROSCIENCE · GILGAMESH

With improvements in remission and durability, upcoming psychedelics may require fewer resources than Spravato

Drug Spotlight

MM120 (Phase 3), LSD tablet — MindMed

Ph 2 data show early efficacy at wk 1; effects persist at 12 wks with an effect size of 0.8 in comparison to 0.4 of SOC following a single dose with ~50% of patients in remission

CYB003 (Phase 3), deuterated psilocin — Adjunctive to SOC — Cybin

Ph 2 study uses 2 doses in the first 3 wks post baseline; data shows durability in efficacy at 12 mos post baseline with ~70% remission rate w/out the use of psychotherapy

BPL003 (Phase 2), 5-MeO-DMT — Beckley Psytech

Ph 2 data in TRD show a 55% response rate on MADRS on day 1 post-dosing with 45% of patients achieving remission at wk 12 following a single dose

Bluestar BioAdvisors

POC = Proof of Concept; SOC = standard of care; wk = week; mos = months; 5-MeO-DMT = mebufotenin; MADRS = Montgomery-Åsberg Depression Rating Scale; TRD = treatment-resistant depression

Sources: PharmaProjects; Company websites

The serotonergic activity of classical psychedelics underlie the heightened concerns for their potential side effects and abuse potential, relative to Spravato and conventional drugs

Relative Safety of Psychedelics compared to Conventional Treatments

Relative Safety Risks and Restrictions
(higher number of blue boxes = greater safety risk)

	Classical psychedelics (psilocybin)	Non-classic psychedelics (esketamine)	Conventional Options (SSRIs, TCAs)
1 Cardio-Vascular AEs	■■■■	■■□□	■□□□
2 Psycho-active Effects	■■■■	■■■□	■■□□
3 Abuse Potential	■■■■	■■■□	□□□□
4 Current Restrictions	■■■■	■■■□	□□□□

Key Trends Regarding Relative Safety

1. In addition to the sympathomimetic risks (e.g., elevated blood pressure for esketamine and hypotension for SSRIs) cardiac toxicities are a concern with classical psychedelics due to their serotoninergic activity (e.g., 5-HT_{2B})
2. The activity at 5-HT_{2A} by classic psychedelics leads to subjective effects and/or risk for mania/psychosis, both which are longer-lasting than esketamine's dissociative effects; psychedelics may also lower the risk for suicidality (for which SSRIs have a black label) and other non-psychoactive side effects like weight gain and sexual dysfunction if psychedelics are truly a one-and-done model
3. Despite surveillance data indicating that abuse potential of psychedelics is lower than opioids, regulatory agencies worry that patients may seek the euphoric effects
4. Due to concerns on the psychoactive effects and abuse potential, on classical psychedelics have the highest restrictions (Schedule I) relative to Spravato (Schedule III) and SSRIs (not scheduled)

DEA = Drug Enforcement Agency

Source: (1) Vargas et al. (2021). Frontiers in psychiatry, 12, 727117. (2) Wsół, A. (2023). Et al., Pharmacological Reports, 75(6), 1362-1380. (3) McIntyre, R. S. (2023). *Expert Opinion on Drug Safety*, *22*(10), 881-883. (4) Yekehtaz et al. (2013), The Journal of Tehran University Heart Center, 8(4), 169. (5) Johnson et al. (2018). The abuse, Neuropharmacology, 142, 143-166.

Multiple pipeline agents aim to improve the cardiac and subjective effects linked to classical psychedelics; access is expected to be significantly controlled to minimize abuse potential

Efforts to Improve Safety Profile of Psychedelics

Safety risks are largely linked to the serotoninergic activity of classical psychedelics (5-HT_{2A}, 5-HT_{2B}, 5-HT_4 receptors)

- **Higher cardiovascular risk** including arrhythmias, valvulopathy, thromboembolic events, cardiotoxicity, coronary spasms
- **"Bad trips"**, i.e. negative subjective effects that can last 6-8 hours and **psychosis/mania** in high-risk patients (e.g., those with bipolar disorder and schizophrenia)
- **Abuse potential** is predominantly driven by misuse in a recreational setting with users seeking the powerful subjective effects with psychedelics; risk can be mitigated well if administered in controlled settings

Due to these safety concerns, a REMS program, similar to that for Spravato, will likely be required. However, future therapies may minimize the post-administration monitoring time and/or improve drug scheduling

Drug Spotlight

EMP-01 (Phase 2a)

R-enantiomer of MDMA that is expected to have fewer cardiac AEs than racemic MDMA

GM-3009 (Preclinical)

A cardiac-safe analog of ibogaine, a next-gen psychedelic with longer efficacy duration

MSD-001 (Phase I)

A combination approach attempting to selectively switch on only the desired psychedelic effects

DLX-001 (Phase 1)

Therapy could remove hallucinogenic effects (note: concerns exists on compromised efficacy)

Source: (1) Vargas et al. (2021). Frontiers in psychiatry, 12, 727117. (2) Wsół, A. (2023). Et al., Pharmacological Reports, 75(6), 1362-1380. (3) McIntyre, R. S. (2023). *Expert Opinion on Drug Safety*, *22*(10), 881-883. (4) Johnson et al. (2018). The abuse, Neuropharmacology, 142, 143-166. (5) Company websites and press releases

Spravato has set up the infrastructure and provided a roadmap for future launch preparation activities and for broader adoption of psychedelics

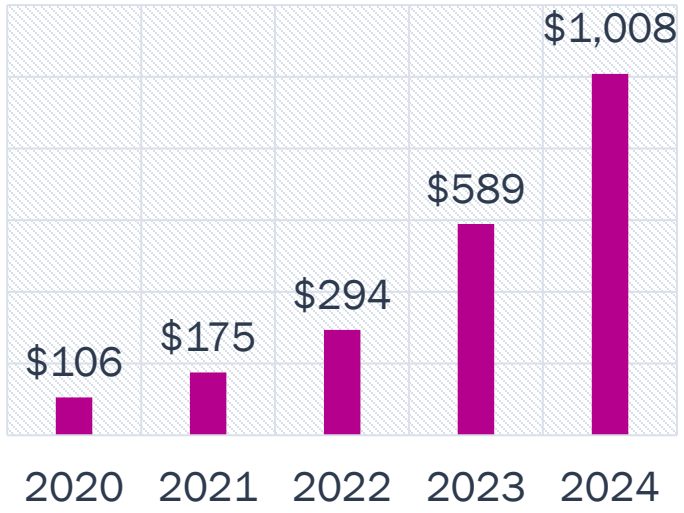
Spravato: Trailblazer for Future Psychedelics

1 Spravato Adoption

After a lackluster launch, Spravato has seen steady growth in the last two years

U.S. Spravato Sales

Johnson&Johnson



>60K+ patients have been treated with Spravato since launch in 2019

2 Catalysts for Adoption

Spravato's recent success can be attributed to at least three major catalysts

- **Greater access:** 2,800 centers are registered to administer Spravato
- **Improved reimbursement:** A study evaluating coverage of 18 plans totaling 180M lives showed that all plans had a policy for Spravato;
- **Strong real-world evidence** further validating the efficacy for TRD has led to increased acceptance among physicians and patients
- **Recent FDA approval as a monotherapy is a future catalyst:** previously, Spravato had to be used together with an oral antidepressant

3 Implications for Future Psychedelics

Spravato has paved the way for a more successful launch of future psychedelics

- **Infrastructure:** Centers set up for administering Spravato are likely going to be early adopters
- **Personnel:** Centers are equipped with personnel who can administer and monitor per REMS requirements similar to Spravato
- **Reimbursement:** Companies (e.g., Compass Pathways) have secured reimbursement CPT codes specific to psychedelics ahead of launch
- **Attitude:** Greater acceptance of Spravato has increased receptivity to other psychedelics

Bluestar BioAdvisors

CPT codes are five-digit codes used to identify medical procedures/services and are required for medical billing and reimbursement

Source: (1) Spravato websites and press releases (2) WSJ, 2024, "J&J's Ketamine-Derived Drug Is Taking Off" (3)Pyschadelic alpha, 2024, Real-World Data Reveals Variability in Access to, and Use of, Spravato

2025 could bring significant funding, positive trial results, and policy reform for psychedelics, but questions remain on the drug class's role in treatment and reimbursement post-approval

Five Key Themes to Watch for 2025 and Beyond

1 *Funding environment: Will an influx of financing facilitate the post-Lykos comeback for psychedelics?*
- Billionaire Antonio Gracias has swooped in as a white knight offering a $100M takeover of Lykos
- Other companies with notable investments in 2024 Q3/Q4 include Negev labs, a backer of Delix, Gilgamesh, and Atai, and Soneira Bio, backed by prominent Google co-founder Sergey Brin

2 *Clinical trial modifications: Will companies attempting to address Lykos' pitfalls succeed?*
- Late-stage companies, including Compass, Cybin, Mindmed are tweaking their pivotal trial designs to address FDA's objections to Lykos MDMA data (e.g., functional unblinding, delineating impact of psychotherapy)

3 *Role of psychotherapy: How will psychedelics be incorporated into the future treatment paradigm?*
- Could other psychedelics be approved and authorized for monotherapy use, like Spravato? How will this impact the psychotherapy business, and what are the implications for clinical psychologists

4 *Future reimbursement: If future psychedelics are a one and done treatment, how will payers cover these agents?*
- What is the appropriate pricing model? What are the expected step edits and prior authorizations?

5 Political climate: How will the new White House administration impact the development of psychedelics in U.S?
- President Donald Trump's inner circle includes proponents for psychedelics -- could the Trump administration usher in policy reform that could positively accelerate authorization of and access to psychedelics?

About the Authors

Monika Trzcinska, PhD *Partner*

MTrzcinska@bluestarbio.com

Boston

Jessica Baylan *Principal*

JBaylan@bluestarbio.com

New York

Emma Janke, PhD *Senior Consultant*

EJanke@bluestarbio.com

New York

521 Fifth Avenue, 25th floor

New York, NY 10175

Office: 212-257-6030

https://www.bluestarbioadvisors.com

Bluestar BioAdvisors

Disclaimer

This presentation has been prepared by Bluestar BioAdvisors LLC ("Bluestar") for the exclusive use of the party to whom Bluestar delivers this presentation (the "Company"). Bluestar makes no, and disclaims all, representations and warranties, express or implied, in relation to these materials and the information contained therein. Bluestar will not be liable for any direct, indirect, special, incidental, exemplary or consequential losses or damages of any kind, including without limitation those damages suffered by any person as a result of relying on any statement or information contained in these materials. To the extent the presentation includes estimates about market and product potential, as well as forecasts of future business or financial performance (including estimates of potential cost savings and synergies), such estimates and forecasts are made as of the effective date of the presentation, are not guarantees and must be independently considered and verified by Company. Actual results will vary from the projections and such variations may be material. Distribution of this presentation to any person other than the Company and those persons retained to advise the Company, who agree to maintain the confidentiality of this material and be bound by the limitations outlined herein, is unauthorized. This presentation has been prepared solely for informational purposes and is not to be construed as a solicitation or an offer to buy or sell any securities or related financial instrument or as legal, tax, accounting or investment advice or recommendation. The Company should consult its own counsel, tax and financial advisors as to matters described herein.

521 Fifth Avenue, 25th floor
New York, NY 10175
Office: 212-257-6030
https://www.bluestarbioadvisors.com