Psychedelic-assisted Therapy in Psychiatry

Overview and Strategic Implications

Mental illness represents a significant burden for health systems, and high unmet need for effective treatments remains largely unaddressed. Psychedelics hold significant promise as a novel treatment class and are poised to be a leading treatment option for several hard-to-treat psychiatric conditions. However, psychedelics face regulatory and commercial headwinds. If approved, access to psychedelics may be limited in the short-term due to anticipated high costs of treatment relative to standard of care and need for developed infrastructure to accommodate the manualized protocols for service delivery. Several publicly traded psychedelic companies are presently valued near or below cash holdings and require imminent injection of capital based on current run rates to continue clinical development. Despite these near-term headwinds, psychedelics are one of the few novel therapy approaches that may revolutionize mental healthcare, and with accumulation of supporting clinical data and necessary infrastructure, they may become a powerful tool for psychiatry. Now may be a unique opportunity for investors to contribute to the development of psychedelics by leveraging the need for cash injections and market consolidation.

THE BRIEF

Scientific Validity

Update on ongoing clinical research and development

Commercialization

Challenges to market access and health system preparedness

M&A

Insights on company performance and investment potential

Introduction

Psychedelic-assisted therapy is undergoing a renaissance, with potential use across hard-to-treat psychiatric conditions including stress, anxiety, depression, eating disorders, and addiction. Approval of MDMA (3,4-Methylenedioxymethamphetamine, commonly known as "ecstasy" [tablet form] and "molly" or "mandy" [crystal form]) in post-traumatic stress disorder is expected in the U.S. in mid-2024 for MAPS PBC, and late-stage clinical development for treatment resistant depression is underway by Compass Pathways for psilocybin ("magic mushrooms"). Other psychedelics include forms of ketamine (currently marketed for treatment resistant depression as "Spravato" by Janssen Pharmaceuticals, Inc), LSD (9,10-didehydro-N,N-diethyl-6-methylergoline-8β-carboxamide, commonly known as "acid", in development by MindMed and others), and DMT (N,N-Dimethyltryptamine, related to the indigenous psychedelic ayahuasca, in development by GH Research and others).

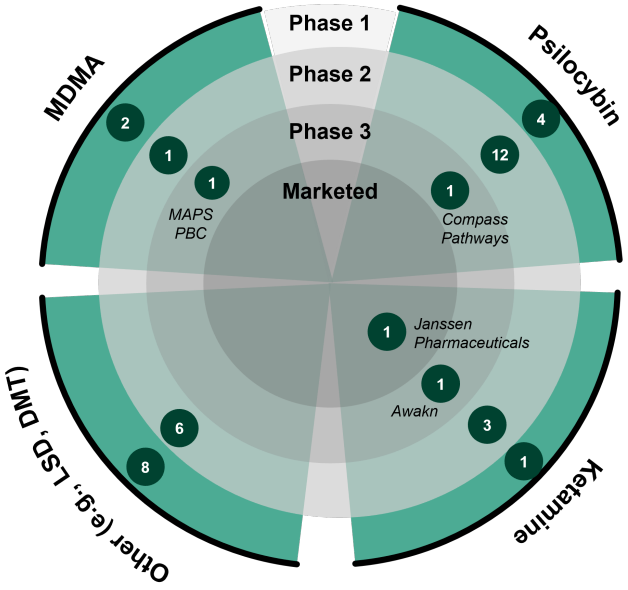
In this article, we begin with a review of the scientific literature for psychedelics and our perspective on how these novel therapies have the potential to fundamentally shift the treatment paradigm in psychiatry. Next, we consider implications for commercialization and reflect on the recent financial performance of major publicly listed psychedelic companies. In the final section, we share our view on the next wave of psychedelic innovation.

Scientific Validity

Psychedelics (serotonergic hallucinogens) are a class of psychoactive substances demonstrated to alter perception, mood, and cognitive processes. In general terms, psychedelics are believed to take effect both on a biological level, binding to serotonin receptors to produce cellular changes and rewire neuronal connections, and on a psychological level, with therapy alongside the psychedelic experience enabling patients to rewrite harmful personal narratives. While psychedelics are deeply rooted in traditional medicine and cultural ceremonies, only recently have there been significant advancements to bring psychedelics to the forefront of modern medicine.

Promising research exists across classes of psychedelics including MDMA, psilocybin, ketamine, LSD, and DMT (Figure 1). Research on MDMA for post-traumatic stress disorder is relatively advanced, having been studied in over five Phase 2 studies and one published Phase 3 study (with full data from a second pivotal trial expected this year). Studies overall indicate potential for safe administration, as well as durable statistically and clinically significant gains in symptom relief. Psilocybin research is largely concentrated in depression and early Phase 2 studies show promising results. Although not strictly a psychedelic, a form of ketamine is the only FDA-approved psychedelic-like asset in Spravato (esketamine). Research on LSD appears more limited, though initial studies demonstrate promise in anxiety and depression.

FIGURE 1 - Overview of Psychedelics Clinical Development Pipeline



Source: Clinicaltrials.gov; Global Data; Citeline; ClearView Analysis.

Despite being limited by small sample sizes, studies on DMT suggest potential for anti-depressant effects. In addition to these traditional psychedelics, novel approaches are entering clinical trials, e.g., Gilgamesh's 5-HT2A agonist which mimics the pharmacology of DMT and MDMA. For the remainder of this section, we focus on MDMA-assisted therapy developed by MAPS PBC and Compass Pathways' psilocybin.

MDMA-therapy for PTSD

MAPS PBC research on MDMA-assisted therapy for PTSD is the most advanced with a strong data package emerging. The first Phase 3 trial for patients with severe PTSD (MAPP1) showed significant attenuation in the CAPS-5 score compared with placebo after three sessions, with reduction in PTSD severity and results durable for at least 6 months (Mitchell et al. Nature Medicine. 2021). In that same trial, exploratory endpoints showed two-thirds of patients on MDMA-assisted therapy no longer met the diagnostic criteria for PTSD at 18-weeks post baseline, compared to one-third in the placebo with psychotherapy alone group. MAPS PBC announced in January 2023 that the confirmatory Phase 3 trial (MAPP2) met both primary endpoints and the key secondary endpoint. Full data results are expected to be published later this year, and we expect they will support applicability of MDMA-assisted therapy in a broader patient population (i.e., less severe PTSD). Furthermore, MAPS PBC announced in April 2023 that interim results from a long-term observational follow-up study showed improvements in PTSD symptom severity of at least six months, and in some patients over a year.

Psilocybin for Major Depressive Disorder

Research for psilocybin is mixed, although early evidence suggests it performs at least on par with anti-depressants (e.g., escitalopram). A small double-blinded, randomized Phase 2 trial versus escitalopram showed no statistical difference at 6 weeks in patients with moderate-to-severe major depressive disorder (Carhart-Harris et al. NEJM. 2021), which in effect reflects potential for psilocybin, particularly given the secondary endpoints in that same trial favored psilocybin over escitalopram (albeit with overlapping confidence intervals). Whereas, another Phase 2 trial in a larger sample demonstrated reduction in depression symptoms on the MADRS for high dose psilocybin patients compared to low dose (essentially placebo), with sustained response at 12 weeks (Goodwin et al. NEJM. 2022). Compass Pathways announced in October 2022 the first ever Phase 3 trial for psilocybin.

While psychotherapy and anti-depressants for PTSD and depression may be effective, high unmet need remains. Anti-depressants have slow onset, significant side effects, and only about half of the patients benefit from them. Indeed, approximately 30% of patients with PTSD and treatment-resistant depression are refractory to standard treatments, meaning there are significant populations (>5 million patients) in need of new approaches. Considering this high unmet need, increased scrutiny over the side effects of fentanyl and other traditional pharmaceuticals, and a deepening mental health crisis exacerbated by the pandemic, there has been renewed efforts to prove the safety and efficacy of alternative therapies in psychiatry, including psychedelics.

Implications for Commercialization

Psychedelics for therapeutic use is soon to become a reality. In July 2023, Australia will become the first country to permit prescribing of MDMA and psilocybin for PTSD and treatment resistant depression respectively, and in mid-2024, the U.S. is expected to be the first country to approve the use of MDMA for PTSD. Momentum is also growing to legitimize psychedelics for therapeutic use at a State level in the U.S., with both Oregon and Colorado moving to create a third path for use at licensed service centers that is neither decriminalization nor therapeutic in nature. Notwithstanding this momentum, the path to commercialization for psychedelics is expected to be challenging. These challenges broadly fall into three categories (Figure 2).

Regulatory and Legal

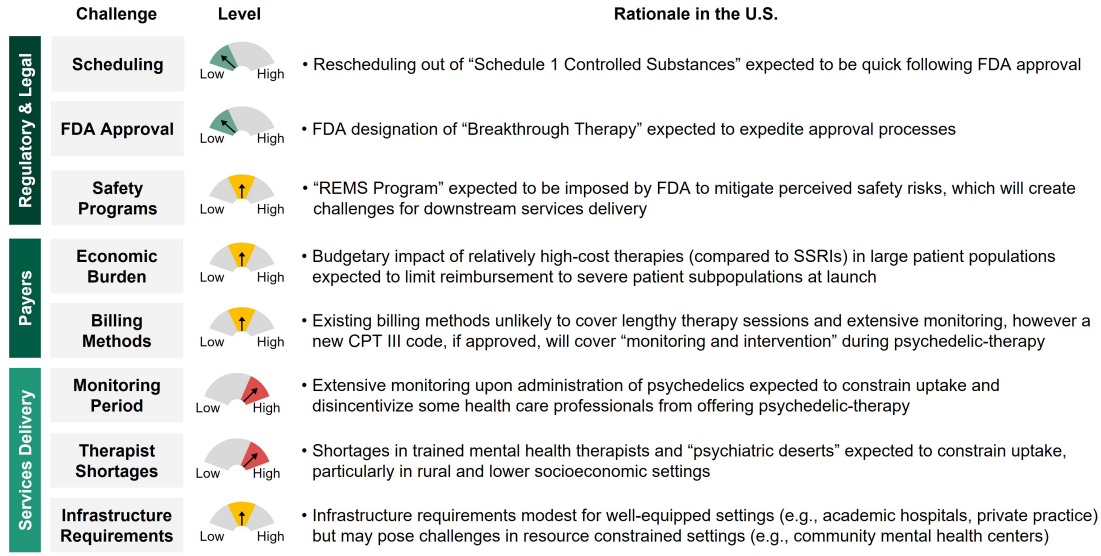
In relation to regulatory challenges, psychedelics are generally classified as controlled substances (e.g., "Schedule 1" or "Class A" drugs, in the U.S. and UK respectively), meaning there are limitations on their development and use. However, the FDA has granted breakthrough designation for both MDMA and psilocybin, which will fast track approval processes, and rescheduling is expected to be quick following FDA approval based on precedent in the cannabis market. Furthermore, MAPS PBC and Compass Pathways

have both received Innovation Passports from the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK, which will accelerate time to market. Our expectation is that regulatory approval will be forthcoming and any regulatory concerns around safety and abuse potential can be mitigated by safety programs (e.g., Risk Evaluation and Mitigation Strategy (REMS) in the U.S.).

Pricing and Market Access

Questions are also anticipated to arise around who will pay for psychedelic-assisted therapy, particularly given a lot of the benefits are the reduction in externalities (e.g., productivity losses, informal care costs for caregivers). This will likely lead to payer hesitations to pay for these novel therapies for broad patient populations. However, with emerging economic evidence that psychedelics are highly cost-effective (Marseille et al. PLOS One. 2022) and can accrue cost savings (Avancena et al. Clin Drug Investig. 2022), it is anticipated that payers will still want to cover psychedelics. The economic burden can be managed, at least in the short-term, by covering psychedelics for severe subpopulations in later lines of therapy (e.g., after failure on two SSRIs), before roll-out to broader patient populations over time. While payer coverage and patient co-payments are anticipated to cover the costs of the psychedelic, providers are often responsible for a significant proportion (or all) of the costs associated with patient monitoring leading to a meaningful opportunity cost. The American Medical Association recently announced a new CPT III code from January 2024 to enable reimbursement for delivering psychedelic-assisted therapies, which, if approved, would address one of the major economic barriers to uptake.

FIGURE 2 - Challenges to Commercialization of Psychedelics



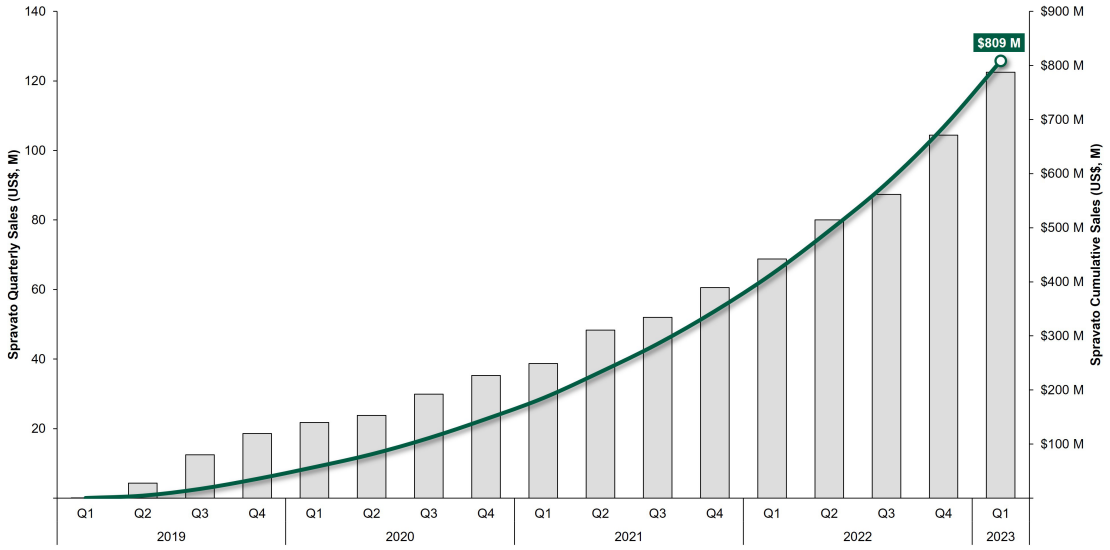
Source: ClearView Analysis.

Health System Preparedness

The most critical challenge is anticipated to be in relation to health services delivery. Based on current protocols, best practice for psychedelic-assisted therapy requires two trained therapists for administration with extensive monitoring periods (up to 8 hours) and pre- and post-therapy sessions, which will have significant downstream consequences for services delivery due to shortages in mental health workers, infrastructure needs, and requirements for novel billing methods.

We saw following the launch in mid-2019 of Spravato (an enantiomer, or form, of ketamine indicated for treatment resistant depression) that lack of health system preparedness led to slow uptake (Figure 3). The major barriers to Spravato utilization at launch included lack of certified centers, stringent monitoring requirements (2+ hours) imposed by the REMS program, and insufficient reimbursement to compensate for staffing and space requirements associated with those monitoring requirements. More recently, rapid ramp up has occurred, driven in part by FDA approval for use in "major depressive disorder with acute suicidal ideation or behavior" in August 2020 but also likely due to lower clinical barriers to delivery. We consider that evidence of this rebound by Spravato indicates a reasonably optimistic outlook for psychedelics.

FIGURE 3 - Spravato Sales

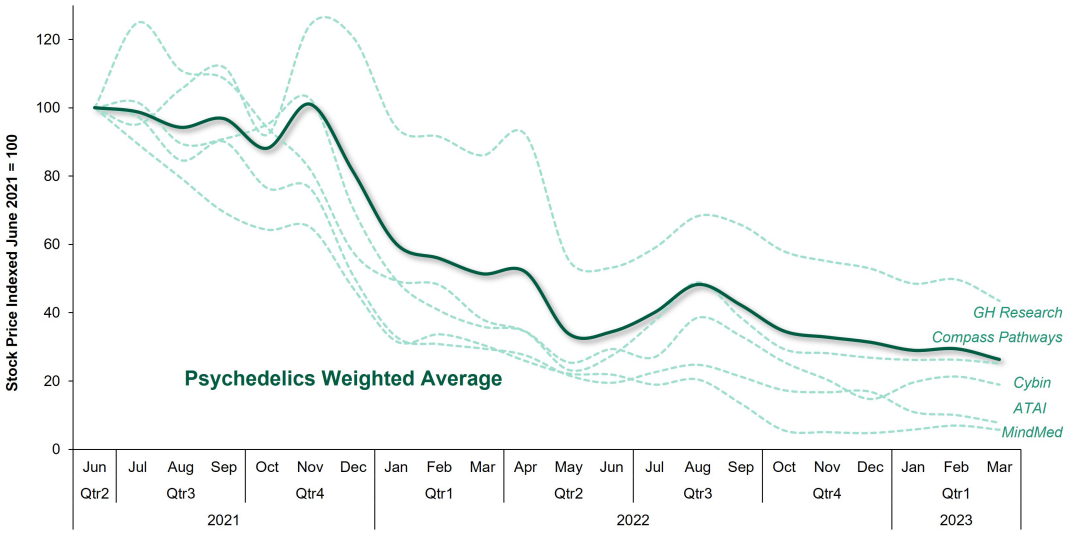


Source: Bloomberg Symphony Health Script Data U.S Estimates 31/03/19 to 31/03/23; ClearView Analysis.

Implications for Investment

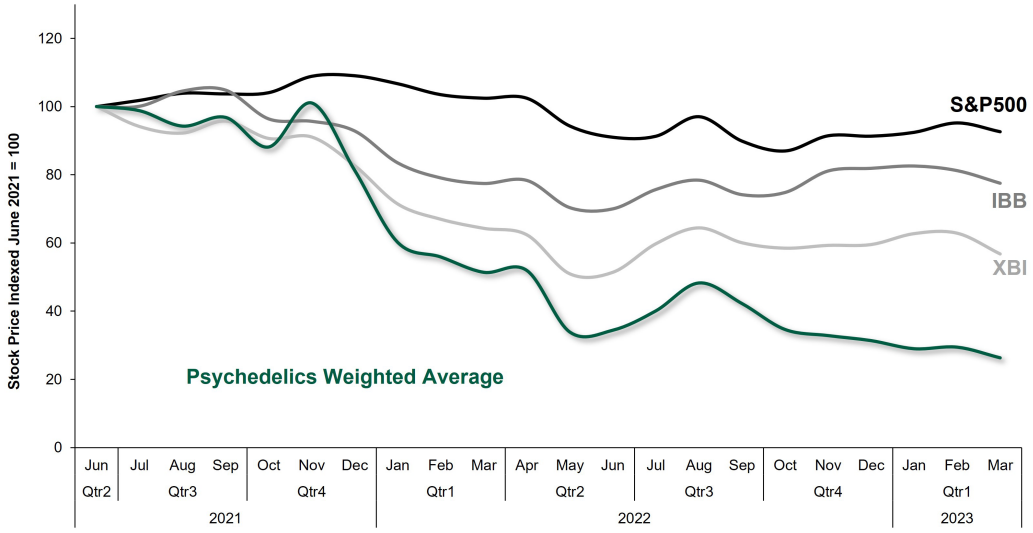
In recent years, psychedelics have shown a lot of promise, with strong funding and high valuations, driven by significant venture capital interest. However, looking specifically at publicly listed companies, the last two years has seen a slowdown, with the high cost of borrowing and general loss of confidence in biotechnology companies correlating with a significant drop in share price for psychedelic companies (Figure 4). Over enthusiasm following the launch of Spravato has likely compounded matters, and the average performance of psychedelic stocks (weighted by market capitalization) has been worse than both the S&P500 and key biotechnology indices (Figure 5). Interestingly, GH Research has outperformed other psychedelic stocks, perhaps in part due to the development of proprietary psychedelics with modified stereochemistry leading to rapid onset (within seconds) and short duration (<30 minutes), which may have led investors to perceive it to have a lower risk profile.

FIGURE 4 - Stock Price of Major Psychedelic Companies



Source: Yahoo Finance; ClearView Analysis.

FIGURE 5 - Psychedelic Weighted Average Stock Price versus Key Indices



Source: Yahoo Finance; ClearView Analysis.

Against this backdrop, opportunities for M&A at a cheap price for investors may exist. Currently, publicly listed companies are largely valued close to or even below cash holdings. Furthermore, based on current run rate these companies will need injection of cash in the next two to three years to continue to develop their pipelines. Therefore, assuming these psychedelic companies can navigate the complications of this market (e.g., commercialization challenges, policy/legal uncertainty), there is likely a lot of potential upside for investors. More recent activity was the sale of Reunion Neuroscience to biotechnology investment firm MPM BioImpact, which was announced on 1 June 2023 (at a 62% premium to U.S. closing price the previous day).

Looking Forward

On the horizon are psychedelics synthesized to retain the neuroplastic effect of psychedelics while shortening or eliminating the "trip". If successful, this could lower the time and cost of administration and lift one of the major roadblocks to scalable delivery of psychedelics. Furthermore, it could also increase addressability to patients who are unable or unwilling to undergo the highly altered mental state associated with psychedelics, which can include hallucinations, dissociation, and mystical-type experiences. However, whereas MDMA (synthesized decades ago) and psilocybin (naturally occurring) are not patentable per se, these second-generation therapies are, likely coming with a relatively higher price and thereby jeopardizing access for patients. Beyond psychiatry, early-stage development is also underway to understand effects in broader range of neurological conditions (e.g., stroke, Parkinson's Disease, and traumatic brain injury). For example, Seelos Therapeutics has a development pipeline spanning central nervous system disorders and rare diseases and has a market capitalization of ~$100 M, making it one of the larger publicly listed psychedelic developers.

In psychiatry, where unmet need is high and there has been a historic lack of innovation, our perspective is that it seems sensible to explore both hallucinogenic and non-hallucinogenic approaches to psychedelic-assisted therapy to understand how experiences with and without the "trip" may have applicability across conditions and patients. Key catalysts for potential investment will be the anticipated approval of MAPS PBC's MDMA-assisted therapy for PTSD (expected mid-2024), preliminary readout of results from Compass Pathways' Phase 3 trial in psilocybin (ongoing), and development of novel reimbursement pathways to address specific health insurance dynamics in the U.S. (expected January 2024). Psychedelics remain a high-risk research field that will require more evidence and data to impact major unmet needs in the coming years.

About ClearView Healthcare Partners

Founded in 2007, ClearView Healthcare Partners is a global strategy consulting firm serving the life sciences sector, with offices in Boston, New York, San Francisco, London, and Zurich ready to support clients in complex engagements with local expertise.

ClearView combines international industry knowledge and deep scientific expertise in every major therapeutic area and across modalities with an extensive network of external stakeholders to deliver practical and actionable recommendations. ClearView's projects include cross-functional support at the corporate, franchise, and product levels for pharmaceutical, biotech, medtech and digital, and diagnostics companies, along with investment support across all phases of the transaction cycle for private equity and institutional investors.

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