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Vision of Commercial Success: Investment and Partnering Landscape for Psychedelics

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Overview

While psychedelic drugs have been historically stigmatized due to their use as recreational drugs, the commercialization of psychedelics and psychedelic-derived compounds for the treatment of psychiatric and neurological disorders has gained significant momentum over the last 5 years. Two events are seen as watershed moments for the surge of interest in psychedelics. Firstly, the FDA approval in 2019 of Johnson & Johnson's Spravato (esketamine) for treatment-resistant depression has been followed by steady commercial growth, posting ~$400M in worldwide sales in 2022. Secondly, Otsuka Pharma's $59M acquisition of Mindset Pharma in 2023 signaled that the biopharma industry sees psychedelics as key elements of corporate development strategies. Indeed, the ecosystem of companies developing psychedelic compounds is substantial (Figure 1), as sponsors aim to improve target-specificity, shorten the therapeutics window, generate clinical data, and optimize the commercial model.

Figure 1:
Psychedelic Drug Development Pipeline

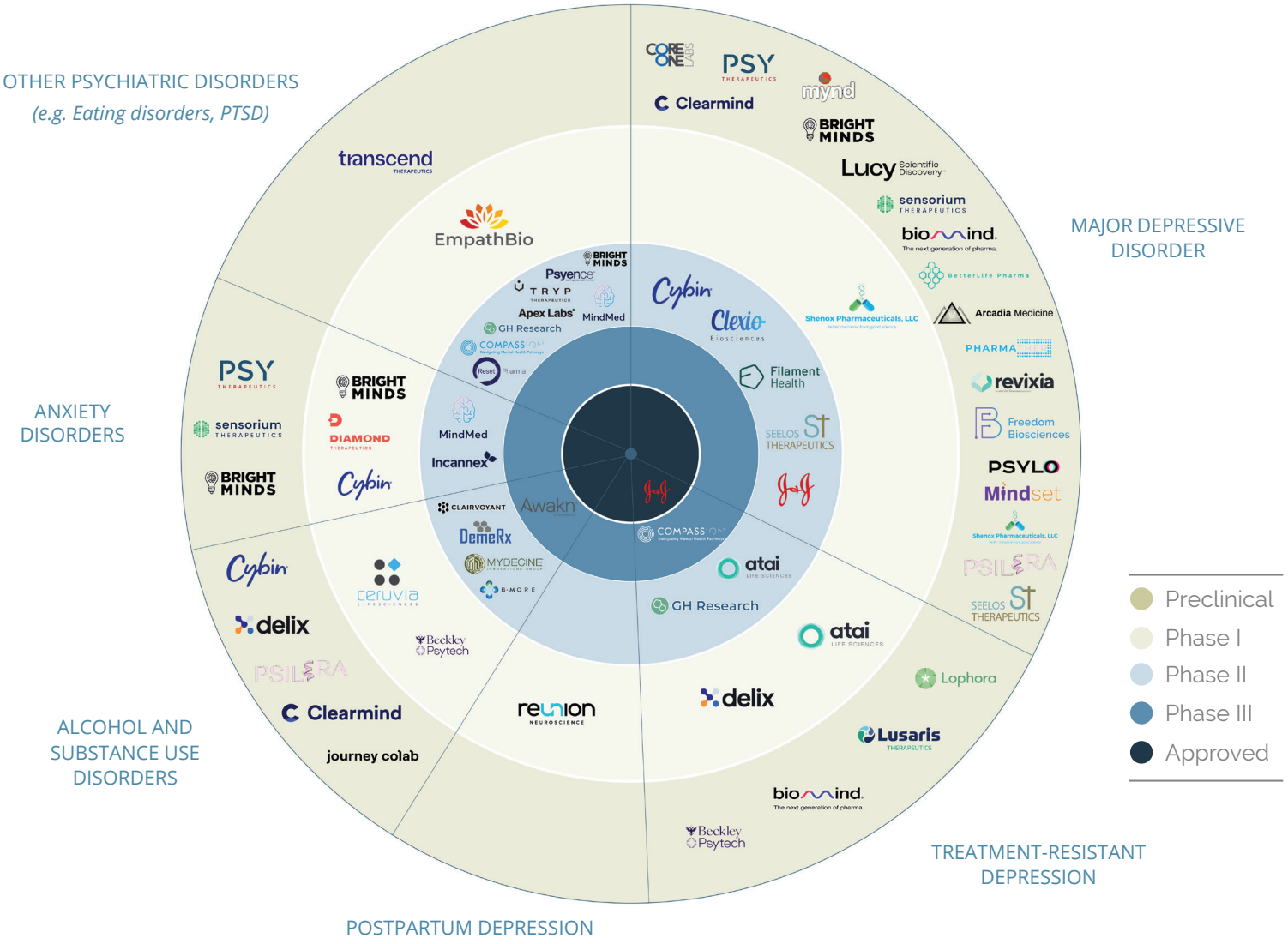
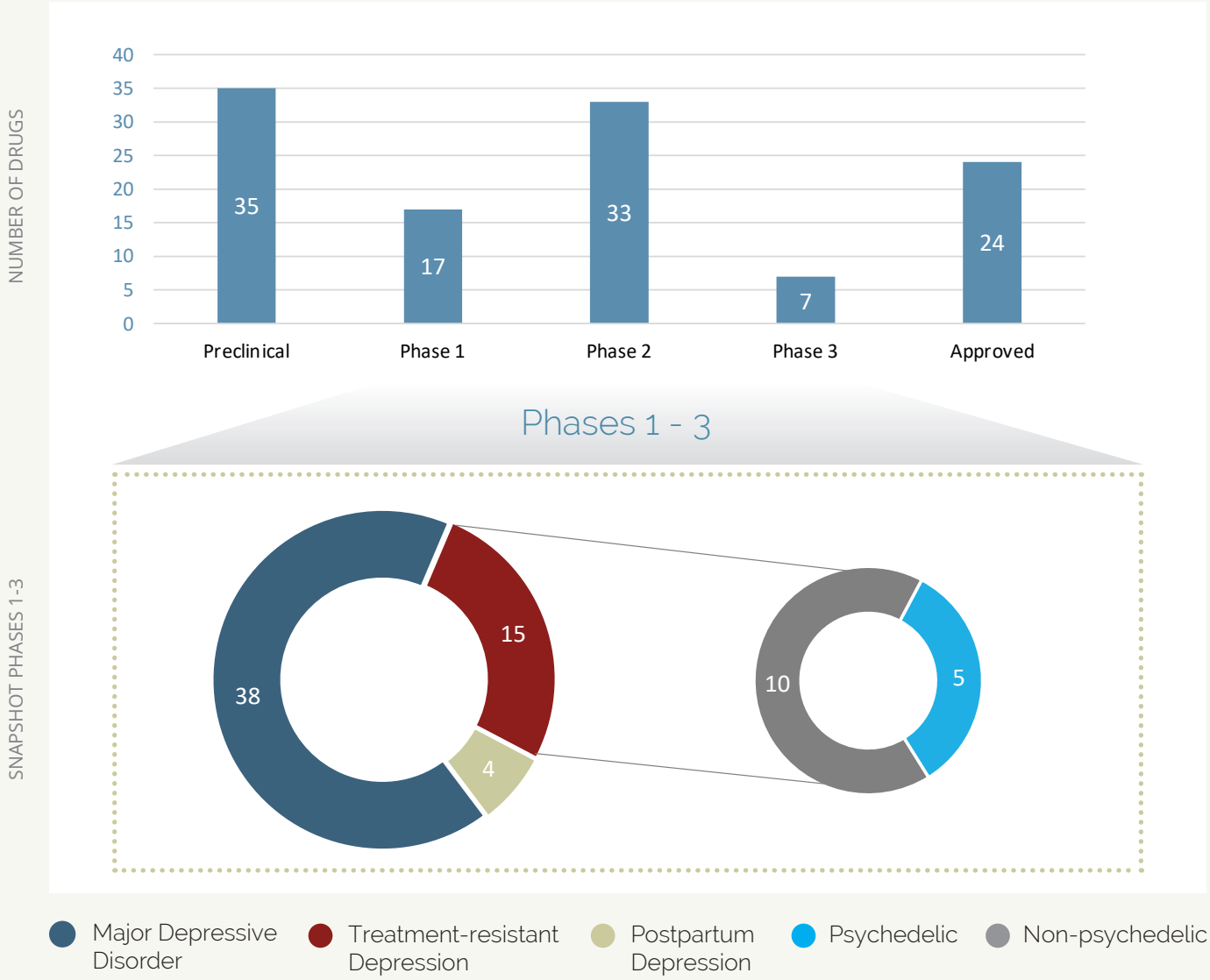
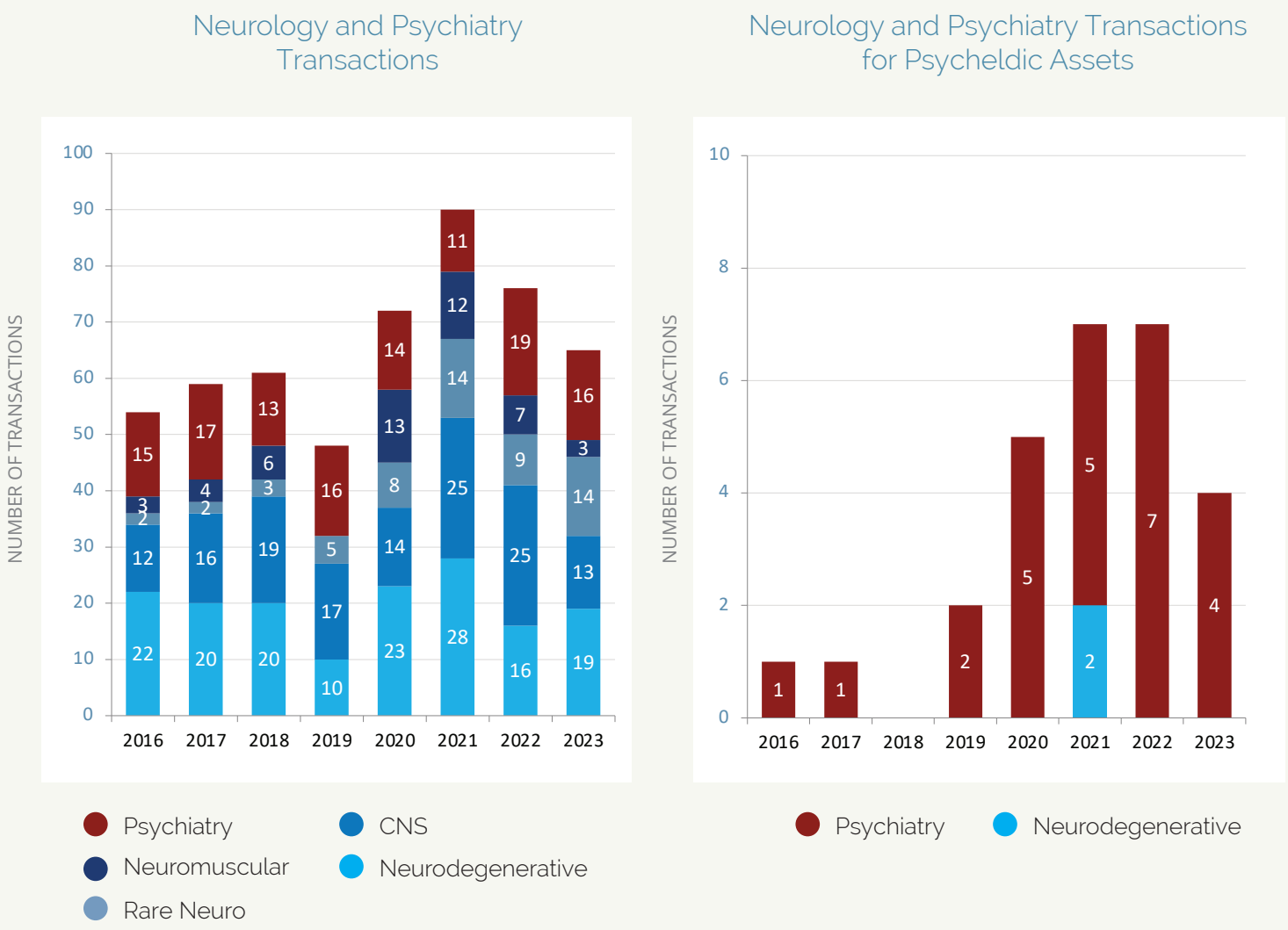


Figure 2:
Depression Drug Development Pipeline



Depression is by far the most active area of psychedelic drug development with most activity in Major Depressive Disorder (MDD), specifically for treatment-resistant depression (TRD) which impacts ~30% of MDD patients and postpartum depression (PPD) that is experienced by ~15% of women within the first year of birth. Interestingly, of the 14 drug candidates in development for TRD approximately one third are psychedelics (Figure 2). The focus of activity within the TRD space is likely due to a combination of unmet need and pricing pressures, given the use of generic SSRIs used as first-line treatment. Aside from depression, psychedelics are also in development for other psychiatric diseases with high unmet need, including substance abuse, PTSD, and eating disorders, with many assets undergoing clinical trials across several indications.

Figure 3:
Neurology and Psychiatry Transactions: January 2016 - September 2023



Neurology/psychiatry has been an active field of M&A and licensing in the biotech industry over the last several years (Figure 3B), with over 500 transactions in an 8-year time span. While CNS and neurodegenerative diseases such as Alzheimer's disease and epilepsy have constituted 56% of deals, within the last three years psychiatry has commanded a share of 19% of deal volume. While overall activity in psychiatry has remained stable since 2016, deals struck for psychedelic assets (Figure 3B) have increased 5x from 2016-2019 (4 deals) to 2020-2023 (21 deals). Overall, a substantial share (~25-50%) of all psychiatric transactions have involved psychedelic mechanisms since 2021. Further, 2023 deal flow continues with ~65 deals as we enter Q4, which puts the sector on pace to nearly reach the transactions executed in 2021.

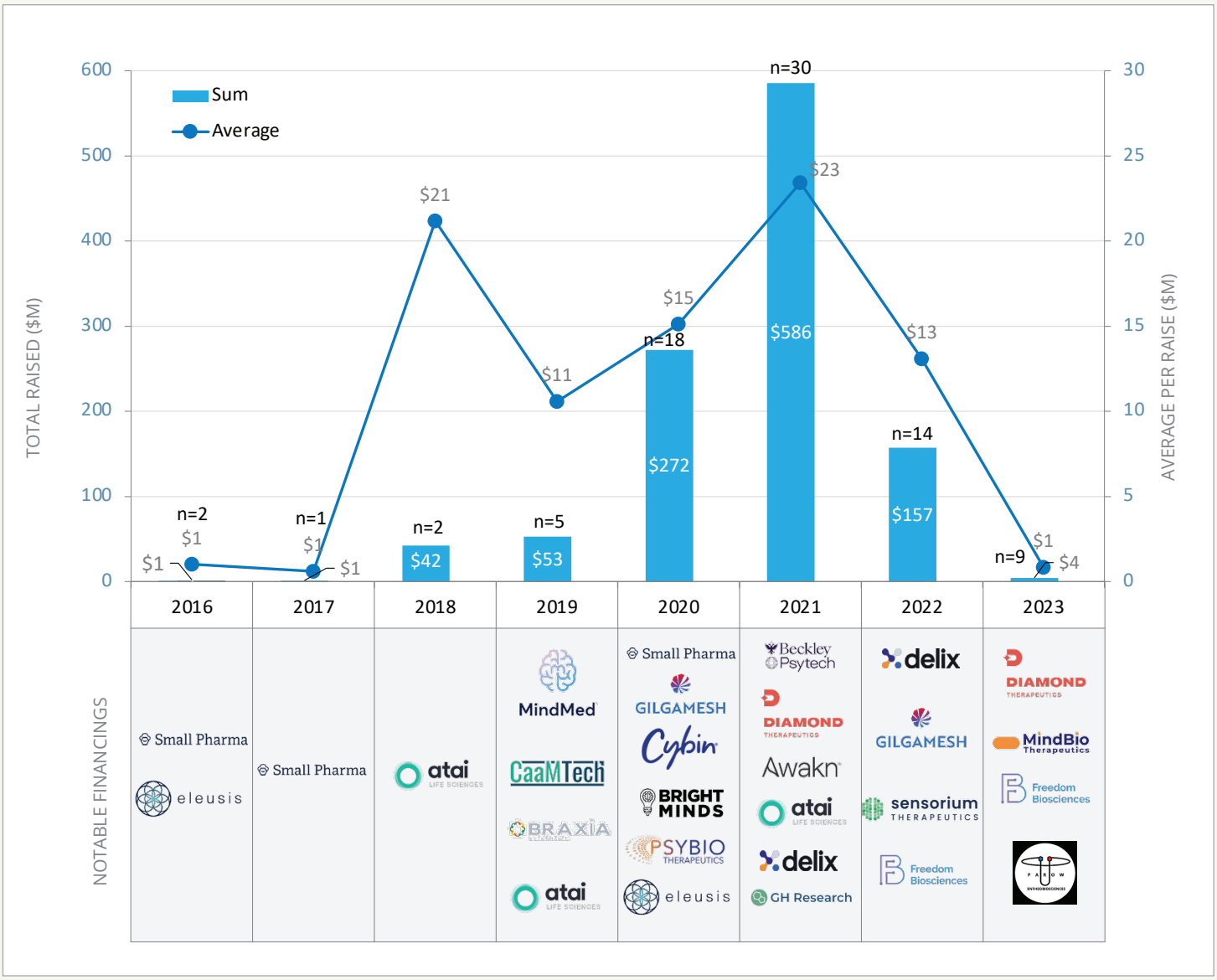
Figure 4:
Psychedelic Deals, Disclosed Terms: January 2016 – September 2023

Principal	Partner	Deal Type	Year	Asset Stage	Upfront Payment ($)	Milestone Payments ($)
Mindset	Otsuka	Acquisition	2023	Preclinical	$59M	-
reunion NEUROSCIENCE	MPM BioImpact	Acquisition	2023	Phase 1	$13.1M	-
AWAKENED	CORE ONE LABS	Acquisition	2022	Discovery	$9.8M	-
lucid. PSYCHECEUTICALS	FSD PHARMA	Acquisition	2021	Preclinical	$9.2M	-
ARBORMENTIS	Relmada THERAPEUTICS	License	2021	Discovery	$15M	$150M
eleusian	GREENSTAR BIOSCIENCES	Acquisition	2020	Preclinical	$3M	-
ADELIA	Cybin	Acquisition	2020	Preclinical	$8.4M	$7.3M
TURING PHARMACEUTICALS	MARINA BIOTECH	Acquisition	2016	Phase 2	$13.3M	$95M

Otsuka Pharma's complete acquisition of Toronto-based Mindset for $59M signifies a major turning point in the transaction landscape of psychedelics, as consolidation had previously been dominated by psychedelic-focused biotech players (Figure 4). The deal came ~1.5 years after the parties announced an initial collaboration to support the development of Mindset's psychedelic medicines through Phase 1a/b clinical trials for an upfront $5M. A few months prior to the deal, Mindset Pharma's lead asset MSP-1014 received approval by the FDA to initiate Phase 2 trials in MDD. The acquisition marks a substantial increase from the ~$10M average upfront deal sizes that have occurred over the last 7 years and marks increased valuation of psychedelic assets.
With the acquisition, Otsuka adds a preclinical drug to its portfolio which includes 4 clinical stage pipeline assets within its successful psychiatry and neurology franchise.

Figure 5:

Psychedelic Venture Capital Financings: January 2016 – September 2023



Overall, Cybin and Atai Life Sciences have been the most active players in the psychedelics space over the last 7 years and have built robust developmental pipelines across a range of indications. Toronto-based Cybin followed up forming a joint venture with Cyclica to create Entheogenix in 2019, with an acquisition of Adelia Therapeutics (2020) and Small Pharma (2023). Atai Life Sciences acquired a majority stake in Perception Neuroscience (2019) before IPO'ing on the NASDAQ in 2021 and increasing its 19.4% stake in Compass Pathways (2021) later that same year.

The commercial and strategic interest from pharma has not gone unnoticed by VCs, who poured in greater than $1B into psychedelic biotech companies since 2020 – with a particular interest in proprietary, redesigned psychedelics as they have stronger IP and aim to shorten the length of action. Since 2020, several financing rounds have exceeded $50M, including Atai (2021: $157M, 2020: $125M), GH Research (2021: $125M), Beckley Psytech (2021: $80M), and Delix Therapeutics (2021: $70M). While the most active investors have been psychedelic- focused VCs, including Negev Capital, The Conscious Fund, Palo Santo, JLS Fund, and the Noetic Fund, GH Research's Series B was led by RA Capital and RTW Investments who have created a broader portfolio. Both Atai Life Sciences and GH Research went on to test the public markets in 2021, raising $225M and $160M, respectively, on their IPOs on the NASDAQ stock exchange.

Further, the psychedelic drug development ecosystem has also been supported by significant funding and scientific advances by major non-profit and academic institutions. The non-profit Multidisciplinary Association for Psychedelic Studies (MAPS) recently completed Ph3 placebo-controlled trials demonstrating that MDMA-assisted therapy can improve PTSD symptoms. NYU Langone, Icahn School of Medicine at Mount Sinai, University of California – San Francisco, University of California – Berkeley, and Massachusetts General Hospital have received over $20M in total since 2020 to establish and grow their psychedelic centers of excellence.

The 3 main barriers to the commercialization of psychedelics are the (1) coverage and resources associated with psychedelics requiring simultaneous therapy or supervision, (2) FDA regulatory hurdles, and (3) societal stigmatization. From the market access perspective, the additional costs of psychedelic-assisted therapies will likely drive payers to limit access to the most appropriate patient population, particularly those patients nonresponsive to front-line treatments. Despite several studies demonstrating the cost-effectiveness of therapy-assisted psychedelics, until broader commercial payers recognize these results, given the dearth of available therapists in the US, manufacturers will likely need to develop programs to support healthcare infrastructure to aid physician-supervised administration of psychedelics. As a result of the current healthcare landscape, psychedelics that do not require therapy or physician-administration and supervision will likely be a differentiated factor for clinical uptake.

Overcoming FDA regulatory restrictions has been considered a major hurdle for broad use of psychedelic treatment of psychiatric disorders, however, several recent events suggest that this is becoming a less limiting factor. Numerous psychedelic assets have received breakthrough therapy designation, including Spravato before its approval and Compass Therapeutics' COMP360, which grants the drugs expedited FDA review. In addition, in June 2023, the FDA laid out the first guidance for US psychedelic trials which suggests the organization expects increased psychedelic drug development and is willing to proactively provide guidelines for trial conduct, data collection, and new drug application requirements.

The stigmatization of psychedelics for the treatment of medical conditions may likely lift as the drugs become decriminalized in society. There were ~5x the number of psychedelic drug reform bills introduced in 2021 than in 2020, suggesting a large push towards medical psychedelic drug decriminalization in the next years. Work published in the *Journal of the American Medical Association* predicts that all states will legalize psychedelics by 2037. The path for psychedelic reform may occur more rapidly than cannabis reform due to the higher likelihood of FDA approval. Oregon was the first state to decriminalize psychedelic drug possession and use in 2020 and is expected to be followed by 10 other states that are currently considering reform.

Given the evolving commercial and regulatory landscape, coupled with keen interest from investors, we expect to see a continued renaissance of these captivating products.

Where the Field is Heading

The psychedelic drug development industry has seen tremendous growth over the last 5 years as there are currently over 50 companies developing psychedelic products for psychiatric disorders alone. Despite this growth, the therapeutic psychedelic space has mostly functioned as its own independent ecosystem, supported by specialist investors and treatments, where available, utilized in specialty clinics. While these activities have built a strong foundation for the psychedelic industry, recent events demonstrate that the drug class is beginning to reach a broader audience of investors and strategic partners with a traditional drug development focus.

We expect that the Otsuka deal for Mindset Pharma will trigger the interest of global pharma companies in psychedelic assets to expand or establish their psychiatric drug portfolio. Not only was the deal the first psychedelic acquisition by a global pharma company, the $59M price tag was 6x the average deal size for psychedelic assets over the previous 7 years. Moving forward, pharma may prefer to take a similar approach as Otsuka and first execute a partnership to control early R&D efforts before committing to a full acquisition. Otherwise, psychedelics will likely need to demonstrate clinical proof-of-concept data and differentiate from the crowded field of psychedelics to reach a transaction inflection point to be viewed as a high-value M&A target. While psychedelics were not resistant to the poor macroeconomic environment of 2023, we have an optimistic outlook on the investor landscape, particularly for next-generation psychedelics with strong IP protection that are engineered to create the ideal product profile and address the areas of high unmet need in psychiatry.

Nevertheless, the commercial model for these medicines has presented a unique challenge for sponsors. Posting strong sales in recent quarters, Spravato's slower-than-expected launch can be attributed to healthcare facilities lacking sufficient infrastructure to support drug delivery as well

as reimbursement hurdles. While physician-administrated therapeutics are standard practice in some therapeutic areas such as oncology and rheumatology, this paradigm is a relatively new model in psychiatry. Healthcare practices must ensure they have the appropriate infrastructure to deliver these medicines (e.g., support staffing and additional rooms to monitor patients). The Spravato Risk Evaluation and Mitigation Strategy (REMS) program requires a 2-hour onsite patient monitoring period post-administration which can disrupt provider scheduling, should a clinic even have adequate space. While current reimbursement codes are adequate for coverage of psychedelic drugs and their administration, there is not a single code that covers physician monitoring and extended psychotherapy sessions which may last several hours. In mid-2023, Compass Pathways and the nonprofit Multidisciplinary Association for Psychedelic Studies collaborated to establish a new temporary CPT III code for COMP360 and MDMA, each currently undergoing Phase 3 trials, with the goal of preemptively building a single code to cover physician time and services and easing reimbursement prior to commercial launch. The CPT III code was enacted to track the work and time of specialty services for psychedelic administration and monitoring which could transition to billable codes needed for reimbursement as early as 2026-2027. The path paved on the infrastructure and reimbursement front by these trailblazers will facilitate smoother drug launches for the commercialization of future psychedelics.

Beyond the evolving commercial model, in TRD, several psychedelics in development are positioned to differentiate by safety, and if effective, could see even greater clinical uptake than Spravato with less restrictive REMS requirements and limited reimbursement hurdles. Engineered psychedelics with improved risk profiles will directly ease launch burdens by broadening qualified healthcare facilities that can deliver the drug. Moving forward, we anticipate sustained interest in developing psychedelics for other areas of psychiatry, such as PTSD and substance abuse, as well as neurological disorders, including epilepsy.

Sources: Biomedtracker, Pitchbook, Cortellis, Siegel et al. JAMA Psychiatry. 2023 Jan 1;80(1):77-83, Marseille et al. PLoS One. 2020 Oct 14;15(10), Avanceña et al. Clinical Drug investigation. 2022 Mar;42(3):243-252

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