A psychedelic renaissance for treating depression?

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Key Takeaways

- Recent deal activities, study readouts and regulatory milestones indicate a resurrection of an old concept - the use of psychedelics for treating major depressive disorder (MDD) and other psychiatric diseases.

- Before the approval of Janssen's Esketamine nasal spray Spravato, the depression market experienced a decade-long innovation gap, with a high unmet need remaining, as more than 30% of patients do not respond to current treatments.

- Challenging development paths with costly trials, large placebo effect rates and massive post-approval marketing costs have impeded access to the depression market for smaller, potentially more risk-affine, and innovative players.

- Building on half a century of anecdotal evidence, psychedelics have recently shown signs of efficacy in a small number of investigator-sponsored, randomized, controlled trials. Psychedelics might offer important benefits over traditional MDD treatments including a fast onset and long duration of responses, as well as a comparably clean side-effect profile and low addictive potential.

- The current treatment model for psychedelic therapy, however, is time and therapy-intensive, when compared to classical antidepressants, which can be taken unsupervised and continually, potentially narrowing psychedelics' market potential.

- Moreover, research and development (R&D), as well as pricing and post marketing strategies for drugs based on controlled substances face their own set of challenges, including a negative image in the media and public, which might thwart their success.

- To create a viable business case for psychedelics, a number of items on the list have to be ticked, including novel IP, unsupervised administration options, a way to account for placebo responses in trials, de-regulation of R&D activities, and a shift in public image.

Resurrection of an old field

Major depressive disorder (MDD or depression) affects ~7% of the population in the United States and presents a significant societal and socioeconomical burden (1). Despite some 30+ approved drugs, more than 30% of patients are not responding to current treatments (2).

Driven by the persistently high unmet need, some developers have turned towards psychoactive, controlled substances, such as ketamine and more recently psychedelics, including Lysergic acid diethylamide (LSD), the active components of “Magic Mushrooms” (psilocybin) and the South American entheogenic brew ayahuasca (N,N-dimethyltryptamine (DMT)) (3). The first major milestone confirming this trend was the 2019 FDA approval of Janssen’s Spravato (esketamine), a nasal-spray formulation of the more active enantiomer of ketamine, which is a dissociative anesthetic that can trigger psychedelic-like effects (3).

In November 2020, German biotech-builder ATAI Life Sciences, which has assembled a portfolio of companies with psychedelic and non-psychedelic approaches to depression, anxiety and addiction, raised $ 125 million in a Series C, backed by tech billionaire Peter Thiel (4), which was followed by a $157 million Series D financing round in March of 2021 (5). One of ATAI’s companies is London-based Compass Pathways, which centers on Psilocybin based treatments. Compass Pathways went public with a $ 146 million IPO in September 2020 (CMPS:NASDAQ), and soon after reached a market cap of more than $ 1 billion. Similarly, the US biotech MindMed (MMED.NE), which focuses on both hallucinogenic and non-hallucinogenic psychedelic treatments went public on the NEO index for only $24 million in March 2020. Less than a year later, they are valued at over $ 1 billion and filed to up-list to NASDAQ (6). This trend is continued, with a number of other psychedelic stocks starting to list on smaller exchanges (7). Given the special status of the field, industry investment in psychedelics has been scarce in the past. One of the established players in the field is the non-profit, MAPS institute, which recently raised $ 30 million in funding for testing the psychoactive substance midomafetamine (MDMA, also known as ecstasy or Molly) in patients with post-traumatic stress disorder (8).

The increasing activity in the field recalls the early stages of the hype around cannabinoid compounds, which now make up a multi-billion-dollar industry for medical and recreational use.

Will psychedelics follow the same trend? How soon could investors expect return on investment and what challenges lie ahead?

The depression market and its challenges

Many industrialized countries face a mental health epidemic, which seems to be even further accelerated by the current Corona pandemic, with surges of depression reported in the US, UK and many other countries. In 2020, 4 in 10 adults in the US reported anxiety or depression in a Kaiser Family Foundation survey, marking a threefold increase from 2019 (9). Similarly, the UK Office for National Statistics reported a doubling in MDD cases when compared to 2019 (10). Even before the pandemic-based restrictions and the associated economic uncertainty unleashed its detrimental effects on mental health; depression constituted a key medical problem with an estimated annual economic burden of $ 210.5 billion in the United States (11).

17 million (or 7%) of Americans experienced at least one major depressive episode in their life, and half of those patients are treated with medication (12). The US depression market is projected to be the major area of growth, estimated to increase from $ 3.5 billion in 2020 toto $ 4.5 billion in 2025 (Figure 1A). Despite this large market, which is further bolstered by adjacent central nervous system (CNS) indications, with sometimes overlapping treatment strategies, both deal activity and total deal values in the CNS area fall far behind the oncology field (Figure 1B&C). Especially upfronts paid for early-stage assets, which can hint towards the risk-appetite and innovation drive within a therapeutic area, are significantly lower for CNS indications (Figure 1C).

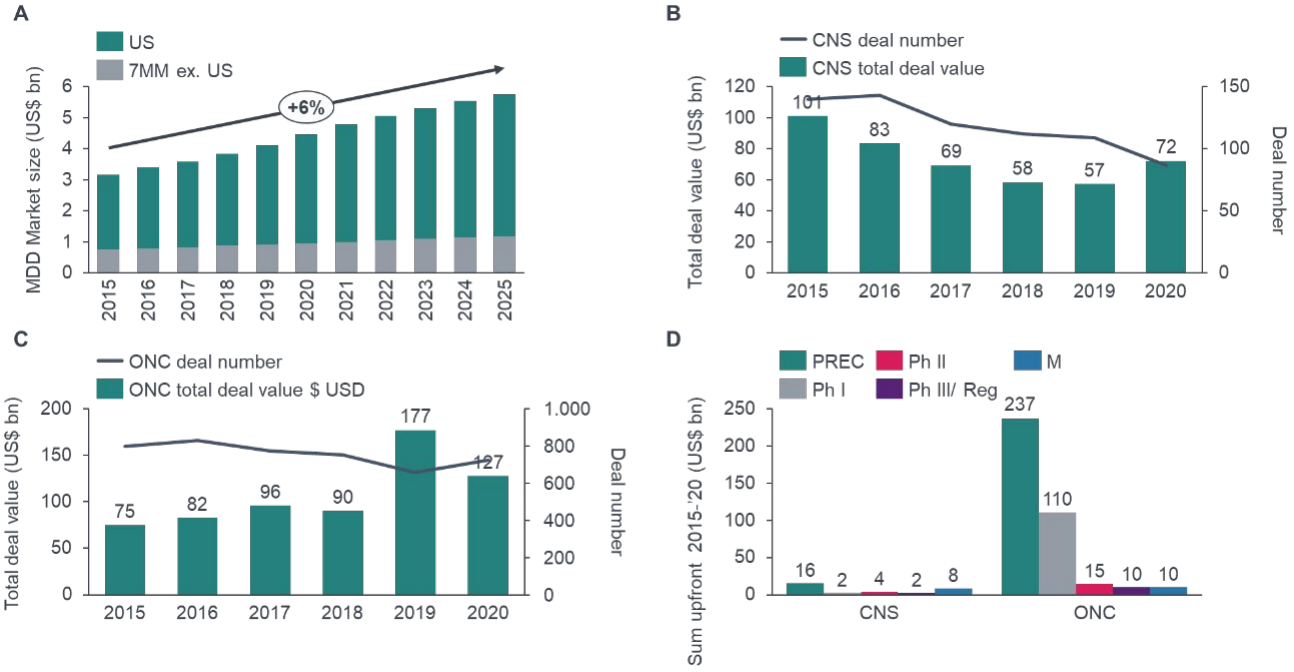

Figure 1: The MDD market and deals. A) Extracted from Global Data (Dec 15th 2020), shown are US market and the other countries of the 7 major markets (France, Germany, Italy, Spain, UK & Japan). Market size in US$ billion. **B-D** Extracted from Global Data (Feb 12th 2021), only completed deals and deals with disclosed financials were considered, limited to 7 major markets. **B,C** Sum total deal value (bn US$) and number of M&A, licensing agreements and collaborations in CNS **(B)** and oncology **(C). D)** Sum upfronts (bn US$) of M&A, licensing agreements and collaborations in CNS and oncology sorted for highest stage of products entailed in the deal between 2015 and 2020. ABBR: MDD: major depressive disorder, ONC: oncology, CNS: central nervous system

Moreover, despite a seemingly crowded market situation, with 30+ approved drugs, medical need remains high in MDD, with more than 30% of patients not responding to first-line anti-depressants. Additionally, onset of efficacy often takes weeks to months and many patients experience side effects from blurred vision and headaches to diarrhea, sexual dysfunction, insomnia, and tremors (2). Worse still, some first-line therapies such as Zoloft (sertraline hydrochloride) initially worsen suicidal tendency and come with respective boxed warnings (13).

Despite this unmet need, innovation has been slow coming since Prozac's market entry in 1987 heralded the age of serotonin reuptake inhibitors. In 2019, the depression market saw two new approvals in niche indications: Janssen's Spravato (Esketamine nasal spray) for treatment-resistant depression and Sage Therapeutics' Brexanolone $GABA_A$ receptor modulator for postpartum depression (14).

Drug development in MDD as in other CNS indications is marked by long and large trials, high failure rates, often huge placebo effects and low patient adherence (15,16). To select patients likely to respond, exclusion criteria are often stringent, limiting the accessible patient pool and further segregating the trial population from real-world patients (17). Moreover, post-approval massive marketing efforts are required (18).

All those factors make the development challenging for anyone but big pharma players with deep pockets in for the long haul, who generally haven't displayed a high-risk appetite in MDD during recent years. While early innovation might be driven by biotechs, later development stages usually depend on big pharma investment, as recently exemplified by Biogen's $ 1.5 billion deal ($875 million upfront) with Sage Therapeutics for their late stage $GABA_A$ receptor modulator SAGE-217(19).

The promise of psychedelics for depression

The study of classic psychedelics, mainly LSD and psilocybin, for psychiatric disorders, either alone or in combination with psychotherapy had seen much traction in the 1950s and 60s. While many of those studies reported benefits of the therapy on depression, addiction, and other psychiatric diseases, lack of scientific rigor and methodological shortcomings make it hard to judge those findings based on modern standards (3, 20).

After LSD was classified as controlled substance in 1968 (with other psychedelic drugs following in subsequent years), the field fell into a hiatus that lasted almost half a century, with a recent upswing in activity (Figure 2). Changes in attitudes and drug policies, as well as the persistently bad situation of treatment-resistant psychiatric patients has revived the idea of using psychedelics and other scheduled substances.

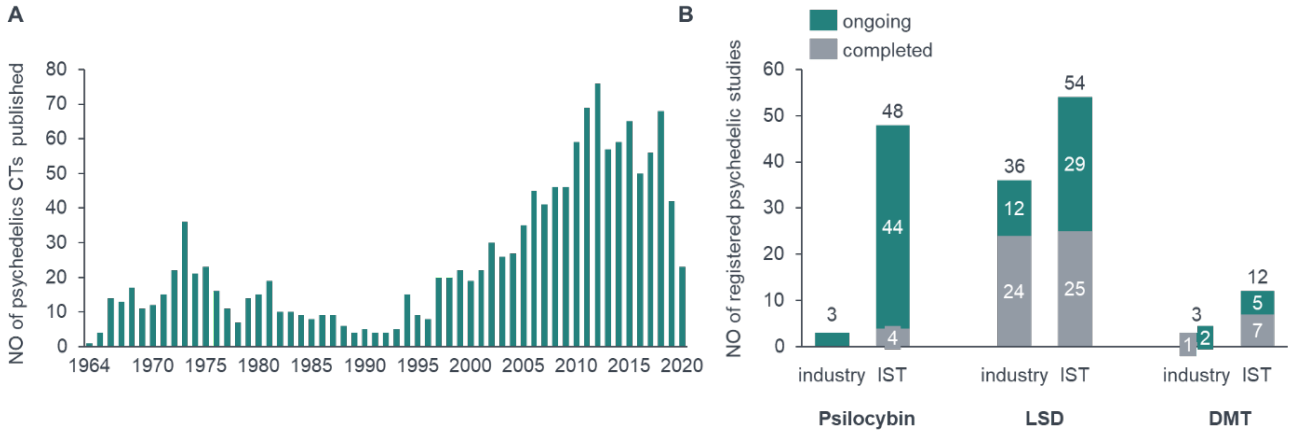

Figure 2: Clinical trials on psychedelics, A) Number of publications on clinical trials including search term 'psychedelic' extracted from PubMed (Dec 15th 2020) B) Number of clinical trials including search terms 'psilocybin', 'LSD' or 'DMT/ ayahuasca' extracted from CT.gov (Feb 12th 2021). Includes all trials, not specifically sorted for individual indications. Studies sorted as "completed" or "ongoing", including "recruiting", "not yet recruiting", active not recruiting" and "enrolling by invitation". Trials in the period from 2004 -2021. ABBR: IST: investigator-sponsored trial

Classical, serotonergic psychedelics, which exert their effect mainly through the serotonin-2-A receptor, include LSD and psilocybin, as well as DMT, the active ingredient from ayahuasca (3,20).

Compass' psilocybin program COMP360 is currently undergoing phase II testing for depression and was granted FDA breakthrough therapy designation for treatment resistant depression in 2018, and for MDD in November 2019 (21). Six other companies are investigating the compound for psychiatric disorders - five at preclinical stage, while the program from PsyBio Therapeutics is in phase I for cancer-related depression. Moreover, the non-profit Usona research institute received breakthrough designation for psilocybin in MDD (22, 23). While there are a number of industry sponsored trials for LSD in other CNS indications (Figure 2), currently all MDD trials investigating LSD are carried out by academic sponsors (Figures 2 & 3). Other psychedelic and psychoactive compounds that act on the Serotonin-2-A receptor tested for MDD include DMT with Small Pharma's SPL 026 and GH Research's GH 001 currently in in a Ph I/II trials, and a tryptamine-based therapeutic from PsyBio, currently in Ph I (Figure 3).

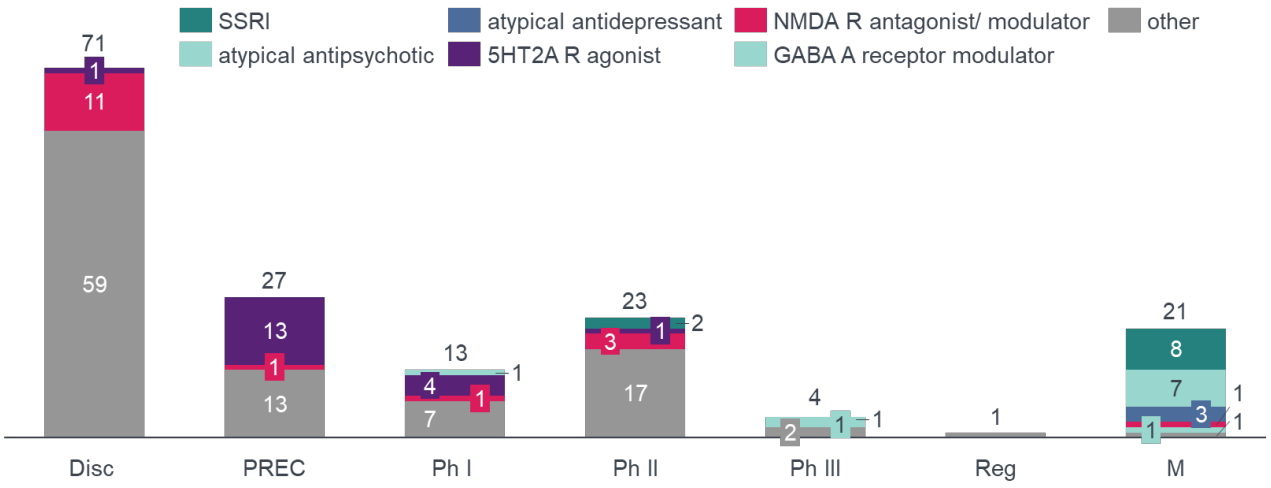

Figure 3: MDD pipeline, extracted from ADIS insight (Feb 12th 2021), limited to 7MM, new molecular entities only, search terms "depression", "major depressive disorder", manually curated to include "bipolar depression", "depressive disorders" (which includes treatment resistant depression and "postpartum depression". SSRIs sorted also to include dual MoAs, such as serotonin/ noradrenaline reuptake inhibitors and serotonin reuptake inhibitors/ serotonin receptor modulators. ABBR: disc: discontinued, M: marketed, NMDA: N-methyl-D-aspartate, Ph: clinical phase, PREC: preclinical and research, Reg: registration SSRI: serotonin reuptake inhibitor, 5HT2AR: serotonin 2A receptor.

Initial results from those (mostly open label) studies, promise fast onset and durability of response on depressive symptoms. Moreover, despite the public image, and scheduling as class I substance by the US Drug Enforcement Administration (DEA), classical psychedelics have no proven addictive potential and only mild physiological side-effects, though psychological side-effects can be dire. Given that only few of the studies on psychedelics published to date are randomized, controlled trials, the interpretation of the true effects remains challenging (20), and results will have to be confirmed against an active placebo (a drug that tries to replicate the psychedelic effect) and/or be compared to established treatments, as is currently done in academia-sponsored trials (23, 24). Moreover, almost all modern psychedelic trials, couple the drugs with talk therapy, making it difficult to disentangle the effects of the drug treatment from the surrounding therapy (Figure 4).

Ketamine, an off-patent anesthetic (and sometimes party drug), can exert psychedelic-like effects, and has been used to treat depression in a hospital setting for years. Its benefit lies in the rapid onset of effect, an obvious game-changer for patients with acute suicidal ideation. Janssen's Spravato (esketamine, a nasal-spray formulation) was approved for treatment-resistant depression even though efficacy was less stellar than for conventional ketamine (14). Though Spravato has fewer side effects than Ketamine, the drug still comes with a boxed warning for risk of sedation, abuse and suicidal thoughts and behaviors, as well as difficulty with attention or thinking and must therefore be taken in presence of a healthcare provider. Several other companies have investigated the same target as Ketamine (the N-methyl-D-aspartate (NMDA) receptor). Vista Gen Therapeutics' oral NMDA modulator, AV-101, which has a different pharmacological profile and potentially lower risk for abuse when compared to ketamine, is currently in phase II for MDD and received FDA Fast Track designation (Figure 3).

Regulatory and uptake challenges for psychedelics

Research and development on controlled substances comes with its own sets of hurdles. For example, research and drug development proposals must be approved by the DEA as well as the FDA (or respective agencies in other countries) and compounds used for research must be stored securely and only a limited number of institutions have approval to perform research on those drugs. Moreover, most psychedelic compounds lack patent protection, making them unattractive for pharma investment and necessitating patentable modification or reformulation as done for Spravato.

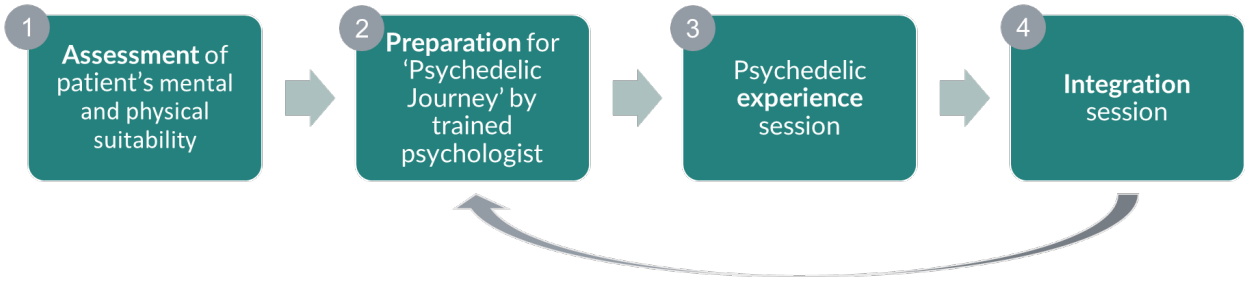

Figure 4: Psychedelic treatment model, adapted from (23). Treatment model comprises 4 stages: 1) Assessment, 2) Preparation 3) Experience 4) Integration.

Another challenge is presented in the current model for psychedelic therapy, which includes a combination of drug treatment and talk therapy (8, 25), making it both time-intensive and unaffordable to many patients (Figure 4). Spravato which has to be taken under supervision, but without the even more complex therapy model envisaged for classic psychedelics (Figure 4), reaches an estimated US$198,000 per quality-adjusted life year, exceeding the cost/benefit threshold (26). That said, despite its challenging profile, Spravato is still projected to gain worldwide peak sales in a blockbuster range.

The development of psychedelics drugs, which can be taken at home and without supervision would be a crucial step for accelerating the psychedelics business model. For classical psychedelics this would likely require producing non-hallucinogenic compounds, as attempted by the company MindMed or as a first step reducing the length of the "trip", attempted by Viridia Life Sciences another company from the ATAI family that aims to develop a short-acting DMT that could be suitable for home-use (6,27). The question remains, however, if psychedelics' mind-altering qualities, which make them unsuitable for home use, are required for their success in treating psychiatric diseases, as has been suggested in a number of studies (20).

Lastly, the negative public image of psychedelics as illegal drugs, which has been established over decades is expected to spawn controversy and could negatively affect regulatory approval, pricing and reimbursement, and reduce the commercial success of such products.

Given those obstacles, at the current stage the psychedelics industry seems unlikely to see the same type of hype as the cannabis industry, which deals with a compound that can be consumed daily and without supervision (7).

Conclusion

The depression market, after a decade-long innovation gap is experiencing a renaissance of an old idea, the use of psychedelics as aids for psychotherapy. This trend has recently spawned investor interest as psychedelic companies begin to enter the clinic. Despite initially good results for this drug class, psychedelics' special profiles, including mind-altering and hallucinogenic properties, the complex treatment model, their classification as controlled substances, and a largely negative public image might challenge their uptake. Nevertheless, if benefits could be proven in larger, controlled trials, the psychedelic treatment model could well mean a revolution for MDD treatment algorithms.

References

1) Greenberg et al. J Clin Psychiatry. 2015 Feb;76(2):155-62. https://pubmed.ncbi.nlm.nih.gov/25742202/
2) Global Data Report on Major Depressive Disorder, October, 2016
3) Inserra et al. Pharmacological Reviews January 2021, 73 (1) 202-277. https://pharmrev.aspetjournals.org/content/73/1/202.abstract
4) https://www.prnewswire.com/news-releases/atai-life-sciences-announces-closing-of-125-million-series-c-financing-round-301178915.html?tc=eml_cleartime
5) https://www.finsmes.com/2021/03/atai-life-sciences-closes-157m-series-d-financing-round.html
6) https://seekingalpha.com/article/4392873-mindmed-severely-undervalued-massive-upside-yet-to-come
7) https://investingnews.com/daily/life-science-investing/psychedelics-investing/psychedelics-stocks-to-watch/
8) https://www.investors.com/news/psychedelics-drugs-eye-legalization-wary-pot-stocks-dive/
9) https://www.kff.org/report-section/the-implications-of-covid-19-for-mental-health-and-substance-use-issue-brief/
10) https://www.ons.gov.uk/peoplepopulationandcommunity/wellbeing/articles/coronavirusanddepressioninadultsgreatbritain/june2020
11) http://www.workplacementalhealth.org/Mental-Health-Topics/Depression/Quantifying-the-Cost-of-Depression
12) https://www.nimh.nih.gov/health/statistics/major-depression.shtml#part_155029
13) Zoloft, FDA label https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019839S74S86S87_20990S35S44S45lbl.pdf
14) Christea & Naudet Lancet Psychiatry. 2019 Dec;6(12):975-977 https://pubmed.ncbi.nlm.nih.gov/31680013/
15) https://www.reachx.co/insights/graham-scholefield/the-decade-of-neuroscience--opportunities--caveats-for-investors
16) https://www.reachx.co/insights/graham-scholefield/failure-due-to-high-placebo-response--a-primer-on-placebos-in-clinical-trials-and-how-to-de-risk-them
17) Halvorson & Humphreys. Ann Depress Anxiety. 2015; 2(5): 1058. https://austinpublishinggroup.com/depression-anxiety/fulltext/depression-v2-id1058.php
18) Schwartz & Woloshin JAMA. 2019;321(1):80-96. https://jamanetwork.com/journals/jama/fullarticle/2720029
19) https://www.fiercebiotech.com/biotech/biogen-bets-1-5b-sage-s-once-failed-depression-drug#:~:text=Biogen%20is%20paying%20%241.5%20billion,that%20will%20shape%20its%20future.
20) Vollenweider & Preller Nature Reviews Neuroscience volume 21, pages611–624(2020) https://www.nature.com/articles/s41583-020-0367-2
21) https://compasspathways.com/compass-pathways-receives-fda-breakthrough-therapy-designation-for-psilocybin-therapy-for-treatment-resistant-depression/
22) https://www.businesswire.com/news/home/20191122005452/en/FDA-grants-Breakthrough-Therapy-Designation-to-Usona-Institutes-psilocybin-program-for-major-depressive-disorder
23) https://clinicaltrials.gov/ct2/show/NCT03866174 (no data published)
24) https://clinicaltrials.gov/ct2/show/NCT03429075 (no data published)
25) Reynolds JAMA Psychiatry. 2020, Editorial https://jamanetwork.com/journals/jamapsychiatry/article-abstract/2772628
26) https://www.thepharmaletter.com/article/icer-says-spravato-has-benefits-but-exceeds-cost-effectiveness-thresholds
27) https://www.fiercebiotech.com/biotech/meet-viridia-atai-unit-exploring-ayahuasca-based-treatments-for-mental-illness