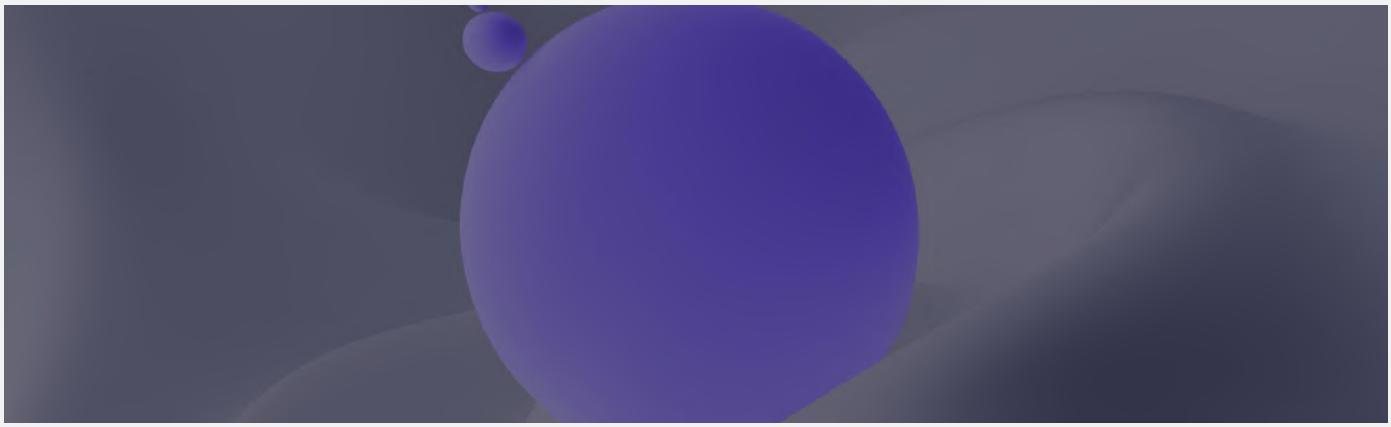
How “Far Out” Are Psychedelic Therapeutics?

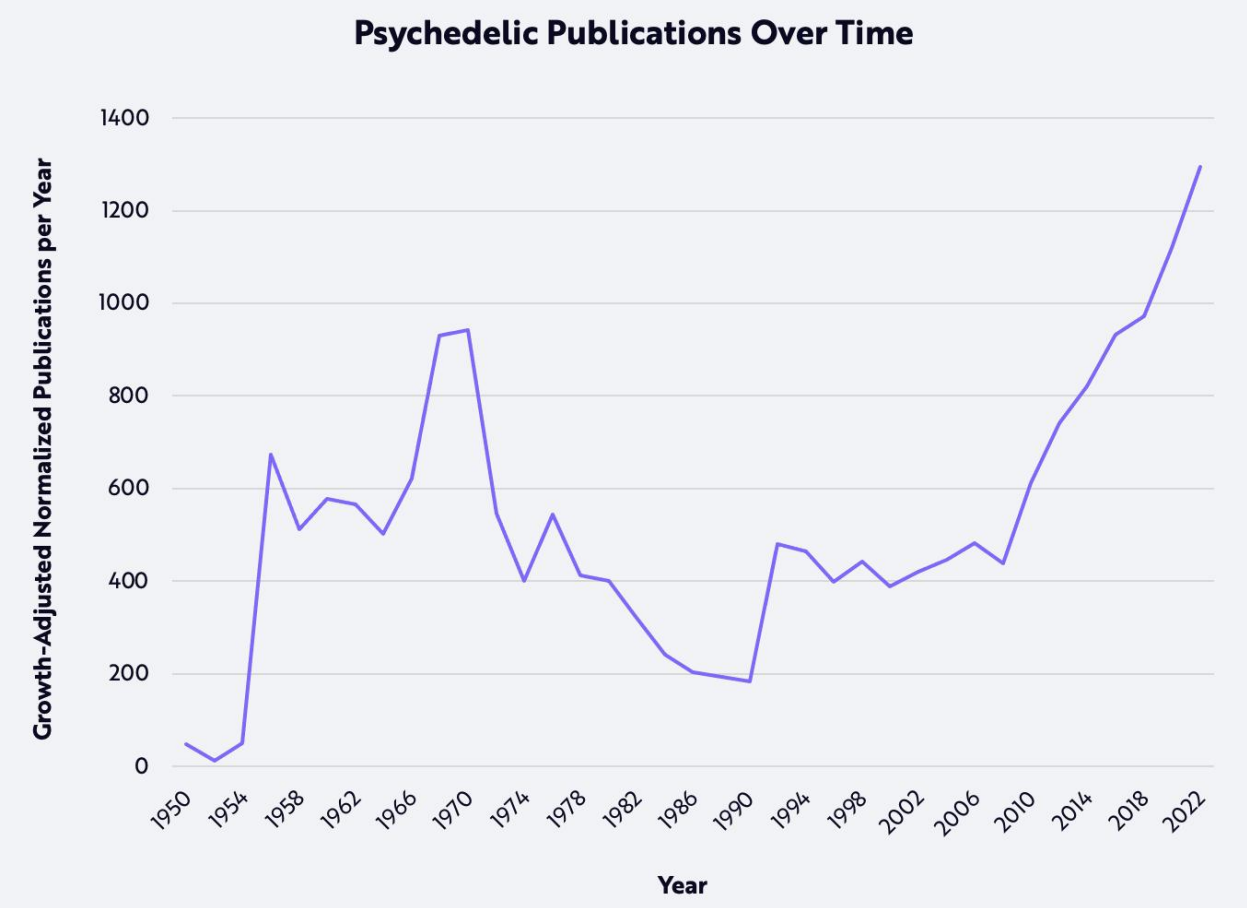
August 31, 2022



By: Pierce Jamieson

Used recreationally, medicinally, or ritually, psychedelic drugs seem to have been ubiquitous throughout human history.[1],[2] The Greek roots of the word “psychedelic” are *psyche* (mind or soul) and *delos* (to reveal). Unfortunately, during the Vietnam era, psychedelics fell into the “hippie” and counterculture movements and lost political support in the United States. This Ideological opposition may have led to the funding restrictions outlined in the 1970 Controlled Substances Act (CSA)—a major regulatory setback for research on psychedelic compounds.

Since then, the field of psychedelic neuroscience and pharmacology has been struggling to break free from those repressed and criminalized cultural elements. Until the 1990s, junior academics and clinicians often were discouraged by their supervisors from pursuing research on psychedelic compounds.[3] In the past three decades, however, a growing community of rigorous academics and physicians has reaccelerated research on psychedelics, as shown below.

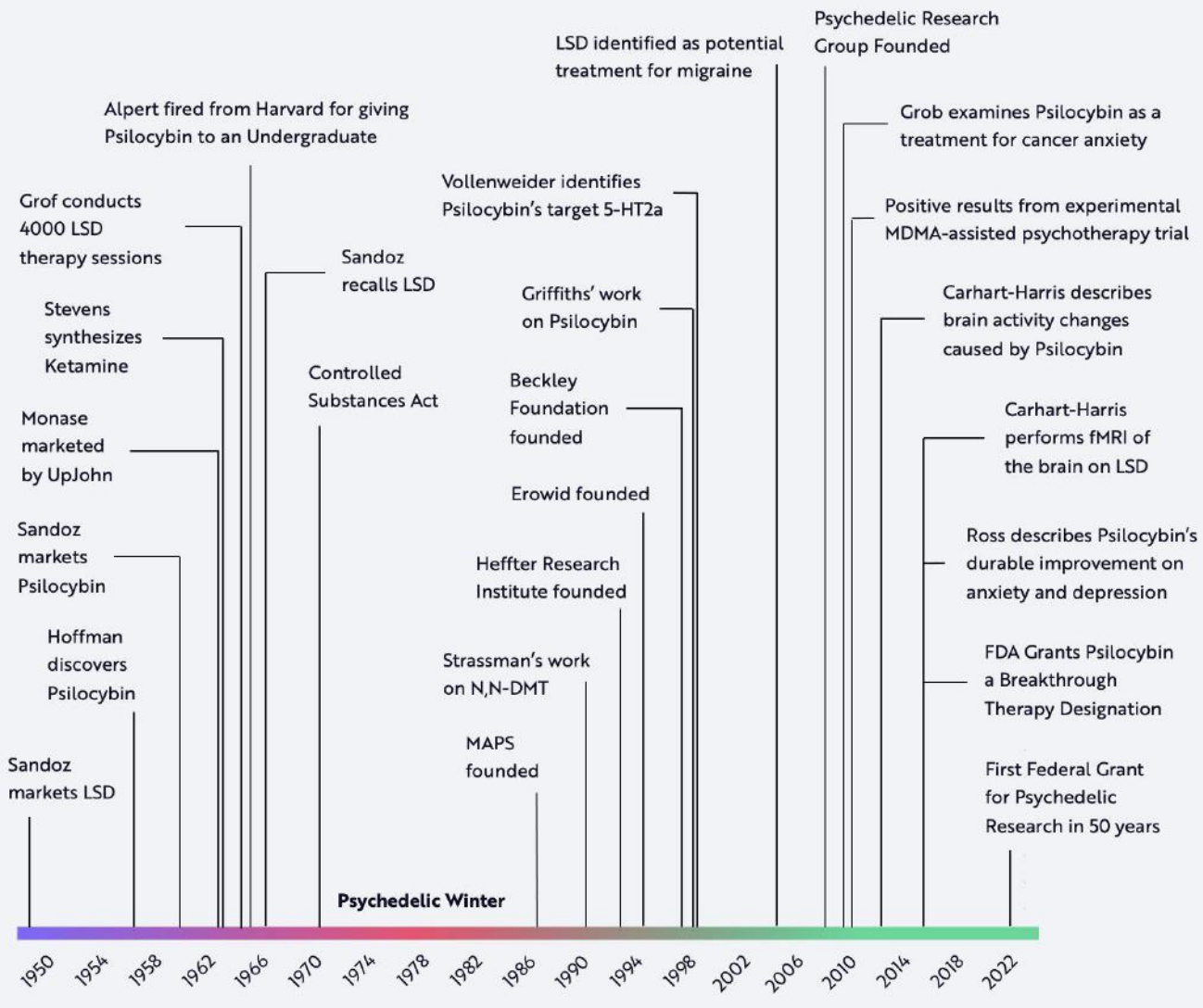


Source: ARK Investment Management LLC, 2022; Data derived from Web of Science

Note: Data were retrieved from the Web of Science reviews database using the following search terms: LSD, PSILOCYBIN, PSYCHEDELICS, and HALLUCINOGENS. The number of PubMed entries with psychedelic or psychedelic-related titles released each year after those numbers were normalized to a base of 100 and adjusted to compensate for the growth in total publications published per year.[4]

By the time the Multidisciplinary Association for Psychedelic Studies (MAPS) was established in 1986, research on the therapeutic potential of psychedelics had resumed.[5] Researchers made considerable progress both in identifying the targets of psychedelic compounds and in localizing the neurons in the brain that express the cell surface receptors linked to many classical hallucinogens.

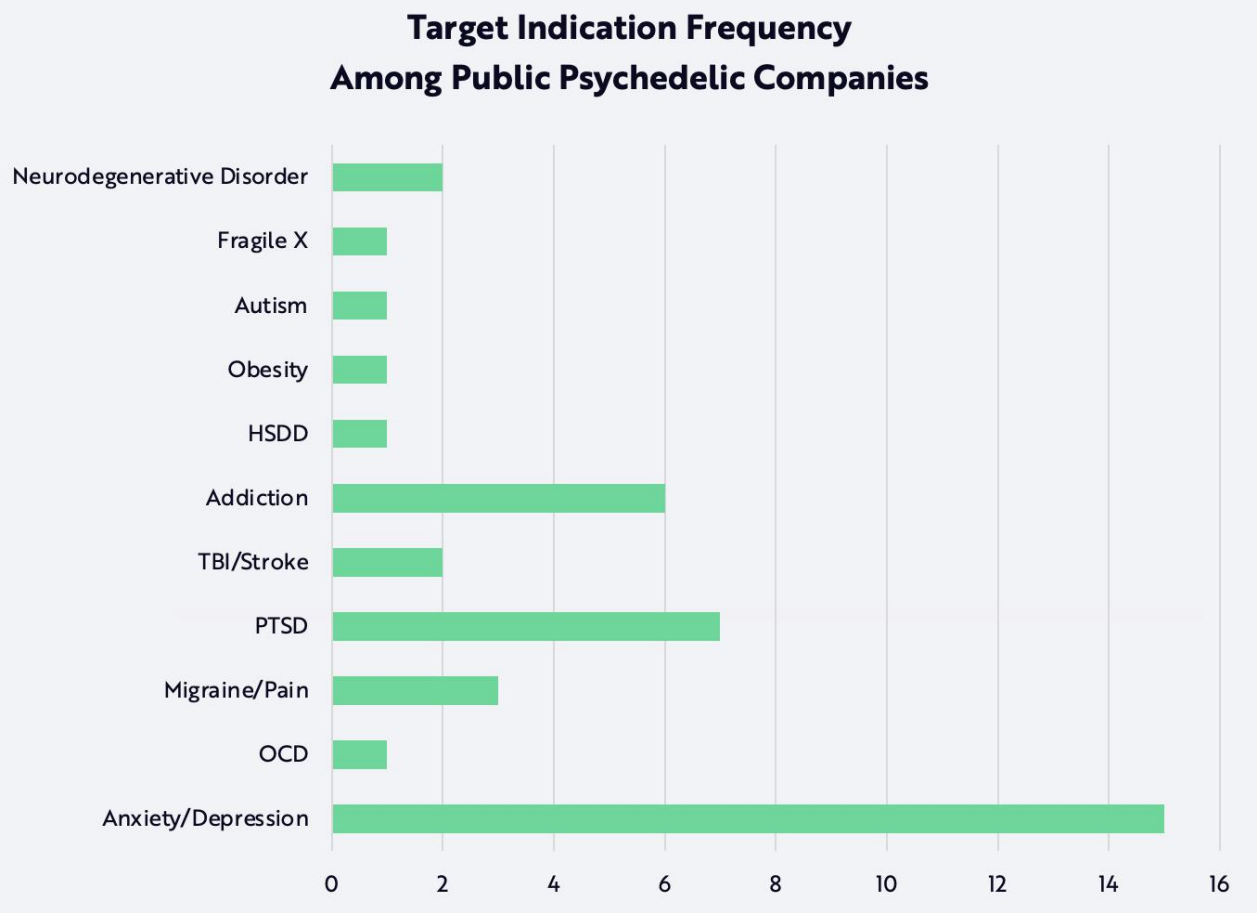
In the 1990s and 2000s, the emergence of fMRI and PET imaging technology provided critical insights into the impact of acute psychedelic experience on brain activity.[6] In the past ten years, researchers have studied the drug receptors associated with psychedelics using techniques like x-ray crystallography and cryo-EM, subjecting them to modern *in silico* drug discovery and ligand prediction.[7] The timeline below delineates several significant events in psychedelic research and regulation since the 1950s.



Source: ARK Investment Management LLC, 2022

Note: "Psychedelic Winter" refers to the relatively low volume of psychedelic research that occurred between 1970 and 1984, not low-volume recreational psychedelic drug use.

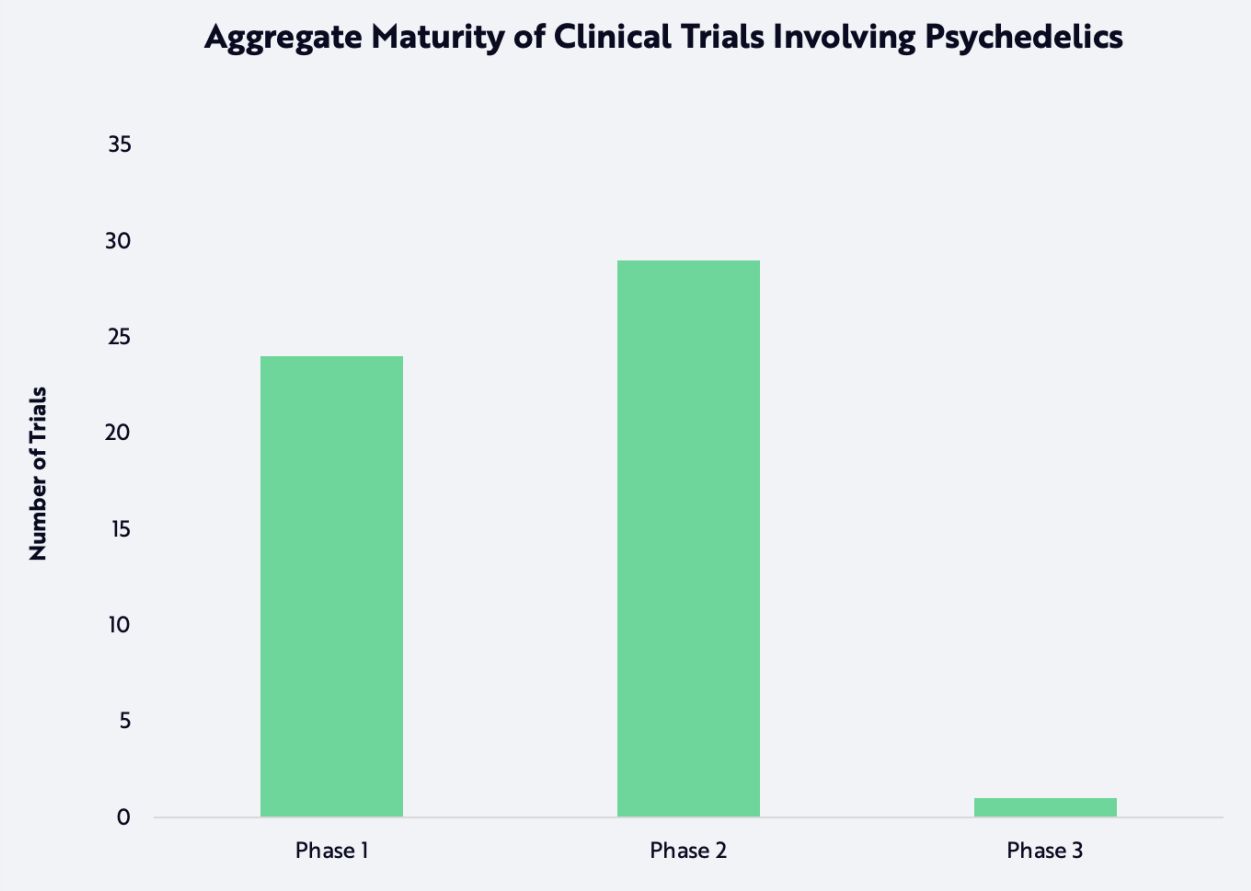
In 2018, some states began decriminalizing psychedelics after the FDA designated the psychedelics Psilocybin and MDMA as breakthrough therapies[5],[8] and the Right to Try Act allowed physicians to administer psychedelics to terminally ill patients.[9] Today, many public and private companies are attempting to convince the FDA to approve various psychedelic or psychedelic-derivative drugs. The graph below illustrates the indications they have targeted most frequently.



Source: ARK Investment Management LLC, 2022

Forecasts are inherently limited and cannot be relied upon. Not a recommendation to buy, sell, or hold any particular security.

With only one clinical trial in Phase 3, psychedelic pharmaceuticals are in the early stages of clinical exploration. The next graph depicts the number of trials involving psychedelic compounds in each phase as of the second quarter, 2022.[10] In our view, conservatively, their combined sales could reach $5.5 billion per year by 2030.



Source: ARK Investment Management LLC, 2022

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In this article, we review psychedelic neurochemistry and explore the current clinical work on psychedelics. We then assess the investment risks and opportunities associated with this pharmaceutical subsector. Our goal is to describe the type of innovation that we believe will play a crucial role in unlocking the potential of these compounds to improve human health.

Psychedelic Neurochemistry

The neurotransmitter 5-hydroxytryptamine (5-HT), better known as serotonin, serves a diverse range of molecular functions in invertebrates, vertebrates, plants, fungi, and even unicellular organisms.[1],[2] Humans express more than fourteen different serotonin receptors in a range of tissues. The downstream signaling associated with these receptors is associated with addiction, aggression, appetite, anxiety, blood pressure, heart rate, sexuality, thermoregulation, memory, perception, gastrointestinal motility, sleep, and more.[11]

One of those receptors, 5-HT2, has three subtypes—5-HT2a, 5-HT2b, and 5-HT2c—and performs a range of functional roles, as shown below. Scientists consider 5-HT2a the most important serotonin receptor in eliciting "classical" psychedelic experiences.[12]

Receptor	Putative Functional Roles
5-HT2a	Perception, Thermoregulation, Cognition, Sexuality, Sleep, Addiction [15,39]
5-HT2b	SSRI/DRI-like function, Migraine, Cardiovascular Function, Appetite, Anxiety [12,13]
5-HT2c	Sexuality, Mood, Anxiety, Addiction [11,15]

Source: ARK Investment Management LLC, 2022

Although other pathways, such as the kappa opioid receptor (KOR) pathway and N-methyl-D-aspartate (NMDA) receptor pathway, have been implicated in a distinct psychedelic or psychedelic-like experience, in this article, we will define "classical" psychedelics as the subset of compounds that are *agonists* (i.e., compounds that bind to a receptor and activate its downstream signaling) of the 5-HT2a receptor.[12]

When ingested, psychedelics interact with 5-HT2a and other receptors, leading to broad and potent changes in brain function. Some of the physical effects include tremors, pupil dilation, and changes in blood pressure, heart rate, and motor function.[13] The primary indications targeted by 5-HT2a agonists are treatment-resistant depression (TRD), major depressive disorder (MDD), post-traumatic stress (PTSD), and migraines.[14]

As noted above, the KOR and NMDA agonists produce a distinct hallucinogenic or psychedelic experience. KOR signaling, for example, plays an essential role in perception, pain, motor function, and addiction.[15] Companies investigating KOR agonists like Salvinorin A and Ibogaine[14] typically are targeting addiction, alcoholism, and opioid use disorder (OUD).

The tables below highlight the sector's breadth by summarizing the range of psychedelics currently in clinical or preclinical trials. This article focuses on Psilocybin because it is in a relatively mature stage of clinical development.

Psychotropic Substance	5-HT2a	5-HT2b	5-HT2c	KOR	Family	Target Indication(s)
DMT	++	+++	+++	–	Tryptamine	TRD, Alzheimer's, Pain, Addiction
Mescaline	–	+++	–	–	Other	Inflammation
MDMA	–	+++	–	–	Phenethylamine	Autism, PTSD
Psilocin	++	+++	++	–	Tryptamine	Depression, Fragile X Syndrome, PTSD
Salvinorin A	–	–	–	+++	Other	Depression, Addiction
Ibogaine	+	–	–	++	Iboga Alkaloid	Addiction
LSD	+++	+++	+++	–	Ergoline	Anxiety, Addiction, Migraine
Ketamine	–	–	–	+	Other	Depression, Parkinson's

Legend: +++ = very high // ++ = high // + = moderate // – = low to not detectable

Source: ARK Investment Management LLC, 2022. Forecasts are inherently limited and cannot be relied upon. Not a recommendation to buy, sell, or hold any particular security. Note: This table depicts a comparison of the potency-normalized strength of serotonin and kappa-opioid receptor-binding for a series of psychotropic substances and includes a list of indications targeted by companies investigating psychedelic or psychedelic-derivative therapeutics in clinical trials.[16]

Psychotropic Substance	Subjective Effects	Potential Adverse Effects	Dependence Liability
DMT	<30-minute intense hallucination	Dizziness, Agitation	Very low
Mescaline	4–8-hour hallucination	Anxiety, Psychosis	Very low
MDMA	4-6 hours of stimulated, euphoric, and entactogenic experience with very mild hallucination	Hyperthermia, Bruxism, Insomnia, Hyperhidrosis, Serotonergic Neurotoxicity	Moderate
Psilocybin	4–6-hour hallucination	Psychosis, Anxiety, Prolonged Derealization	Very low
Salvinorin A	<30-minute hallucination	Psychomimesis, Dysphoria, others	Very low

Psychotropic Substance	Subjective Effects	Potential Adverse Effects	Dependence Liability
Ibogaine	4–6-hour hallucination	QT interval elongation, Sudden Cardiac Death, Nausea, Ataxia	Very low
LSD	6–15-hour hallucination	Psychosis, Anxiety, Prolonged Derealization	Very low
Ketamine	~1 hour of euphoria and sedation	Amnesia, Nausea, Depression	Moderate

Source: ARK Investment Management LLC, 2022

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Acute Psychedelic Experience

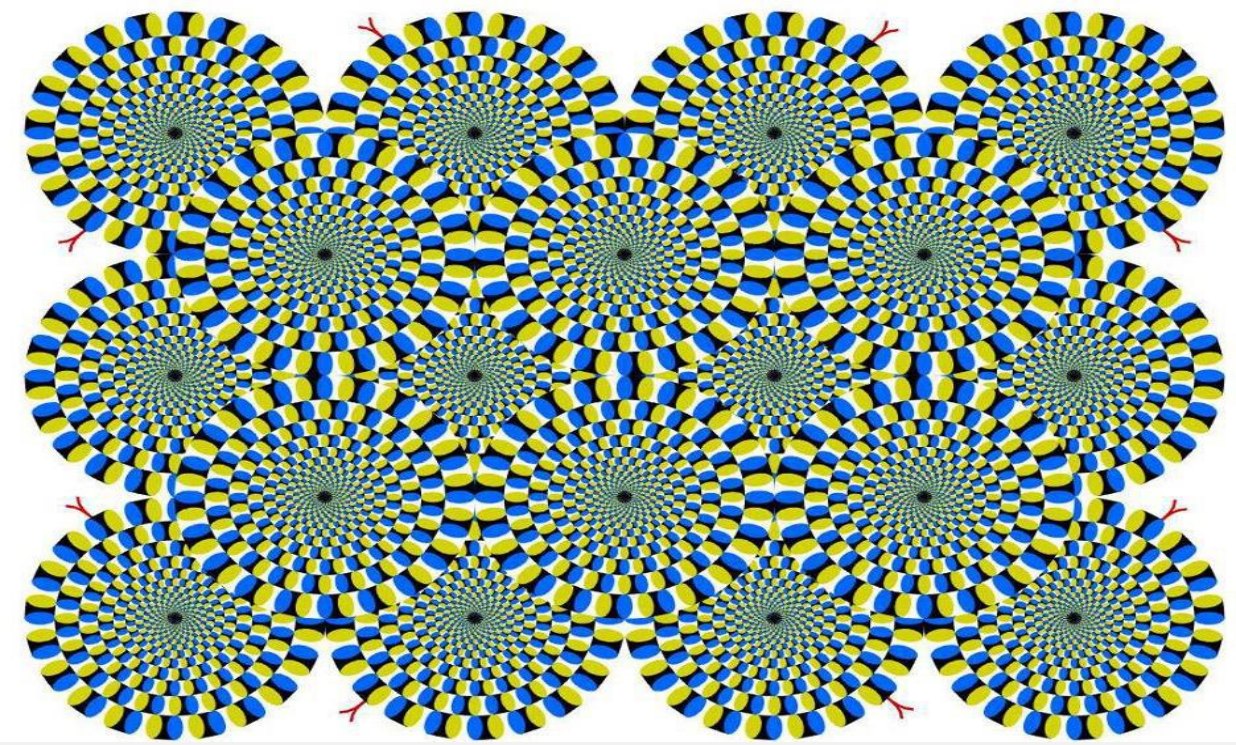
Because of the challenges associated with measuring acute psychedelic experience objectively, academics have focused on understanding the neurochemistry of psychedelic compounds, hoping for a clear explanation for these effects. Although the utility of psychedelic compounds as psychiatric drugs may or may not be linked inextricably to the character of these experiences, we believe they cannot be overlooked in an honest attempt to evaluate psychedelics for therapeutic potential.

In his TED talk, *Your Brain Hallucinates Your Conscious Reality*, Anil Seth, a professor of Cognitive and Computational Neuroscience at the University of Sussex, observed that perception depends not only "on the signals coming into your brain from the outside world" but also, "…if not more, on perceptual predictions flowing in the opposite direction."

What if those "perceptual predictions" were to become much stronger or weaker than normal? Would each stimulus feel muddled or difficult to distinguish? Would everything look the same?

Google's "Deep Dream VR, AI-Driven Hallucination Machine" has created a VR experience that attempts to simulate the effects of overly strong object-classification predictions on perception, which, while not a perfect simulation of psychedelic experience, provides what we believe is a compelling model to understand the hallucinogenic impact on human visual processing, as shown here.

To appreciate the two-way street of perception and how the mind can fill information gaps to present a conscious mind with a working model of reality, consider images such as the Akiyoshi Kitaoka's *Rotating Snakes*, shown below. This static image causes something known as the "peripheral drift illusion" by producing a signal that tricks the part of the brain responsible for motion perception.



Source: Akyoshi Kitaoka's Rotating Snakes https://www.illusionsindex.org/i/rotating-snakes

Note: This is not a GIF.

While some academics like Robin Carhart-Harris and Roland Griffiths are revealing the nature of the psychedelic experience, the link between perceptual distortions and mystical experience remains unclear. Even so, several studies offer evidence that the consumption of classical hallucinogens like Psilocybin can result in durable psychotherapeutic benefit.[19]

Psychedelic Neuroscience Brass Tacks

Some studies link psychedelics to an increase in functional connectivity across brain networks. That finding is consistent with synaptic density increasing in pigs after Psilocybin administration. It also corroborates the *Proceedings of the National Academy's conclusion* that Psilocybin increased dendritic spine formation in the cortical neurons of mice, improving synaptic plasticity.[20]

Early evidence suggests that the so-called "psychoplastogenic" effects of psychedelics can be linked to the psychedelic experience itself.[19] Without the psychedelic experience, for example, Tabernathalog, an analog of the non-classical psychedelic Ibogaine, did induce psychoplastogeneic effects in mice.[21] Notably, Psilocybin administration has been correlated with a drop in blood flow to the amygdala, which governs fear and anxiety.[22] Psychedelics seem to reduce alpha waves, or electrical rhythms, in specific brain regions.[23] Alpha rhythms are linked to perceptual processing in the "posterior cingulate cortex," the reduction of which seems to result in ego-loss during the acute psychedelic experience.[23]

Related work suggests that Psilocybin disengages the "default mode network" (DMN), a brain network responsible for storing autobiographical information and understanding interpersonal relationships and perspectives on the past and the future. Further, the degree to which the DMN "resets" seems to predict the response to treatment. These data suggest that Psilocybin's psychotherapeutic benefit relies on dose thresholds high enough to induce the "reset" of DMN.[23],[24] While not strong enough to dismiss it, these findings suggest that Psilocybin "microdosing" is not effective in the treatment of depression.

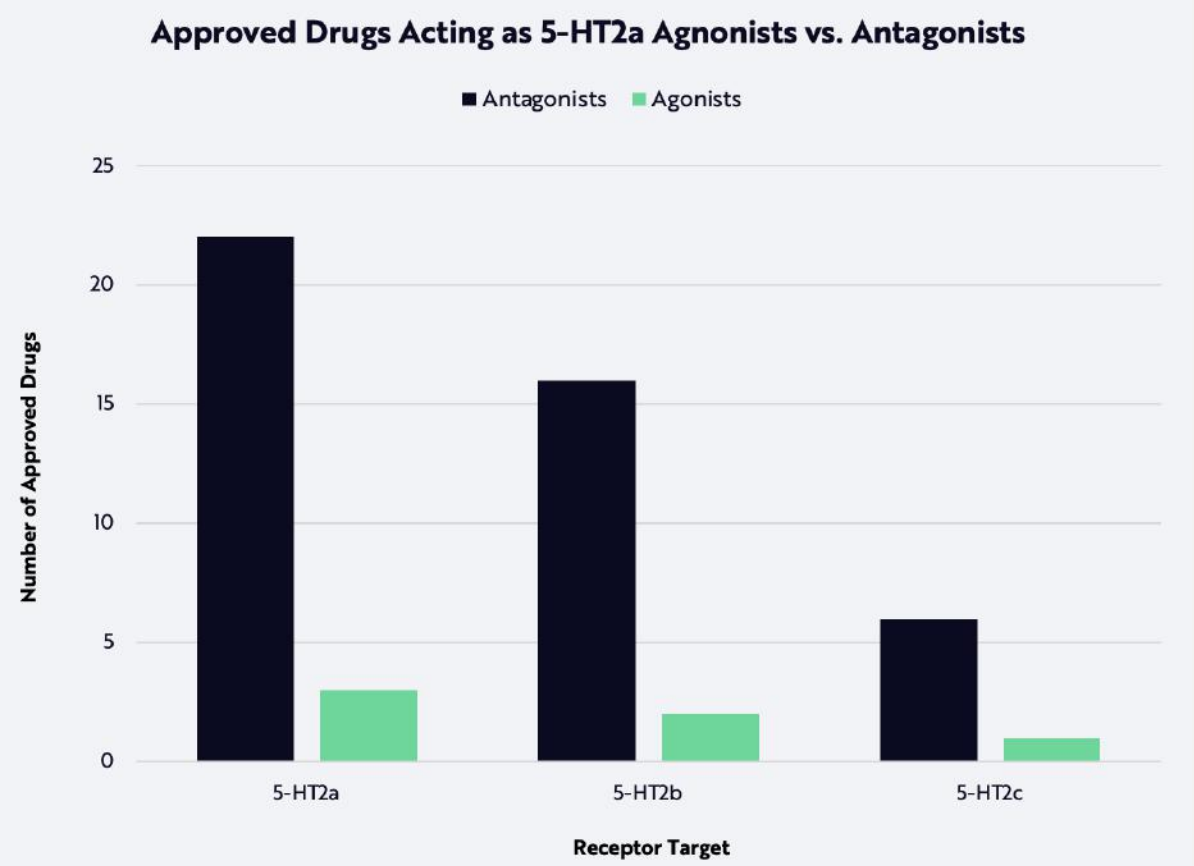
As Robin Carhart-Harris notes, however, the DMN narrative oversimplifies the complex underlying mechanism. He and other scientists have surfaced a link between psychedelic experience and the degree of connectivity between and among "unimodal" and "transmodal" brain networks.[25] Unimodal networks process information from one sensory modality, like visual or auditory, while transmodal networks show an increase in activity that is not associated with any one sensory input source. Transmodal regions seem to serve as intermediaries, interconnecting and integrating both sensory and cognitive information.[25]

Other studies find that psychedelics can increase unimodal-transmodal crosstalk, or the "compression" of cortical hierarchy. A similar compression can be observed in patients with Schizophrenia, implying a neurological basis for the conflation of concrete and abstract cognition in both Schizophrenic and psychedelic-induced brain states.[26] Unsurprisingly, one of the most common drugs for the treatment of Schizophrenia, Thorazine, is a 5-HT2a antagonist, or blocker.[17]

A breakdown in the brain's ability to distinguish between concrete and abstract highlights the importance of the environment in the psychedelic experience. While guides, music, or other comforting stimuli are common in studies, dimensioning the importance of each factor in clinical outcomes is a methodological challenge.

Approval Risks

The moratorium on psychedelic drug research between 1970 and 1990 delayed efforts to improve upon the pharmacological characteristics of 5-HT2a agonists like Psilocybin and N,N-Dimethyltryptamine (DMT). That said, many pharmaceutical drugs, including the migraine therapies Zolmitriptan and Bromocriptine, share a chemical backbone with classical psychedelics.[17] CSA's restrictions did not prevent pharmacologists from finding molecules in the same family as psychedelics. Instead, they seem to have obstructed efforts to understand the therapeutic possibilities for molecules that act as agonists at the 5-HT2a receptor. The number of *antagonist* drugs (blockers) that the FDA has approved has dwarfed that of *agonist* drugs (activators) at the 5-HT2 receptor, as shown below.[17]



Source: ARK Investment Management LLC, 2022

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Interestingly, the bias against 5-HT2a agonists may be rooted in more than antiquated regulation or cultural stigma. While research has shown that most classical psychedelics rarely lead to adverse neurotoxic, cardiac, or psychiatric events,[27] the drugs that function as 5-HT2a agonists—and *were* approved by the FDA—sometimes do. Three partial 5-HT2a agonists—Efavirenz (HIV antiretroviral), Mefloquine (antimalarial), and Methysergide (migraine prophylactic, approval withdrawn)—have been associated with cardiac valve dysfunction.[17] While this does not suggest that 5-HT2a agonism itself causes cardiac arrhythmia, it does suggest that there may be an overlap between compounds that function as 5-HT2a agonists and compounds that modulate cardiac action potentials.

Consider Ibogaine, a psychedelic drug derived from the root bark of the tree *Tabernathe iboga.* Since the 1990s, scientists have studied Ibogaine as a potential therapeutic for the treatment of addiction.[28] Despite evidence to suggest that it is more effective than many of the existing options for the treatment of opioid use disorder (OUD), the FDA has not approved Ibogaine. While the FDA may seem biased against drugs that give rise to psychedelic experience, another explanation is that Ibogaine has been associated with 27 cardiac-related fatalities, many in patients with no preexisting cardiovascular conditions.[18]

The challenges associated with conducting clinical trials for psychedelic compounds complicate matters even further. They require stringent screening procedures that limit sample sizes and statistical power.[29] Further, self-selection can bias results, particularly in indications with endpoints that rely on the measurement of subjective experience. Finally, the blinding of both clinicians and participants in trials is difficult because the difference between the placebo and experimental compound is obvious.[30]

The FDA's designations of Psilocybin and MDMA as breakthrough therapies suggest that the tide is changing, though political dynamics still could become barriers to approval for many of these substances. The government currently classifies controlled substances into five different schedules, as shown below.

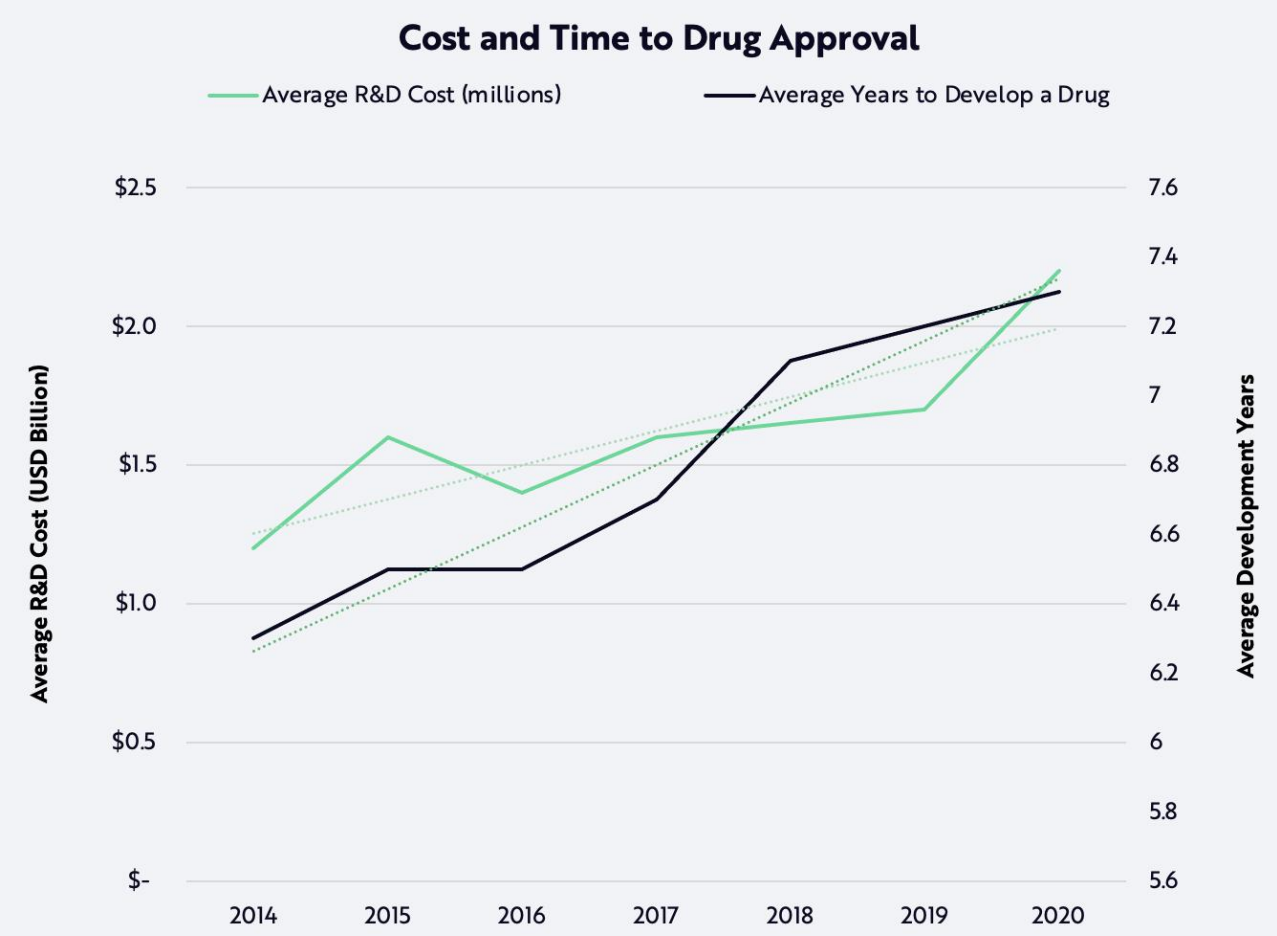
Schedule	Drug Examples	FDA Description
Schedule I	LSD, MDMA, Psilocybin, Mescaline, Heroin	High abuse potential and no approved medical use
Schedule II	Cocaine, Morphine, PCP, Methamphetamine	High abuse potential
Schedule III	Ketamine, Hydrocodone, Anabolic Steroids	Moderate abuse potential
Schedule IV	Xanax, Valium, Rohypnol	Low abuse potential
Schedule V	Codeine-based cough medicines	Very low abuse potential

Source: United States Drug Enforcement Administration

The degree of the felony or misdemeanor associated with drug possession in these schedules can vary on a state-by-state basis. The FDA's approval of Psilocybin, today a Schedule I classical hallucinogen, could reduce it to a lower schedule, potentially reducing the DEA's ability to prosecute those who possess or distribute it. However, if the FDA approves a specific pharmaceutical formulation of Psilocybin, anything but that formulation might still submit to Schedule I status.

Recently, regulators have allowed researchers to conduct clinical trials on controlled substances more efficiently. However, Nora Volkow, Director of the National Institute for Drug Abuse, noted in her December 2021 testimony to the US House of Representatives Health Subcommittee that research on Schedule I substances "..takes longer, [is] much more costly, [and] cumbersome, [so much so that] even experienced researchers have reported that obtaining a new Schedule I registration, adding new substances to an existing registration, or getting approval for research protocol changes is time-consuming."[31]

Clinical development time correlates strongly with program costs, as shown below. Historically, 22% of clinical trials have failed for lack of funding.[29]Longer clinical development cycles correlate highly with participant dropouts and incorrect dosing, further reducing the likelihood of approval.[32]



Source: ARK Investment Management LLC, 2022

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In our view, Psilocybin could provide incremental improvements in treating major depressive disorder (MDD) and treatment resistant depression (TRD), particularly when combined with conventional antidepressants and cognitive behavioral therapy (CBT). To prevent serotonergic toxicity and other negative interactions, however, patients taking selective serotonin reuptake inhibitors (SSRI) or other antidepressants will need two to four weeks to wean from other medications.

Business Risks and Prospects of Psychedelics

In the United States, the estimated cumulative economic burden associated with major depressive disorder (MDD), opioid use disorder (OUD), and post-traumatic stress disorder (PTSD) in 2022 is ~$1.4 trillion per year, as delineated in the table below.[33-42] The direct healthcare costs are ~$270 billion. ARK estimates that, in 2022, the annual pharmaceutical sales opportunity associated with these indications in the United States is $44 billion, or ~3.1% of the total economic burden.

	Major Depressive Disorder	Opioid Use Disorder	Post-Traumatic Stress Disorder
Direct Healthcare Costs (USD, Billions)	$141.7	$89.0	$42.0
Indirect Costs (USD, Billions)	$184.3	$786.0	$189.0
Total Burden (USD, Billions)	$326.0	$875.0	$231.0
Annual Deaths (USD)	88,000	93,000	5000
Adult Prevalence (US)	4.7%	2.45%	3.6%
Pharmaceutical Sales (Estimate, USD, Billions)	$37.8	$0.9	$4.69

Source: ARK Investment Management LLC, 2022

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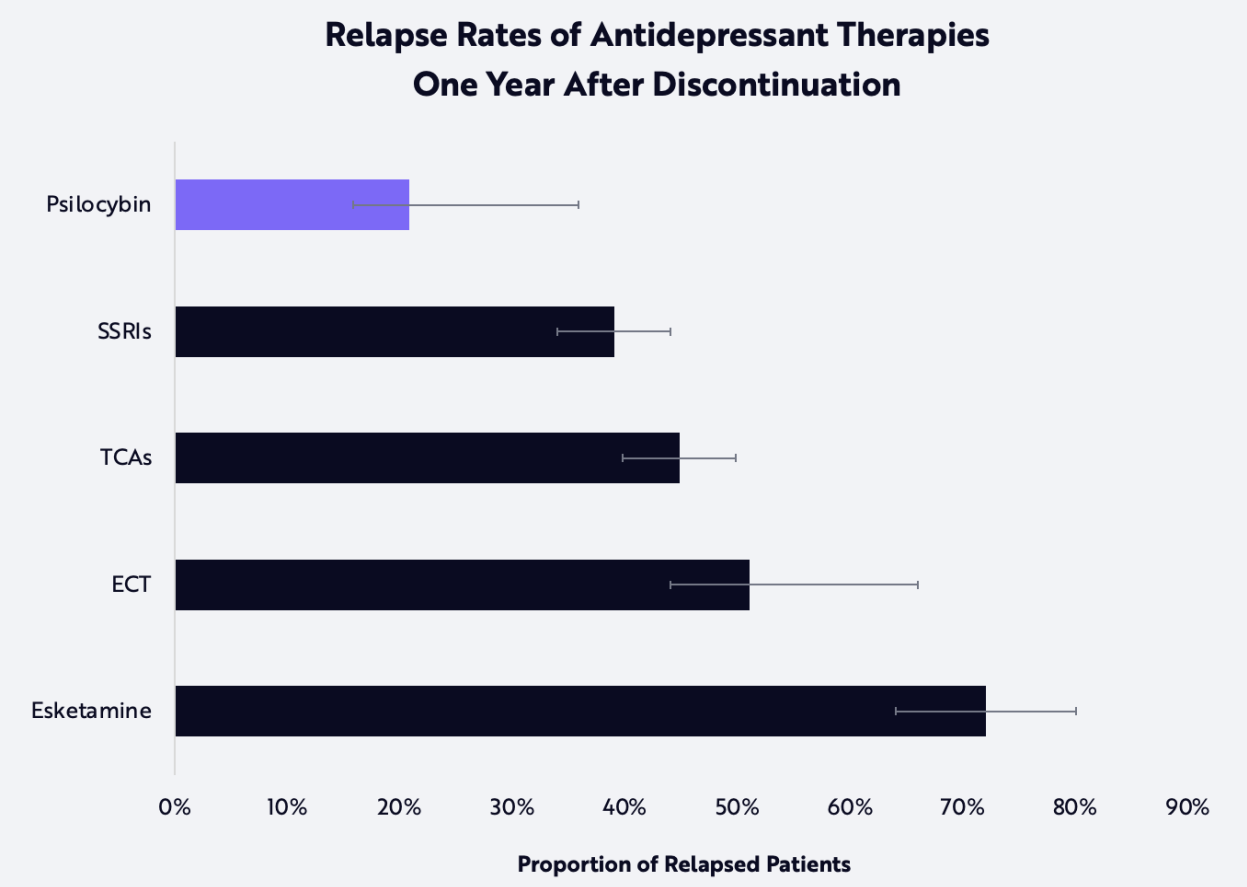
To treat MDD, conventional pharmacotherapy with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) can take months of dose calibration, with efficacy varying significantly from patient to patient.[43] This approach is cost-effective for depression of moderate severity. As depression becomes more severe, conventional treatments like SSRIs are much less cost-effective.[44] To highlight the problem, the United States Center for Medicare and Medicaid Services (CMS) estimates that only 20% of patients treated for MDD respond partially without remission, while 50% do not respond at all.[45] One study found that 55% of MDD patients discontinued treatment after five months.[46] Because healthcare payers are more likely to cover—and patients are more likely to adhere to—medications with higher efficacy, ARK expects psychedelic therapies to accrue significant value.

In our view, one of the most important factors limiting the sales of psychedelics is that they require physician supervision. To estimate the pricing and costs of Psilocybin under current regulations, consider the economics of Esketamine (Spravato). Esketamine (also called S-Ketamine), is the S-enantiomer of the drug Ketamine. Since the 1960s, Ketamine has been used or abused as an anesthetic and tranquilizer. Ketamine elicits euphoric, dissociative, and amnesiogenic effects that have made it a popular street drug. Esketamine is Johnson & Johnson's attempt to repurpose Ketamine for the treatment of MDD and TRD. While not a psychedelic, Ketamine typically is administered at specialized treatment centers and requires two hours of supervision after dosing. Due to its roughly two-week durability, one year of Esketamine treatment can consist of twenty or more administration sessions.

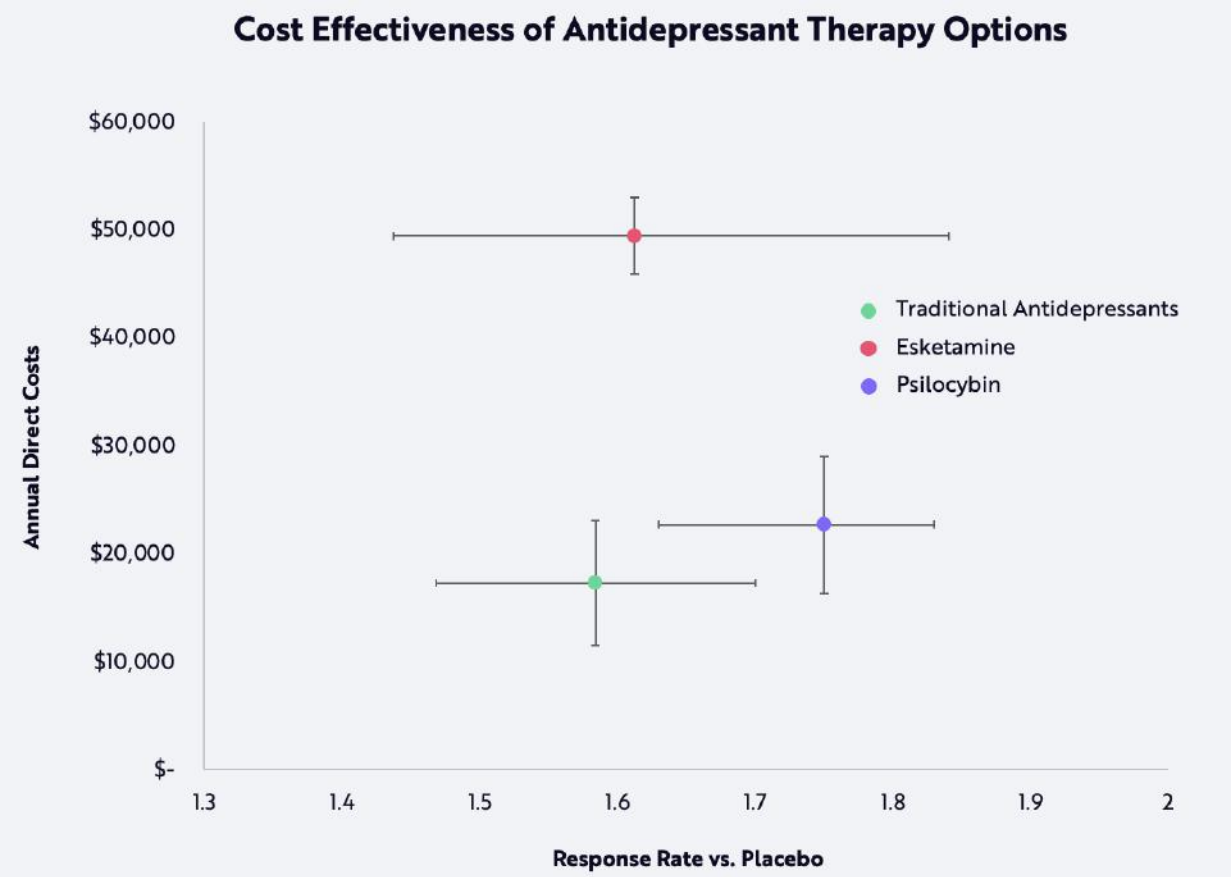
According to early clinical evidence[47],[48] Psilocybin is more efficient and effective in the treatment of moderate to severe depression due to its annual or biannual administration schedule and lower relapse frequency. The chart below illustrates Psilocybin's clear durability advantage. The one-year depression relapse rate associated with Psilocybin is roughly 2.5 times lower than Esketamine's.



Source: ARK Investment Management LLC, 2022

Forecasts are inherently limited and cannot be relied upon. Not a recommendation to buy, sell, or hold any particular security. Note: These data were aggregated from multiple studies and may not be perfectly comparable due to differences in experimental methods. Electroconvulsive therapy (ECT) was included as a non-pharmaceutical comparison. The 30-day relapse rate was used in the case of Esketamine due to low data availability on Esketamine one-year relapse rates. The end of the bar represents the median value of observations contained in selected metanalyses, and error bars represent minimum and maximum reported values.[47,49-51]

In clinical trials, the response rate to Psilocybin has been 5-10 percentage points higher than the response to Esketamine. Based on "cost per depression free day" (DFD), if the cost of administration—including physician supervision, support staff, testing—were to remain relatively fixed, we believe insurers are likely to be willing to pay $16,900 per dose of Psilocybin to achieve the same outcome as Esketamine, as shown in the scatter plot below. We assessed the response rate of different antidepressant therapies by dividing the number of improved patients in the treatment group by the number of improved patients in the control group. Based on this cost-benefit analysis, Psilocybin scored better than traditional antidepressants and Esketamine.



Source: ARK Investment Management LLC, 2022

Forecasts are inherently limited and cannot be relied upon. Not a recommendation to buy, sell, or hold any particular security. Note: While robust data are available for the cost ranges of SSRIs, TCAs, and Esketamine, the potential cost range of Psilocybin treatment is ARK's estimate. Response rates for SSRIs and Esketamine were derived from systematic reviews. However, the putative response rate for Psilocybin was based on early clinical evidence of a relatively small sample size. Importantly, since this graph represents a meta-analysis, these numbers may not be comparable due to differences in experimental methods, dosing, and demographics between studies. The error bars represent high and low ranges found for annual direct costs (pharmacy, inpatient, and outpatient costs) and response rate. [44,47,52,53]

Consider the tables below, which represent comparison-based methods for estimating Psilocybin's potential average wholesale price. As shown in Tables 1 and 2, we calculated the cost per depression-free day (DFD) by dividing the total direct costs per year (therapy/supervision and pharmacy costs) for each treatment option and adjusting that number based on the efficacy difference between the two methods as assessed by average response rate vs. placebo. Given the sums patients/insurers pay for Esketamine and conventional antidepressants, we believe that these tables suggest what payers are likely to be willing to pay per dose of Psilocybin.

Table 1	Psilocybin	Esketamine
Price/Dose	$16,900	$295
Response Rate vs. Placebo	1.75	1.67
Total Direct Costs Per Year	$48,200	$45,900
Cost/Depression Free Day	$132	$126
Efficacy-Adjusted Cost/DFD	$126	$126

Table 2	Psilocybin	Esketamine
Price/Dose (or Month)	$2,330	$219
Response Rate vs. Placebo	1.75	1.59
Total Direct Costs Per Year	$19,060	$17,261
Cost/Depression Free Day	$52	$47
Efficacy-Adjusted Cost/DFD	$47	$47

Source: ARK Investment Management LLC, 2022

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The other method we used, as shown below, provides the hypothetical price of Psilocybin when the cost per quality-adjusted life year (QALY) is fixed at roughly the midpoint between the other treatment options. We calculated the cost per treatment by adding the drug price and the estimated costs of administration (testing and supervision by trained staff).[54-56]

Table 3	Esketamine	Psilocybin	Antidepressants + Talk Therapy
Drug Price	$295	$4,300	$219
Administration Cost	$2,295	$11,500	$1,438
Change in QOL	0.219	0.230	0.269
Duration (years)	0.083	0.500	0.083
QALYs	0.018	0.115	0.022
Cost/QALY	$125,695	$100,000	$64,155

Source: ARK Investment Management LLC, 2022

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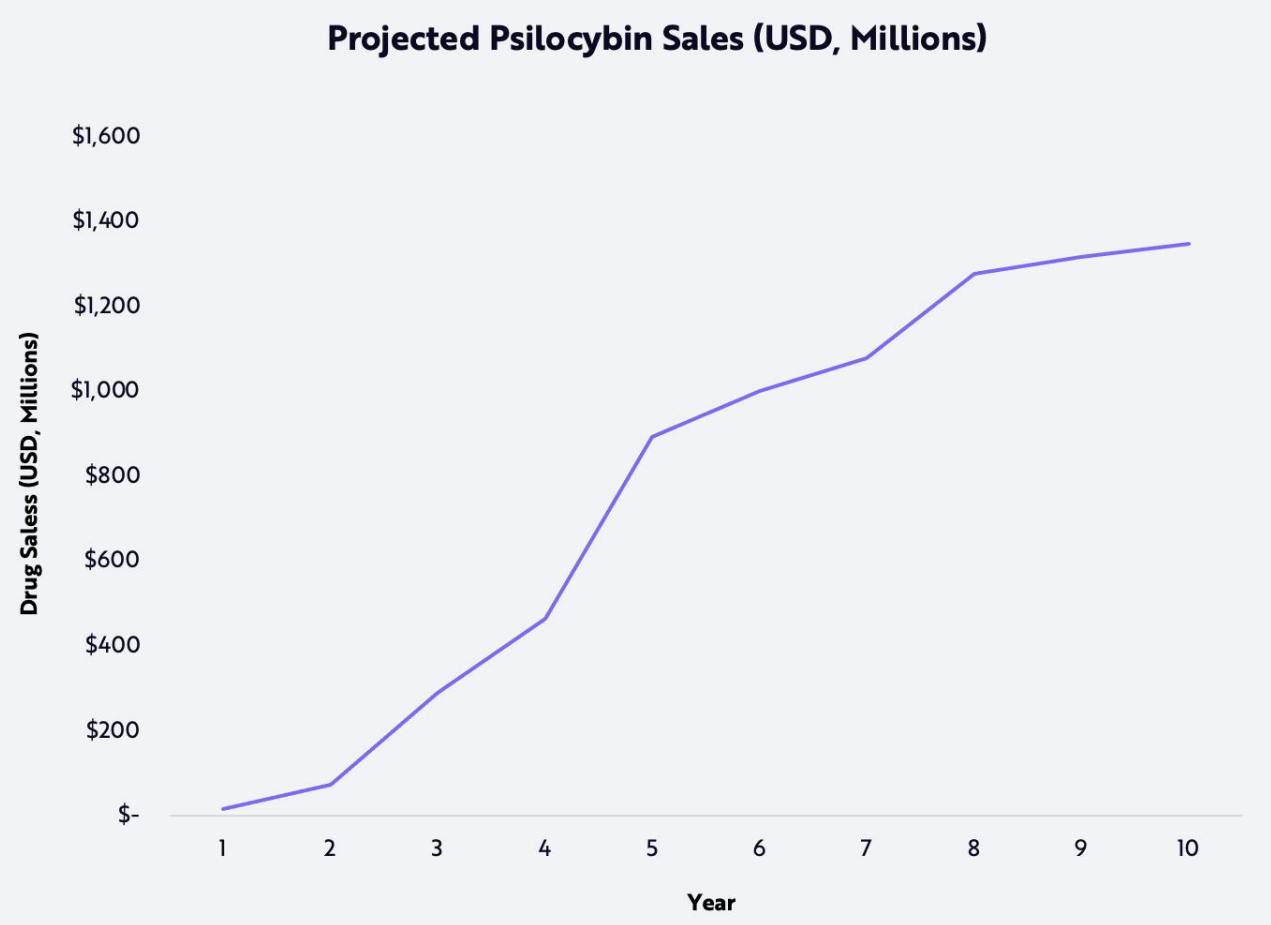
Given the current costs of administration associated with Esketamine, we believe payers would be justified in spending over $16,900 per dose on Psilocybin therapy. That price, however, reflects the inefficiencies of Esketamine's business model better than it represents a good estimation of Psilocybin's price at launch. A price of $4,300 per dose, or $8,600 per year, for

Psilocybin not only would bring the cost per depression-free day down to $62, but would also bring the cost/QALY to $100,000, which meets an important willingness-to-pay (WTP) threshold for many international markets. It also represents a rough midpoint between Esketamine and conventional treatment methods using the cost/QALY comparison.

At $4,300 per dose, ARK estimates that Psilocybin-assisted psychotherapy could reach nearly 7.5% of patients with TRD, leading to $1.4 billion in revenue at peak sales within ten years of commercialization. That could translate to a $5.5 billion-dollar, ten-year net present value for Psilocybin sales for treating MDD and TRD in the United States alone. Furthermore, the drug discovery phase typically has been estimated to account for roughly 30% of development costs.[57] If drug discovery is unnecessary for most psychedelic drugs, clear profit margin advantages are implied.

While the cost projections above may seem high, the data suggest that Psilocybin has advantages in durability, safety, and efficacy relative to other treatment options for patients with MDD. Moreover, Psilocybin has the potential to alleviate burdens associated with the direct and indirect costs to the healthcare system. The CDC estimates that depression is a major cause of productivity loss among working adults and comes at a cost of 200 million workdays lost per year.[58]



Source: ARK Investment Management LLC, 2022

Forecasts are inherently limited and cannot be relied upon. Not a recommendation to buy, sell, or hold any particular security.

Year	1	2	3	4	5	6	7	8	9	10
Psychiatrist Adoption	0.6%	3.0%	11.7%	18.7%	36.1%	40.5%	43.6%	51.6%	53.3%	54.5%
Psychiatrists	271	1,329	5,252	8,428	16,234	18,207	19,602	23,234	23,963	24,516
Psilocybin Patients	2,309	11,326	44,743	71,803	138,305	155,116	167,001	197,939	204,150	208,866
Drug Sales (USD, Millions)	$14.9	$73.1	$288.6	$463.1	$892.1	$1,000.5	$1,077.2	$1,276.7	$1,316.8	$1,347.2

Source: ARK Investment Management LLC, 2022

Forecasts are inherently limited and cannot be relied upon. Not a recommendation to buy, sell, or hold any particular security. Note: ARK built the projected pharmaceutical sales curve shown in the graph and table above by estimating the rate of psychiatrist adoption of Psilocybin. We derived data on the rates at which psychiatrists adopt new medicines from Huskamp et al. (2013), adjusted based on the published polling data that reflects psychiatrists' attitudes toward psychedelic drugs, as reported in Corrigan et al. (2021). We also attenuated the data by estimating the lag time involved with training and infrastructure build-out, assuming that 25% of a psychiatrist's average patient caseload suffers from moderate to severe depression, that 75% of those patients would not be eligible for Psilocybin due to one or more exclusion criteria, and that each potential patient would represent the yearly sale of 1.5 doses of Psilocybin at $4,300 per dose.[59-61]

In the sales curve above, we projected that Psilocybin sales could reach nearly $1.4 billion dollars per year at a price of $4,300 dollars per dose. However, this projection was made using conservative assumptions about patient eligibility and psychiatrist acceptance. The indication for which a drug is first approved often is narrower than its target population at a mature state. This is particularly true for criminalized drugs like Psilocybin, which, before receiving approval for at least one indication, must struggle with their Schedule I status. While $1.4 billion might be a

reasonable sales estimate for Psilocybin as a treatment of TRD and more severe MDD, it seems possible that the uses of Psilocybin will expand to more moderate forms of depression as psychiatrists recognize its efficacy relative to SSRIs, which today represent a $15 billion dollar market in the United States. The clinical data suggest that Psilocybin is more effective, and scientists continue to reveal ways in which the neurophysiologies of many common mental health conditions overlap.

One example of this phenomenon was the rapid growth of Fluoxetine prescriptions to 35 million in the ten years after its approval in the United States—nearly doubling the prevalence of depression at that time. Suicide rates fell from 12.5% to 11% during that timeframe, suggesting that psychiatrists were at least somewhat justified in their prolific use of Fluoxetine.[62] In the process, Fluoxetine caused a shift in prescription trends and the manner in which depression is treated. If Psilocybin were to reach a similar blockbuster status at the price we think it can command, the peak sales implied within ten years could be $3.5 billion.

Conclusions

In this article, we explored the therapeutic merits and investment prospects associated with psychedelics, specifically Psylocibin. While this abridged summary of the ongoing work on psychedelics is by no means comprehensive, we hope that it is a useful starting point for investors interested in evaluating the space. While psychedelics have the potential to improve the way psychiatric conditions like MDD, TRD, PTSD, and OUD are treated, they also come with economic, regulatory, and health risks that should be considered carefully by investors, drug developers, and patients.

Several factors could limit Psilocybin's potential price to a degree not fully considered in this paper, including: competition from Psilocybin retreat centers in places like Jamacia; competition from compounds with similar modes of action but shorter pharmacokinetics, like N,N-Dimethyltryptamine (DMT); a lack of treatment infrastructure; and barriers to adoption associated with lingering cultural stigma. While the patent law around psychedelics remains slightly ambiguous, analysts should remember that enantiopure alternatives, deuterated forms, and other chemical modifications could circumvent barriers to competition and keep drug costs high. Investors also should consider the degree to which the psychedelic-assisted psychotherapy dynamic could concentrate the economic opportunity in the drug administration side of treatment, rather than in the sale of pharmaceuticals.

In the coming years, ARK expects that scientists will continue to find new compounds that cause beneficial psychoplastogenic effects, improving the granularity with which neuroscientists understand the brain's many networks and their associated crosstalk. Forthcoming breakthroughs should reveal more about the nature of psychedelic experience and allow clinicians to diagnose mood disorders more effectively while developing more effective and safe therapeutic agents.

Through this lens, the psychedelic movement might be less a triumph against cultural stigma than a revolution in neuropharmacology. We believe psychedelics could usher in a new era of neuroscience in which the insights gleaned through functional neuroimaging over the last twenty years will be leveraged to solve some of the long-standing public health issues associated with mental illness.

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