Psychedelic Medicine

A Brief History and Current Progress

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Introduction

In modern translation, Renaissance means rebirth, revival, and recovery. And if you have been watching, even a little bit, the popular press coverage around the medicinal use of psychedelics, it is easy to see why that descriptor has been attached. After a long winter of being relegated to illegal, Schedule I drugs, nature's pharmacy of psychedelic compounds is going through a rebirth of exploration and acceptance for the treatment of an increasingly wide range of mental health issues. It has been a long time coming. After promising studies in the 1950s and 1960s showing the use of LSD and psilocybin in treating addiction, depression, and end-of-life distress, all research ended with the criminalization of LSD and psilocybin in 1970. Similarly, in the 1970s and 80s, MDMA began to see use as a therapeutic treatment for anxiety and trauma. Unfortunately, MDMA met the same fate as LSD and, with rising recreational use in the U.S., was listed as a Schedule I drug.

The scheduling of the compounds (LSD, MDMA, psilocybin) was against the protests of clinicians who used them therapeutically and would instantly lose access to the drugs. It is useful to pause and understand exactly what it means to be a Schedule I drug.

To go into this most stringent category:

1. the drug or other substance has a high potential for abuse
2. the drug or other substance has *no currently accepted medical treatment use* in the U.S.
3. the drug has a lack of accepted safety for use under medical supervision.

The researchers who fought against these classifications lost their battle. But even knowing what we did "back then," it is clear that the classification may have been more a matter of politics and national sentiment around recreational drug use and less about their therapeutic potential. They could have been classified as Schedule III, been removed from recreational circulation, and still allowed for continued therapeutic use and research. Just for comparison, cocaine and methamphetamine are Schedule II.

The full story of psychedelics' transformation from nascent therapeutic treatments to Schedule I classification is too long for this format. Still, it is told with typical storytelling prowess by Michael Pollan in his 2018 book, "How to Change Your Mind." Shared in his thoughtful, always inquisitive style, it was a bestseller and a wake-up call for many around the world on the potential impact of these compounds. For some, though, who had been "keeping the lights on" in hopes of returning these compounds to therapeutic practice, this Renaissance could not come soon enough. The tireless efforts of the Multidisciplinary Association for Psychedelic Studies (MAPS Foundation), the Beckley Foundation, and researchers like Dr. Roland Griffiths, among many others, never gave up the quest to have these compounds restored to use for their therapeutic potential.

Perhaps you might be wondering, what's the big deal? We have antidepressants and anti-anxiety medications. Isn't this a solved problem? Some current estimates suggest 10 percent of the global population face mental health issues (~800 million), and ~300 million of those specifically face depression. Thirty three percent of those individuals will be treatment-resistant, meaning no treatment for depression currently on the market alleviates their suffering. That's 100 million people.

Additionally, the global numbers for post-traumatic stress disorder PTSD) are staggering and include another 300 million individuals. PTSD isn't just about war; it's about survivors of many kinds of trauma — refugee camps, political persecution, sex trafficking — sadly the list goes on and on.

Here's the big deal: What clinicians and researchers are finding (again) is that psychedelic substances are not just treatments; they have the potential to be cures. Let's breathe that in. Individuals, who have been facing a lifetime of suffering from anxiety, depression, and trauma, might be cured. This is the part of the story that makes my hair stand on end and brings tears to my eyes. This is precisely why the psychedelic renaissance is so exciting. It gives hope to a hopeless field.

It's been almost a decade since a new antidepressant was approved in the U.S., and while these drugs were well tolerated, most were no more effective than treatments introduced in the 1980s. Current antidepressants don't work for a sizable population of those suffering from depression. Additionally, individuals may need to remain on those treatments for life.

In a sign of hope and of this new Renaissance, ketamine was recently approved for the treatment of depression in 2019. This is arguably a huge step forward in its therapeutic potential, but the drug itself has been around since 1970, primarily used as an anesthetic. While it's exciting that it is approved, it's not "new." I will quickly insert the caveat that these compounds are not a DIY cure. We are not talking (yet) about sending individuals home with a prescription! Clinicians and practitioners in this field will assert that the medicine with the right "set and setting" are currently the only way to assure the

therapeutic efficacy of these compounds and ensure that the patient has a safe and transformative experience. This in itself is exciting because it reconnects the therapeutic medicine to the therapeutic experience. Something that had been sadly separated, at least in the U.S., for a long time.

The psychedelic Renaissance is not limited to previously identified compounds. It has caused a resurgence and renewed excitement around medicinal chemistry and neuropharmacology. Perhaps we can use some of these ancient and synthetic compounds to further unlock the brain's workings and "unknot" the troublesome states of anxiety, addiction, and depression.

The Science of Psychedelic Medicine

Now that we've covered a little of the history and context setting, we will dive into the science a bit more and uncover why these compounds have the impact that has been described. It's worth taking a moment to understand a revolution that is happening within the field of neuroscience as well.

For a long time, neuroscience was split between two scales. On one hand, were the molecular neurobiologists — really digging in and understanding the composition and chemistry of the synapse, which is the major communication unit of neurons in the brain. They went to work cataloging each protein, receptor, and neurotransmitter that entered the synapse and did its work exciting, inhibiting, or modulating the firing of neurons. This was amazing work, no question. On the other hand, were the cognitive neuroscientists who were less concerned with the firing of individual neurons and more interested in the areas of the brain that "light up" during specific tasks and thought processes. They used tools like PET scans and fMRI to see which regions of the brain were specifically activated or deactivated during tasks. I have, at times in a humorous tone, called this "blob-ology" — because it really was focused on regional activation rather than the brain in concert, as a whole.

More recently, neuroscientists have been taking a more holistic view of the brain's activity, spurred in part by research on the connectome. This concept builds upon the idea that while individual regions of the brain are certainly associated with aspects or behaviors, it is really the brain as a highly interconnected network that drives our experience.

It is here where we link back up with the story of psychedelic medicines. Originally, when subjects were placed in cognitive task environments and had their brains scanned, researchers assumed that the brain was resting — or not engaged in meaningful activity when not otherwise tasked. This was proven wrong in the 2000s when it was shown that

the brain was quite active in this supposed “resting” state. In 2001, Dr. Marcus Raichle coined the term “default mode network” (DMN) — which through further research, has been shown to be active during thoughts about autobiographical information, emotions about oneself, and self-reference, among other things. Not so quiet after all! In talks, I often refer to this jokingly as the “thinking about thinking about oneself” network. It is the quintessential monkey-mind network. The work of Dr. Judson Brewer at Brown University showed that it was precisely activity in this network that decreased in the brains of experienced meditators. The DMN is a complex network with subsystems, each of which may play a unique role.

While the neural system is complex, the pieces have started to fit together. Further studies involving brain imaging in studying depression and trauma seemed to indicate that these mental health conditions may be dysfunctions of the systems in the default mode network. The brain’s ruminative nature may run amok and shift toward depressive states that it cannot break out of. And not surprisingly, both psilocybin and LSD have effects on the DMN functioning in the brain. In a first-of-its-kind study, Dr. Robin Carhart-Harris showed through brain imaging the effect of psilocybin on the brain. It reduces the activity in the DMN. Ok, now this is getting exciting.

The clinicians and researchers who began working with psychedelic compounds in the 1950s and 1960s didn’t have the tools to understand what was happening in the brain during psychedelic experiences. The DMN wouldn’t even be discovered until the next century! They just knew it worked, but they couldn’t explain why. Now, during the psychedelic Renaissance, we have the tools to put ALL of the pieces together. For a current review, see Dr. Carhart-Harris’ excellent review of the landscape.

Patients treated with psychedelics, especially those who have meaningful doses in controlled therapeutic experiences, often report something akin to “ego death” — their sense of self dissolving away, and this element is recorded as a significant clinical event. Now that we understand the role of the DMN in reinforcing our sense of self, it makes sense why these compounds can undo that. Certainly, the DMN is not the ONLY answer here, but its role seems very important both neurophysiologically and therapeutically. While I won’t delve deeply here into the variations in serotonergic receptor sub-types, it is important to note that molecular neurobiology and network-based cognitive neuroscience are now working to understand both the synaptic mechanism of these drugs and their network effects in the brain.

We are fortunate that we don’t have just one compound to explore; we have many. Included In this category are the tryptamines, known as serotonergic hallucinogens: LSD, psilocybin and 5MeO-DMT, ayahuasca (DMT) and ibogaine. MDMA, a methamphetamine compound, also targets the serotonergic system through transporter reversal, thus causing the release of serotonin at synapses. Ketamine, historically an anesthetic, is an NMDA receptor antagonist. The newer enantiomer, esketamine, has recently been

approved as a nasal spray for treatment-resistant depression. Note again: ketamine is the only currently approved treatment that is available outside of a clinical trial (e.g., by prescription in a clinic) in the U.S. The compounds, while at times causing similar effects, can demonstrate different mechanisms of action and may be useful in different therapeutic conditions. After the tireless efforts of researchers, MDMA received breakthrough therapy designation by the FDA in 2017 for PTSD and psilocybin received the same designation for major depressive disorder starting in 2018. While these designations won't change the current scheduling status of the drugs, it opens up the pathway for their eventual approval and use in the clinic. Currently, all of the compounds mentioned above are in clinical trials for addiction, anorexia, anxiety, migraines, depression, PTSD, and OCD.

In addition to the core compounds themselves, a Renaissance in medicinal chemistry now flourishes to help find either novel agonists, enantiomers, or even entirely NEW chemical entities with similar medicinal properties with a wider range of potential applications. For example, while an 8-hour psilocybin trip may be transformative, it may not be for everyone! It is important to explore shorter-acting compounds. Clinical studies currently involving microdoses of the current tryptamines are studying if the entire psychedelic "trip" is necessary to reap the resetting benefits. Can a psychedelic become 'merely' psychoactive and have the same effect? This point is particularly important because patients who have been on long-term therapies for treatment-resistant depression may need to consider other pharmacological targets, as long-term use of antidepressants makes them poor candidates for the mechanism of action utilized by psilocybin. Additionally, with the staggering numbers of individuals facing mental health conditions, there will need to be a revolution in treatment delivery that accompanies the Renaissance. Hundreds of millions of individuals would be candidates for this life-changing treatment. Some clinicians are currently contemplating a "deep experience + maintenance" combination. This means a patient would have a longer transformative experience to "reset" the brain and then a lower dose of continued treatment to ensure the brain pathways are completely rewired.

Currently, an 'in clinic' approach is advocated for the delivery of these medicines. While the treatment space is evolving, those like Field Trip Health and others are focusing on ketamine treatments for now — while paving the way for integrating other current compounds whose status may transition from illegal to prescription. The clinicians in the field are quick to remind that the "set and setting" and integration post-therapy are as important as the medicines themselves in realizing the transformative results. Outside of the U.S., retreat centers are offering similar experiences for those willing, as individuals have been for decades, to travel for access to these medicines.

I would be remiss if I didn't mention the excitement around the new companies appearing on the scene to address multiple aspects of this psychedelic Renaissance. In particular, the number of companies developing new compounds is exploding. Some companies like

ATAI Life Sciences focus on a combined approach, building a portfolio of companies to address various clinical targets. Others like CaaM Tech, Delix, Tactogen, Gilgamesh Pharmaceuticals, and Beckley Psytech (among many) target new compounds to help increase the toolkit of available compounds for clinical use. Psilocybin alpha is one of the most up-to-date sources of information on all of these companies. The most prominent psychedelic IPO this year, so far, was atai Life Sciences, entering the public markets at a >$2B valuation. Certainly a high watermark for this space.

To anchor our discussion back in reality, the most important thing is that these transformative medicines make it into the lives of the people who need them most. That is true science in the service of humankind.

In 2021, Prime Movers Lab led the Series A of Gilgamesh Pharmaceuticals, a $27mm round, and participated in the latest round from Beckley Psytech through an SPV. The Prime Movers Lab team remains deeply engaged in this area and continues to look for investments that have the potential for the most significant impact.

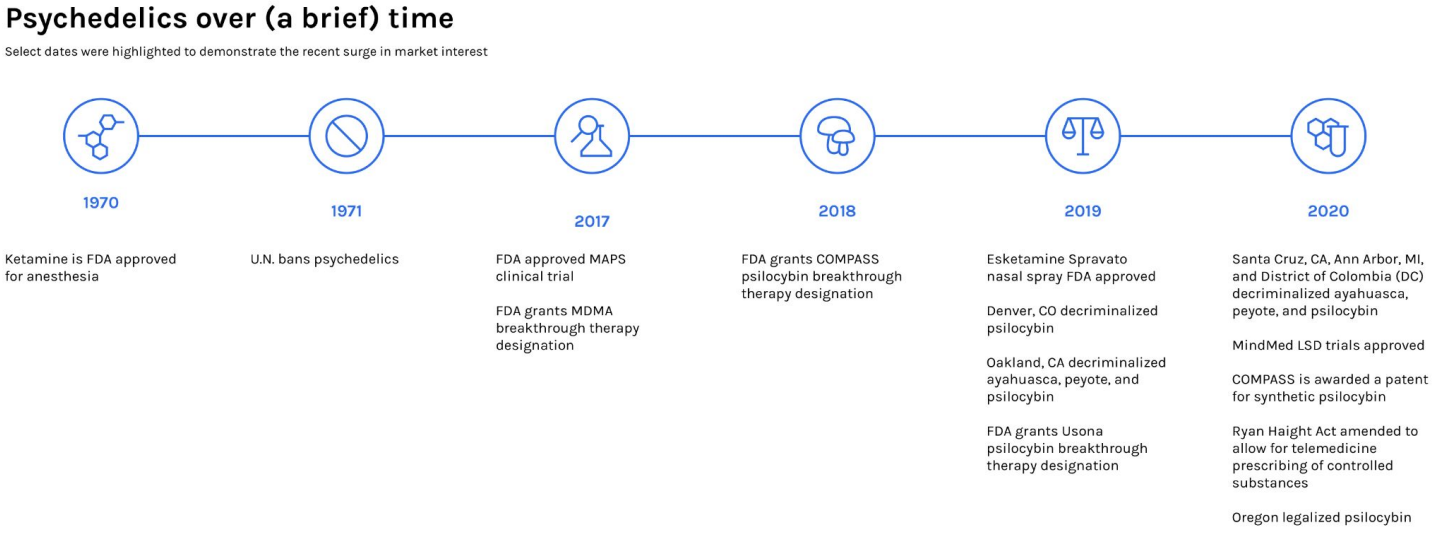
Psychedelic Therapies - Investing Landscape

As part of the Psychedelic Renaissance now occurring, companies both new and old are emerging onto the landscape. In addition, universities and research centers are beginning to address the clinical implications of this work. It is an exciting, emergent, and highly chaotic ecosystem at the moment. Lots of resources and capital are flowing in all directions.

The current work is informed and inspired by the research from many decades ago, on the use of psychedelic substances to treat a variety of mental health disorders ranging from depression, anxiety, and addiction, to trauma and other behavioral disorders like OCD. With the criminalization of these substances in the 60s and 70s, research ground to a halt. Meanwhile, the mental health landscape was dominated by a few pharmaceuticals, with varying success. There has been VERY little innovation in this arena in the last 30 years. In fact, many of the large pharmaceutical companies killed off their neuropsychiatry divisions to the detriment of mental health globally. Fortunately, they are starting to wake up again and pay attention. With the looming mental health crises - work began anew, taking a more modern look at these compounds. Sadly, the MAPS clinical trials did not restart until 2017 - a 46-year gap.

There are three things happening simultaneously in the psychedelic landscape right now.

1. **Clinical trials with existing compounds** (e.g psilocybin, MDMA as they exist today) for treatment of mental health disorders. These typically occur at universities or hospitals, under FDA approval for the trials. These studies are being used as the basis for legalizing the compounds, at least in a clinical context. The clinical trials are primarily focused on establishing the efficacy of the various "traditional" medicines. These trials are searchable through clinicaltrials.gov.
2. **The hunt for NEW compounds** (novel chemical entities) that address some of the same molecular targets as the compounds already in use but that might vary in their efficaciousness, hallucinogenic properties or other elements. A list of companies involved is provided below. This is a "hot" area, as the natural compounds have side effects or issues that may not make them perfect in the long run.
3. **Clinics building out the treatment infrastructure** for administration of psychedelic compounds. The first of these is ketamine clinics, which many assume will be quickly followed by MDMA in 2022-2023. The quality of these clinics ranges from assisted therapy to nothing more than your average sterile doctor's office. Prices can be high for full treatment (>20k) and currently are out of pocket.



History of psychedelics research in the last three decades. Source: Blossom & PSYCH - The Psychedelics as Medicine Report: Third Edition; https://psych.global/report

Legal classification of psychedelics

Drug	UN Status	US Status	Canada Status
Ayahuasca	Uncontrolled	Schedule I/ Exemptions	Schedule III/ Exemptions
Cannabis	Schedule I	Schedule I	Schedule VIII
DMT	Schedule I	Schedule I	Schedule III
Ibogaine	Uncontrolled	Schedule I	Controlled
Ketamine	Uncontrolled	Schedule III	Schedule I
LSD	Schedule I	Schedule I	Schedule III
MDMA	Schedule I	Schedule I	Schedule I
Peyote/ Mescaline	Schedule I/ Exemptions	Schedule I/ Exemptions	Schedule III/ Exemptions
Psilocybin	Schedule I	Schedule I	Schedule III

Due to FDA regulations that have been in place since the 1970s, all psychedelics in the U.S. are Schedule 1 drugs. Exemptions refer to specific use in religious ceremonies for those medicines.

Source: Blossom & PSYCH - The Psychedelics as Medicine Report: Third Edition; https://psych.global/report

Of the drugs listed above, only ketamine was approved by the FDA in 2019 (drug: Spravato. made by Janssen, nasal inhalation, practitioner administered) for severe depression. “Traditional” racemic ketamine (injected) is also used off-label for depression and other disorders. Ketamine clinics are now dotting the globe taking advantage of this opportunity. We will discuss the clinic environment later. There are individual FDA approvals for specific clinical trials, as approved for a specific topic and indication.

Because of the overwhelming clinical reports of the efficacy of the compounds, very high profile institutions have begun work and are starting centers to address this topic, including Johns Hopkins University, Imperial College London, UW-Madison, NYU Langone, Yale, and UC Berkeley. These institutions are not just participating in the research but have initiated Centers of Excellence to attract and retain talent and attract donation dollars to these extremely important topics. This research is far from fringe.

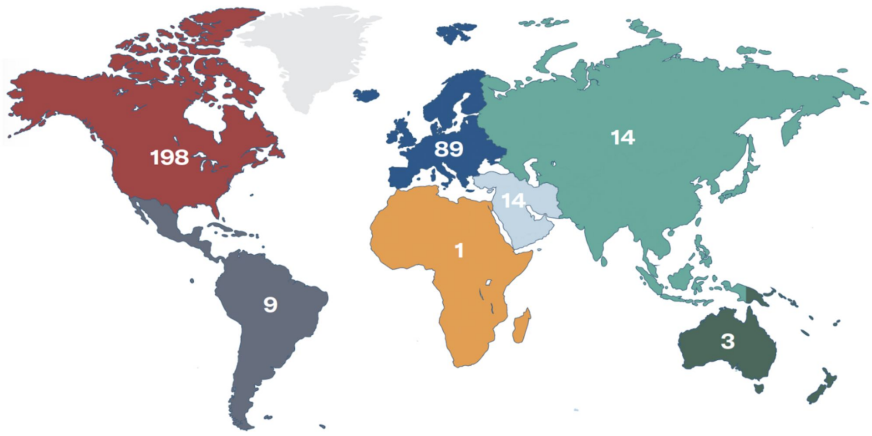
Founding of dedicated psychedelic research centers

Year	University Research Centers Status	Seed Funding
2019	Centre for Psychedelic Research at Imperial College London	$4 million
2020	Center for Psychedelic and Consciousness Research at Johns Hopkinds University	$17 million
2020	UC Berkeley Center for the Science of Psychedelics	$1.25 million
2021	Center for Psychedelic Psychotherapy and Trauma Research at Mount Sinai	$2.1 million
2021	Center for the Neuroscience of Psychedelics at Mass General	
2021	UCSF Neuroscape Psychedelics Division	$6.4 million
2021	Translational Psychedelic Research Program at UCSF	$3.4 million
2021	Project on Psychedelics Law and Regulation at Harvard Law School	

Dedicated centers for the study of psychedelic medicine research, Source: Blossom & PSYCH - The Psychedelics as Medicine Report: Third Edition; https://psych.global/report

The ongoing clinical research does NOT mean the compounds are widely available. They are just available through the auspices of clinical trials. Canada has started to approve compassionate use for some compounds (e.g. psilocybin) for individuals with terminal cancer. The Netherlands has some of the most permissive laws for using these compounds, but their use is restricted to the Netherlands.

Total number of clinical trials since 2000



NORTH AMERICA		LATIN AMERICA		EUROPE		AFRICA	
MDD	83	MDD	3	MDD	23	TRD	1
TRD	31	TRD	6	TRD	16		
PTSD	27	SUD	1	PTSD	5		
ANXIETY	9			ANXIETY	2		
SUD	10			SUD	5		
EATING DISORDERS	4			EATING DISORDERS	1		

MIDDLE EAST		ASIA		OCEANIA	
MDD	8	MDD	11	MDD	2
TRD	1	TRD	1	TRD	1
PTSD	3				

Location of ongoing clinical trials in psychedelic research. Source: Blossom & PSYCH - The Psychedelics as Medicine Report: Third Edition; https://psych.global/report

Health conditions and the psychedelic substances with the potential to treat them

Health Condition	Psychedelic Substance								
	Psilocybin	LSD	MDMA	Ketamine	Ibogaine	Ayahuasca	DMT/ 5-MeO-DMT	Mescaline/ Peyote	Salvinorin A/ Salvia
Depression (MDD) (TRD)	✓	✓	✓	✓		✓	✓	✓	✓
Bipolar disorder				✓					
Suicidal Ideation				✓					
Anxiety	✓	✓	✓	✓				✓	✓
Autism (social anxiety)			✓	✓					
PTSD	✓	✓	✓	✓		✓	✓	✓	
Eating Disorders			✓	✓		✓			
Alcohol Use Disorders	✓		✓	✓		✓			
Opioid Use Disorders				✓	✓	✓			
Chronic Pain			✓	✓					
ADHD		✓							
Cluster Headaches	✓	✓							
Stroke							✓		
OCD	✓			✓					
Inflammation		✓		✓				✓	

Potential combinations of psychedelic substances and their mental health targets. Source: Blossom & PSYCH - The Psychedelics as Medicine Report: Third Edition; https://psych.global/report

There is some tension in the practitioner field surrounding intellectual property developed around these “natural” medicines. Some practitioners are seeking to prove their clinical efficacy and use the compounds “as they are.” A fraction of practitioners oppose the commercialization occurring and are concerned about unscrupulous attempts to claim the intellectual property. The traditional compounds themselves are not patentable in their original form. Other practitioners, who perhaps may not come from the psychedelic community but are mental health practitioners and psychiatrists, welcome additional innovations because not all patients may want such comprehensive, transformative experiences. They may simply wish to have relief from their current suffering in a more accessible form. In addition, some compounds can’t be used with individuals who are on some prescriptions for depression, etc. (selective serotonin reuptake inhibitors: SSRIs). Thus, some practitioners see the innovation as opening UP the treatment options to more individuals, not harming the sanctity of plant medicine. There is likely room for both, but there is tension. From the venture investing side, the emphasis has been on novel chemical entities and newly protectable IP. However, given the vigorous activity in this space, it remains to be seen how it will shake out in the end.

With the absence of the typical big pharma players in the ecosystem, emerging “new pharma” companies have moved in to take up that interest, and frankly, languishing intellectual resources available on the market. ATAI Life Sciences is one of the most notable players on the stage right now, a German company founded by Christian Angermeyer in 2018. ATAI has a holding company approach, where they either start or take controlling positions in other psychedelic startups. They have been scooping up talent, companies through M&A, joint ventures, etc. The table below is a current listing of their company holdings. Note: Perception (Arketamine) was the previous company of the current CEO of Gilgamesh Pharmaceuticals, a Fund 2 company for Prime Movers Lab. In addition, Kures was founded by Gilgamesh Co-founder and medicinal chemist Andrew Krugel.

ATAI Life Sciences (ATAI), a German company, went public in June 2021 through a traditional IPO. Their current market capitalization is ~$2.1B. ATAI is also a majority shareholder in COMPASS Pathways (CMPS), which also publicly trades on the NASDAQ, with a $1.2B market cap as of Oct 2021. COMPASS, a U.K. company, was founded in 2016, and seed-funded by Christian Angermeyer in 2017, and eventually rolled into the ATAI portfolio. It went public prior to, and separate from, the ATAI IPO.

ATAI Company	Main Compound	Indication	Stage of Clinical Development
COMPASS Pathways	COMP360/Psilocybin	Treatment Resistant Depression	Phase 2
Perception Neurosciences	PCN-101/R-Ketamine	Treatment Resistant Depression	Phase 2
Recognify Life Sciences	RL-007	Cognitive Impairment assoc. Schizophrenia	Phase 2
DemeRX IB/NB	DMX-1002/Ibogaine DMX-1001/Noribogaine	Opioid Use Disorder	Phase 1 (IB)/Preclinical (NB)
Gaba Therapeutics	GRX-917/Deuterated etifoxine	Generalized Anxiety Disorder	Phase 1
Neuronasal	NN-101/N-acetylcysteine	Mild Traumatic Brain Injury	Pre-clinical
Viridia Life Sciences	VLS-01/DMT	Treatment Resistant Depression	Pre-clinical
EmpathBio	EMP-01/MDMA Derivative	Post Traumatic Stress Disorder	Pre-clinical
Revixia Life Sciences	RLS-01/Salvinorin A	Treatment Resistant Depression	Pre-clinical
Kures	KUR-101/Deuterated Mitragynine	Opioid Use Disorder	Pre-clinical
PsyProtix	Precision psychiatry therapeutics	Treatment Resistant Depression	Clinical Stage

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ATAI is a powerhouse! Other companies that are late-stage and nearing a go-public status include Eleusis, founded in 2013 (one of the oldest), and Beckley Psytech, founded in 2019 and associated with the Beckley Foundation, one of the most esteemed foundations in the psychedelic medicine space. Prime Movers Lab participated in Beckley Psytech's most recent round through an SPV. We expect there to be more IPO and SPAC activity in this domain in the next two to three years. This year the Conscious Fund did announce the Conscious Acquisition Company for the explicit purpose of taking companies in the psychedelic medicine domain public. A first acquisition target has not yet been announced.

Although no "big pharma" companies have yet made acquisitions in this space, there are some interesting signs. Jazz Pharmaceuticals acquired a cannabinoid molecule drug company, GW Pharma, for $7.2B in May of 2021. This indicates interest in using these types of plant-derived drugs for critical neurological conditions, in this case, epilepsy. Timing-wise, the cannabinoid drug development market is ahead of psychedelics but proves a useful benchmark. Similarly, ATAI portfolio company, Perception Neurosciences, has recently struck a deal with Japan-based Otsuka Pharmaceuticals for a $20mm upfront payment and licensing in Japan to bring a next-generation ketamine treatment to Japan. We expect the "acquisitiveness" of big pharma to heat up considerably as the new novel drug compounds begin Phase 1 trials and show efficacy. By all accounts, these are the data they are waiting for to make moves in this domain.

Because of the energy, investment, and moves in this space, smaller companies have gone public quickly (whether or not they are ready.) This is particularly prevalent in Canada, where many of the traditional compounds are Schedule 3 (vs. Schedule 1 in the U.S.), and so the regulatory environment is more favorable. Unfortunately, predatory investment banking practices also seem rampant. This appears to be related to how the cannabis industry rolled out in Canada, as many are the same players. These companies are not seen as good targets for venture investing, as their exit profiles are modest.

However, they may be downstream targets for relatively inexpensive acquisitions if their compounds and clinical results look promising.

The following companies have gone public within the last few years and make up the publicly traded element of the psychedelic investing ecosystem. Many of these have gone public through the Canadian exchanges, but several are available through U.S. trading providers. More recently, companies have been uplisting to the U.S. exchanges to get better coverage and trading volume. Most remain in the sub $5/share category, with a few exceptions. AdvisorShares has recently launched a Psychedelics ETF (PSIL), an actively managed fund, covering some of these companies. PSYK from Horizons (CAN) is an index fund of popular North American listings, and PSY Defiance is an ETF that holds psychedelics and cannabis companies. PSY Defiance has a minimum market cap of $75mm, so many smaller players are excluded.

TSX Venture Exchange	Field Trip Health (FTRP) Numinus (NUMI)	Small Pharma (DMT) PsyBio Therapeutics (PSYB)
NEO Exchange	MindMed (MMED) Cybin (CYBN) Mydecine Innovations (MYCO)	Filament Health (FH) Awakn Life Sciences (AWKN) Ketamine One (MEDI)
NASDAQ	Compass Pathways (CMPS) MindMed (MNMD) ATAI Life Sciences (ATAI)	Enveric Biosciences (ENVB) Field Trip Health (FTRP)
NYSE	Cybin (CYBN)	
Canadian Stock Exchange	Mindset Pharma (MSET) Revive Therapeutics (RVV) HAVN Life Sciences (HAVN) Red Light Holland (TRIP) Braxia Scientific (BRAX) Mind Cure Health (MCUR) Entheon Biomedical (ENBI) Better Plant Sciences (PLNT) Tryp Therapeutics (TRYP) New Wave Holdings (SPOR) Lobe Sciences (LOBE) PharmaTher (PHRM)	Hollister Biosciences (HOLL) Bright Minds Biosciences (DRUG) Silo Wellness (SILO) Novamind (NM) Neonmind Biosciences (NEON) Levitee Labs (LVT) PharmaDrug (PHRX) Psyence Group (PSYG) Optimi Health (OPTI) Psyched Wellness (PSYC) Wesana Health (WESA) BetterLife Pharma (BETR)

Many companies that are focusing on the delivery of psychedelic medicines through clinics are also publicly listed. The psychedelic “retreats” are typically conducted OUTSIDE of the U.S., although sites in more legally permissive states are listed. Many of the clinics are working towards establishment in state and local jurisdictions that may be more favorable.

Again, Schedule 1 compounds are still illegal, so the states have been focused on decriminalization statutes and reduced enforcement. The following is a list of companies affiliated with the psychedelic clinical experience, including the more traditional “set and setting.” Field Trip Health has been most active in this space and has nine clinics open globally, with more on the way.

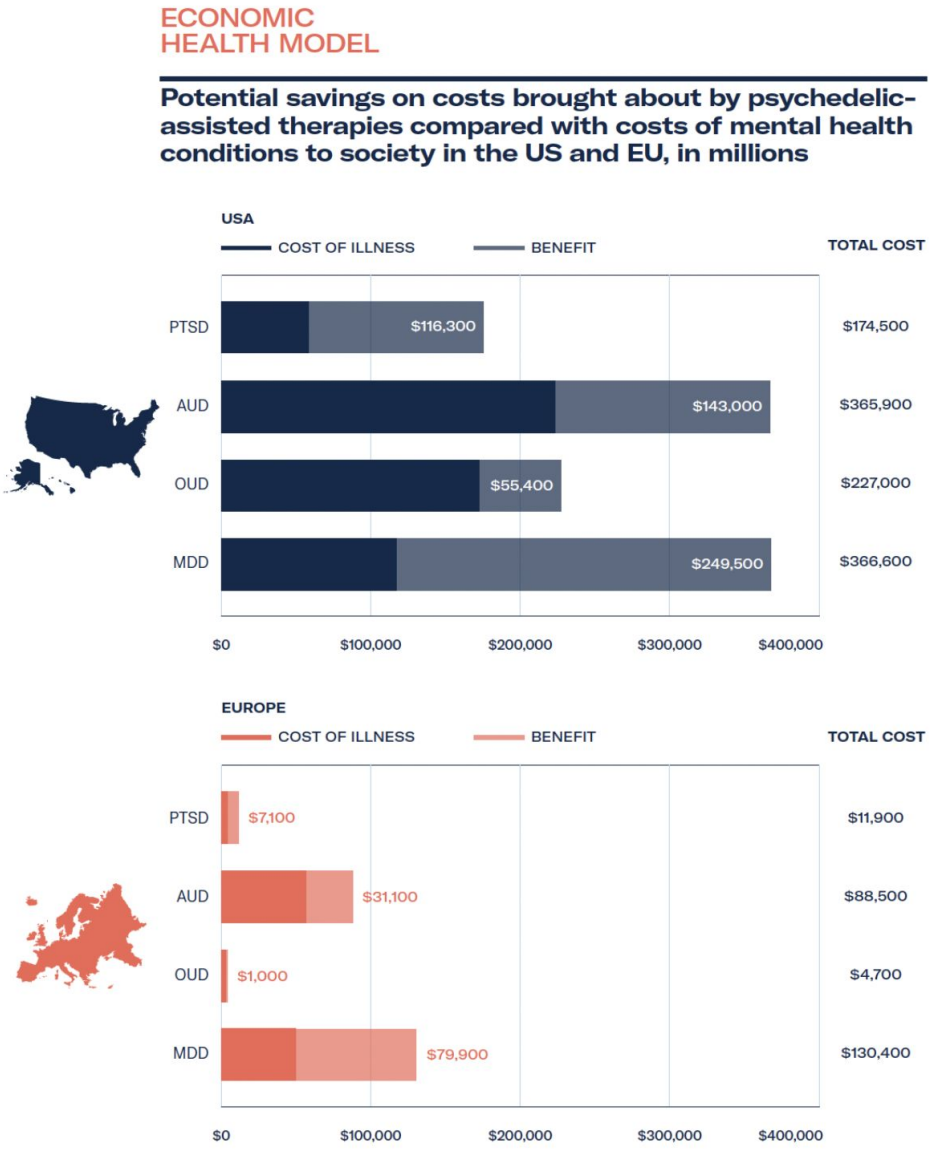
Company	**Clinic Type**
Field Trip Health (FTRP)	Ketamine Clinics
Braxia Scientific (fka Champignon Brands)	Ketamine Clinics
Novamind	Ketamine Clinics, psilocybin retreats
Wake	Psilocybin retreats
MycoMeditations	Psilocybin retreats
Eleusis	Ketamine Clinics
Numinus	Ketamine Clinics
Synthesis	Psilocybin retreats

“Vanilla” ketamine clinics, with less of a focus on the “set and setting,” are numerous. At last count, there were over 350 ketamine clinics in the U.S., and growing. There is a lot of concern among practitioners with this rapid uptick. But the availability to administer ketamine “off label” in health and wellness clinics has prevailed. Many of the clinics are more similar to a dentist’s office than centers of healing. The companies mentioned above are working to integrate healing into healing environments, but there is a LOT of work to do here. These are complicated questions and must be taken seriously, both in investing and execution. And although ketamine is legal, it is currently one of the most deadly. It is a powerful anesthetic and, if mishandled, can result in death. Issues with ketamine clinics have the potential to set the field back if there are incidents.

Mental Health - Market

Sadly, mental health conditions are on the rise globally, and many issues, including major depressive disorder and addiction, are recalcitrant to pharmaceutical interventions. The market for these therapies and solutions will only increase in the future. The numbers are stunning and require urgent attention. The cost of these illnesses is in the hundreds of billions for treatment, which only increases with the cost of time and productivity lost.

Ketamine Clinics in the US, map from askp.org/directory



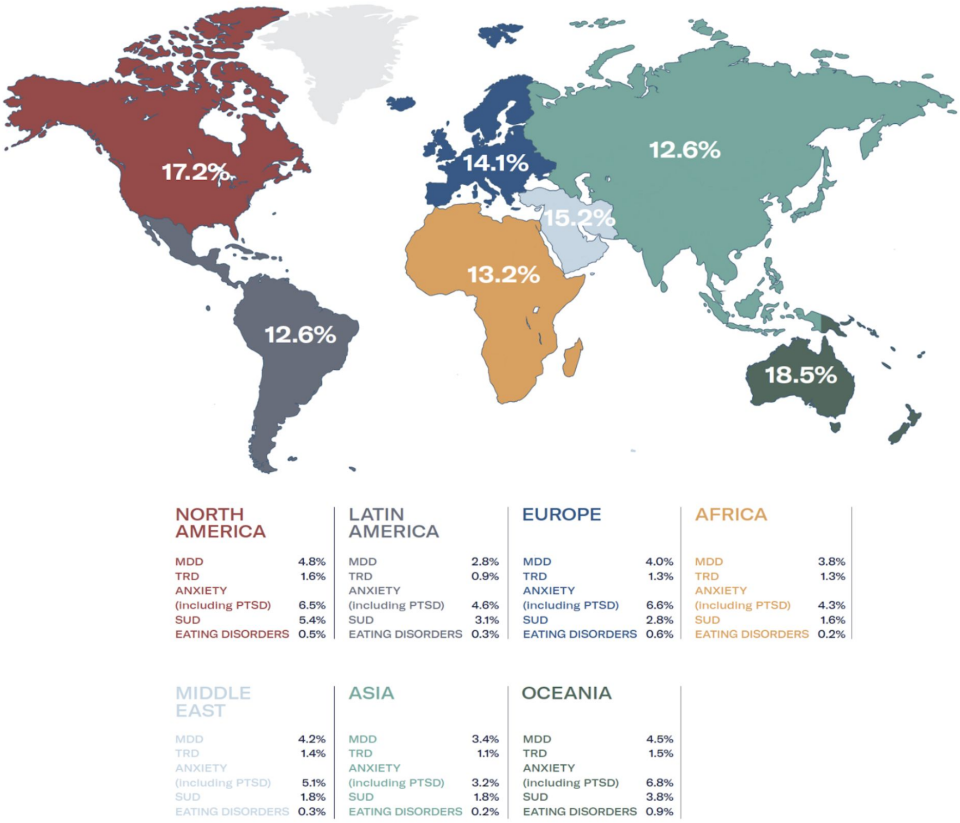
Cost and benefit of treatment for common mental health conditions in the U.S. and Europe. Source: Blossom & PSYCH - The Psychedelics as Medicine Report: Third Edition; https://psych.global/report

Facts about mental health conditions

People with mental health conditions (millions)	Mental Health Conditions
970	Substance abuse disorders
282	Anxiety disorders
258	Major depressive disorder (MDD)
77	Treatment-resistant form of depression (TRD)
269	Post-traumatic stress disorder (PTSD)
105	Alcohol use disorder (AUD)
70	Other substance use disorder (SUD)

Global prevalence of common mental health conditions, Source: Blossom & PSYCH - The Psychedelics as Medicine Report: Third Edition; https://psych.global/report

Percentage of mental health and substance use disorders (2017)



Percentage of the global population suffering from common mental health conditions. Source: Blossom & PSYCH - The Psychedelics as Medicine Report: Third Edition; https://psych.global/report

The number of individuals suffering from mental health conditions is staggering. Since many are untreated or treatment-resistant, novel therapies are a welcome addition to this situation.

As “big pharma” moved out of neuropsychiatry in the 2000s, it left a big gap in the market. The development in psychedelics and related compounds are addressing that gap. Simply put, the goal of the work with psychedelics is to cure mental health disorders. And that is what the founders, companies, practitioners, and clinicians are working towards every day.

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