PSYCH:
THE PSYCHEDELICS AS MEDICINE REPORT

Third Edition

OCTOBER 2021

POWERED BY

Blossom

About

The Psychedelics as Medicine Report | About Us

Unlocking the commercial potential of psychedelics.

A premium business-to-business media and content platform for the psychedelic science and healthcare industry.

ABOUT PSYCH

PSYCH is a premium business-to-business media and content platform for the psychedelic science and healthcare industry.

As our collective understanding of and attitudes towards psychedelics shift dramatically, we are witnessing a global rise in clinical trials, academic research and commercial investment. Psychedelics are poised to disrupt the way we approach healthcare.

The use of psychedelics as medicine has opened up a new industry growing exponentially at a rapid pace.

PSYCH tracks key psychedelic players, innovations and milestones, providing trustworthy insights to help investors cut through the noise and identify real opportunities.

PSYCH provides a coercive perspective on the commercial impact of changing global regulations, drug discovery and corporate activity. We connect operators to a qualified audience with access to capital, ready to support industry growth and help them achieve their goals.

PSYCH unlocks the commercial potential of psychedelics.

PSYCH is part of Psych Capital Plc.

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Making psychedelics as medicine accessible.

Empowering our partners to make better business decisions.

ABOUT BLOSSOM

As psychedelics move from the fringes of society to dinner table conversation, there is a need to know how they can help the most people. Which psychedelic will help who, when and where? Who will we be able to trust, and what is 'state of the art' in psychedelic research? When can we expect psychedelics as medicines to scale?

Blossom is the premier location where those working with psychedelics find insights that help them to turn psychedelics into medicine to improve the mental health of billions of people.

Blossom speeds up the development of psychedelics as medicine. We help operators, investors, researchers and policymakers make informed decisions by providing data, information, and insights on research, companies, public and governmental attitudes towards psychedelics as medicine.

As psychedelics leave the lab and shape to become the next breakthrough in medicine, Blossom connects clinical trials with the companies commercialising the results. We are building the bridge between psychedelic invention and wide-spread availability.

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ACCESS OUR DATABASE
blossomanalysis.com | floris@blossomact.com

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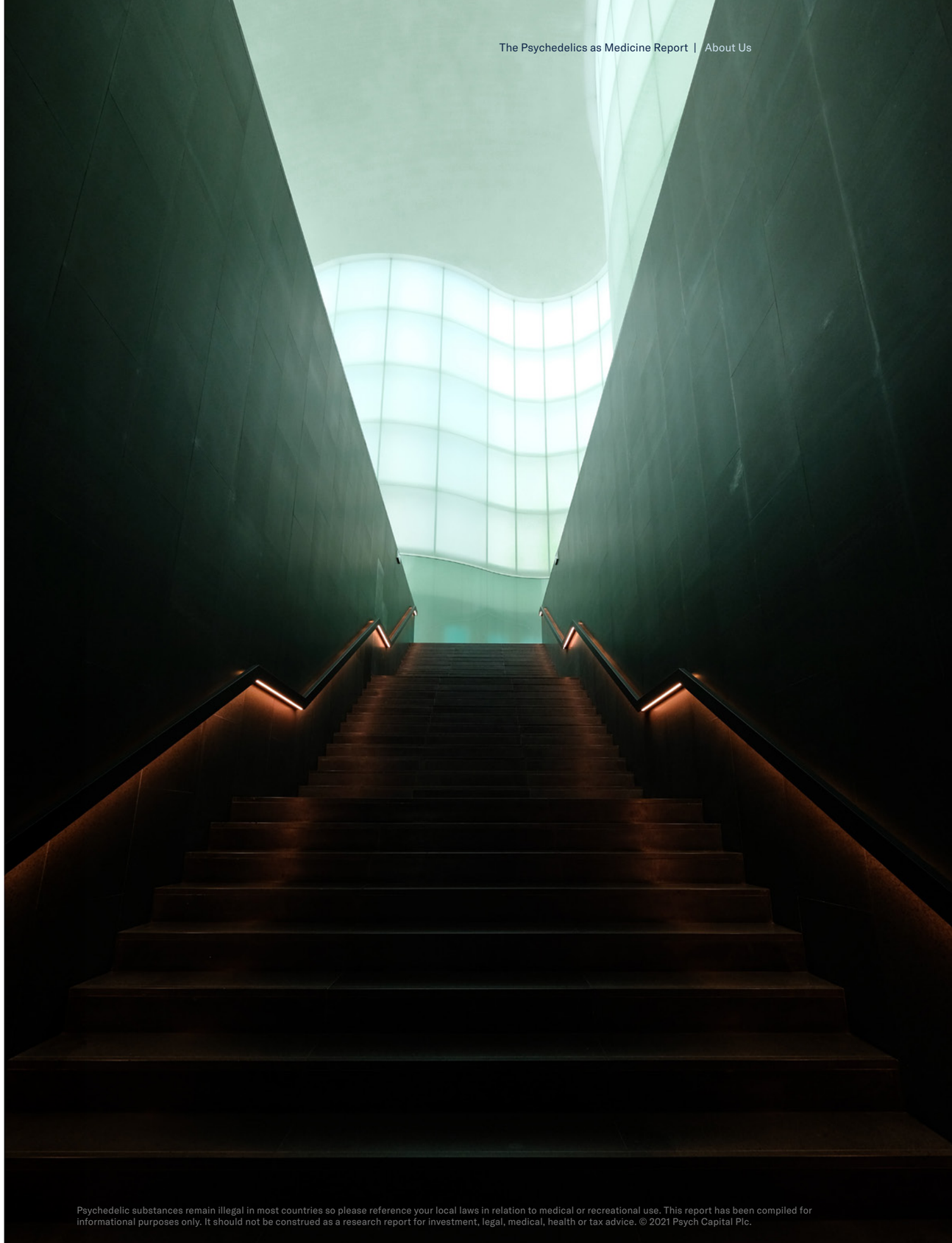

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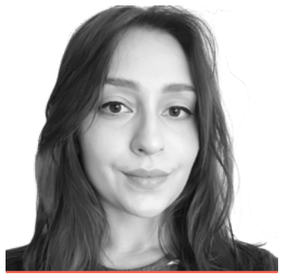
TEAM

Our joint team works with industry-leading psychedelic companies, forward-thinking investors and global policymakers to unlock psychedelics as medicine.

William Potts
CEO
Psych Capital Plc.

Floris Wolswijk
Director
BLOSSOM

Russell Cafferty
Communications Lead
PSYCH



Beriwan Ceren
Associate
Psych Capital Plc.

Stephen Murphy
Co-founder
PSYCH

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CONTACT DETAILS:

London
A: 17 Hanover Square
London W1S 1BN
United Kingdom

info@psych.global
@psychglobal_
psych.global

info@blossomact.com
@blossomact
blossomanalysis.com

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SPONSORSHIP OPPORTUNITIES

PSYCH is the trusted source for data and information on established and burgeoning psychedelics market. PSYCH produces thought-leading industry reports, conferences and a weekly industry newsletter circulated to 25,000+ operators, investors and professionals.

If you would like to partner with PSYCH and access the largest B2B audience in glboal psychedelics, please contact our Global Sponsorship Manager, Charlie Walker, charlie.walker@psych.global

Sponsorship with PSYCH is a unique opportunity to promote your business and brand to influential figures in the blossoming psychedelics' market. Our research, data and content reach key stakeholders in the industry, from pharmacologists and therapists to politicians and producers of psychedelic medicine. As companies and investors compete for a foothold in the market, this is an invaluable opportunity to put your brand front and centre in the industry's most influential reports and conferences.

Charlie Walker
Global Sponsorship Manager
PSYCH

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Table of Contents

The Psychedelics as Medicine Report | Table of Contents

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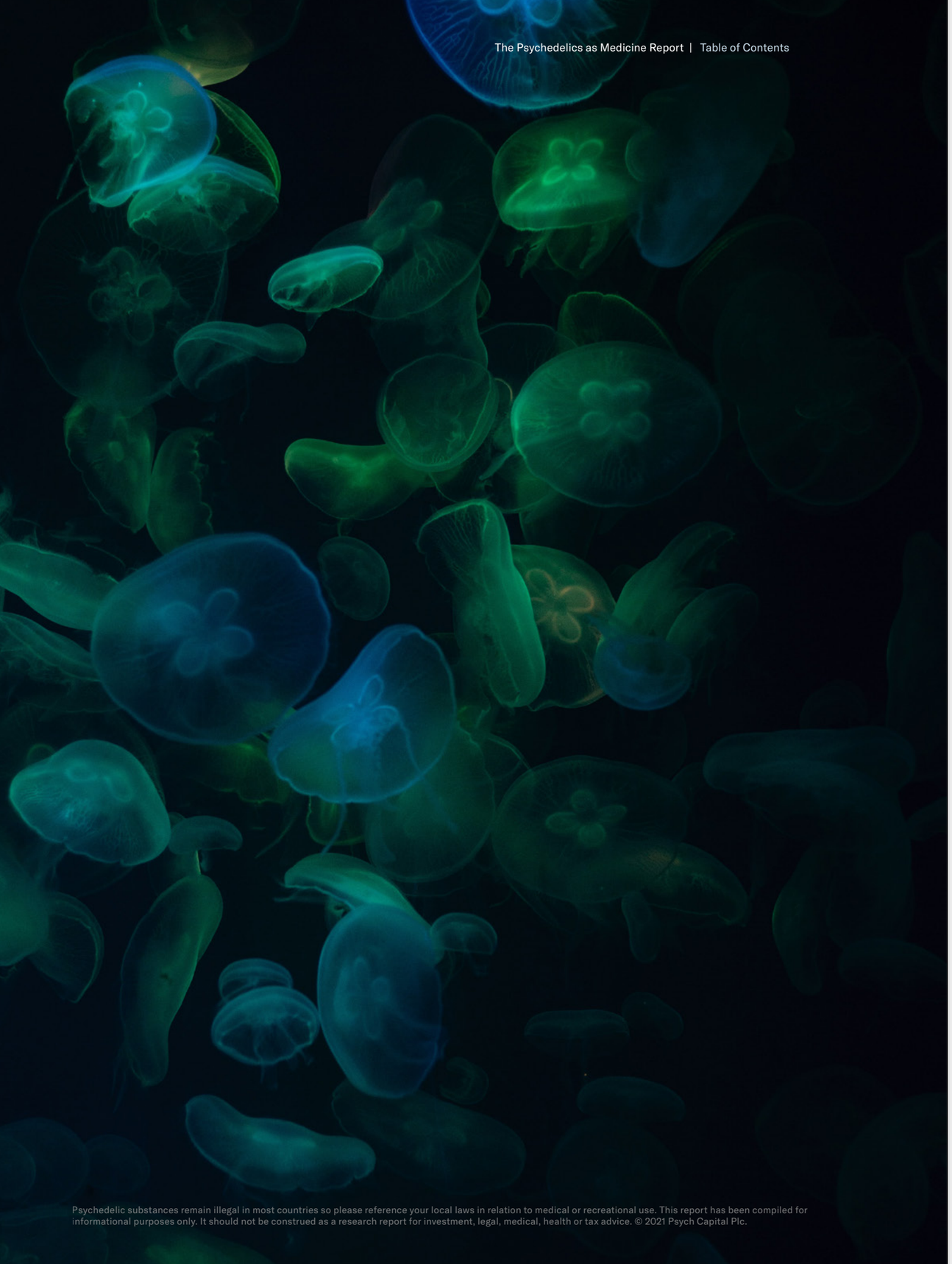

The Psychedelics as Medicine Report | Table of Contents

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Introduction

William Potts,
CEO
Psych Capital Plc.

PSYCH is proud to bring you the third edition of The Psychedelics as Medicine Report, profiling all major psychedelic drugs, both naturally derived plant-based varieties such as psilocybin, ibogaine, ayahuasca and mescaline, along with those synthetically manufactured in laboratory settings, such as LSD (lysergic acid diethylamide), ketamine, MDMA (3,4-Methylenedioxymethamphetamine) and novel second-generation psychedelics.

A year after the release of the second edition in September 2020, the world is still grappling with the COVID-19 pandemic. All of us have collectively lived through unprecedented times as the world has stood still for more than a year. Not only was our physical health in danger, but the looming threat and months-long lockdowns has also had a severely negative impact on our collective mental health. At the same time, the immensely quick development of effective vaccines has offered us hope for the future. A future where we will not only be able to tackle threats from outside but will also be able to improve the mental health of billions.

Once given to more than 40,000 patients, psychedelics were banned from the psychiatrist's office in the Convention on Psychotropic Substances of 1971. These political decisions were a result, not of the danger of psychedelics, but as a response to the 'hippie' counterculture of the 1960s. Soon after they were banned, research into psychedelics became all but impossible.

Now, 50 years later, we are in the midst of a psychedelic renaissance. A wave of high-quality research has prompted renewed interest in psychedelics as medicine. Whereas psychedelics may have never left the general public, they are now being rediscovered by researchers, entrepreneurs, investors, and before too long, patients.

Our fully updated report will present you with an expert overview of the market opportunity that psychedelics as medicine offer. It identifies the regulatory landscape and provides unique insights into consumer and healthcare providers' attitudes, and outlines which psychedelics are poised to disrupt conventional treatments for a wide array of debilitating mental health conditions, affecting hundreds of millions of people worldwide.

Finally, it offers key insights into the extraordinary opportunities that psychedelics will present to early movers in this nascent industry, including interviews with pioneering experts already operating in the therapeutic psychedelics' space.

We hope you enjoy reading the latest edition of The Psychedelics as Medicine Report.

LEAD SPONSOR FOREWORD

Florian Brand
Co-founder and CEO
atai Life Sciences

It's been a memorable year for our team at atai: COVID-19 has remained a huge challenge globally (particularly on the mental health front) but – as individuals and as a company – we have been buoyed by atai's stellar growth and successful IPO. We are continuing to build a diverse portfolio in an industry with potential for growth, and I believe that we are well situated to continue advancing our bold vision—to heal mental health disorders so that everyone everywhere can live a more fulfilled life.

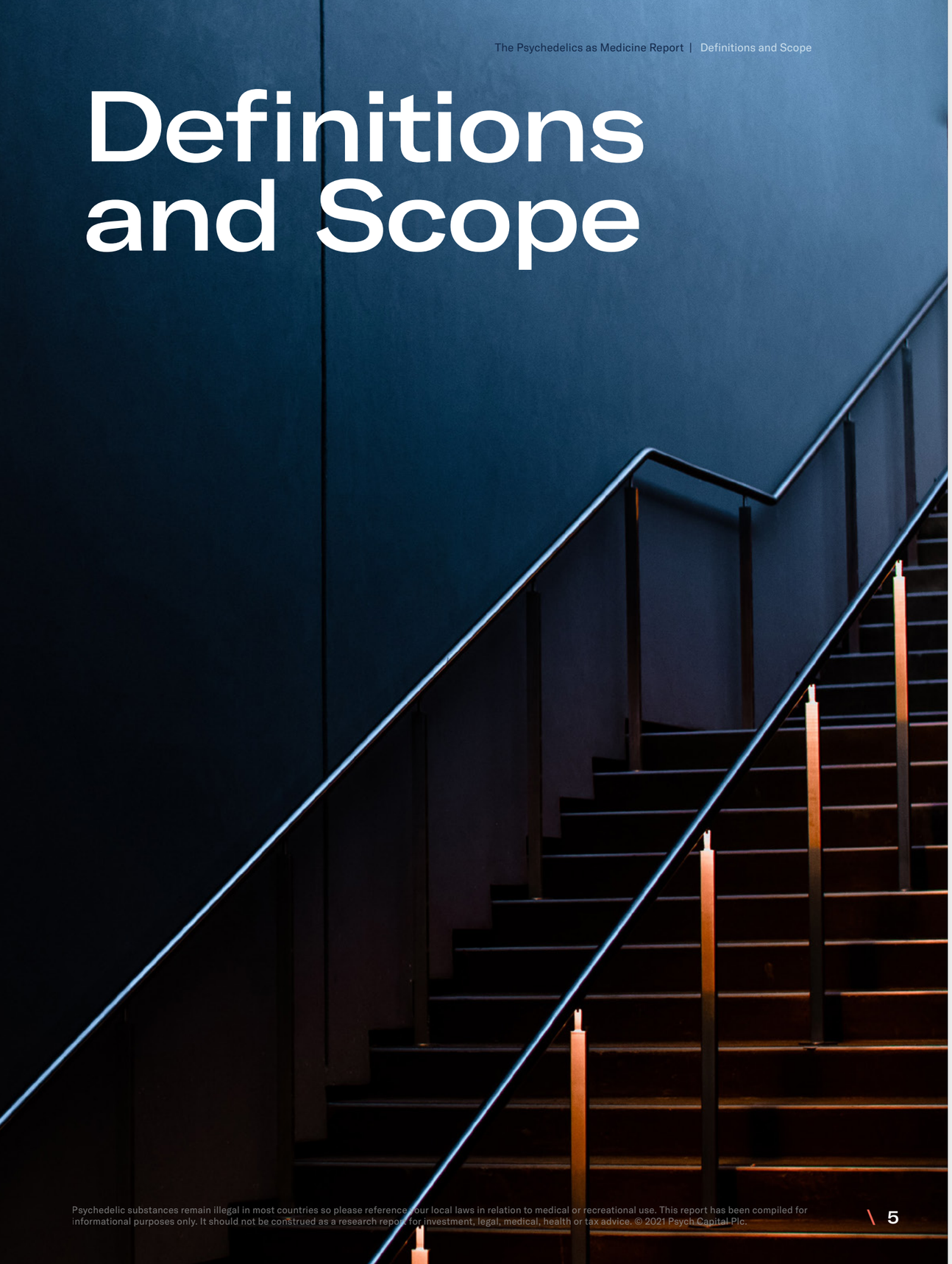
Pandemic & the most vulnerable:
Prior to COVID-19, we felt strongly that the hundreds of millions of people living with (often undertreated) mental health disorders constituted a global crisis. Billions suffering, millions not responding to current treatments, trillions of dollars lost. The knock-on effects are huge: the CDC recently reported an almost 30% increase in overdose deaths in the U.S., with the death toll close to 93,000 in 2020. COVID-19 was known to impact the most vulnerable, but the stats bring new meaning to that fact.

Growth & recognition:
In the midst of this pandemic, we've continued to build. On the back of a $157 million Series D financing round in March, we launched an initial public offering in June raising approximately $259 million in gross proceeds. In addition to our successful IPO, we are proud of numerous accomplishments in 2021. Our ambitious partnering efforts led to the first major partnership between a company developing psychedelics and Big Pharma with a licensing deal between atai's portfolio company, Perception Neuroscience and Otsuka, an industry leader in innovative mental health therapies. We also take pride in our strategic partnership with IntelGenx on novel transmucosal delivery technologies, EmpathBio's partnership with Bionomics on PTSD and, most recently, the launch of InnarisBio in partnership with the University of Queensland.

With this impressive and growing commitment to high quality collaborations, I believe that our distributed business model provides a foundation to enable us to capitalize on the efforts of our exceptional development team to progress our programs.

For too long, we have been reliant on limited treatment options for patients suffering from mental health disorders, while potentially useful treatment modalities, including psychedelic compounds, have been overlooked or underused. Like all those who have contributed to this year's Psychedelics and Medicine report, we believe that it's high time patients had access to more innovative treatments. I'm confident that atai will be a leader in this movement aiming to bring enormous benefit to patients, their families and loved ones, and the world.

Definitions and Scope



The Psychedelics as Medicine Report | Definitions and Scope

DEFINITIONS

The psychedelic substances profiled in this report are either naturally occurring, such as psilocybin, ayahuasca and ibogaine; or, like LSD and MDMA, are (semi-)synthetically manufactured in a laboratory setting. Naturally occurring psychedelics, such as psilocybin, can also be synthetically manufactured. Novel psychedelic compounds can also be synthesised based on existing substances.

Serotonin (5-HT)

Serotonin is a crucial hormone found in the brain, gut, and throughout the central nervous system (CNS). In the brain, it serves a role as a neurotransmitter, or neuromodulator, and is involved in functions related to mood, cognition, learning, memory and happiness. Many conventional antidepressant drugs work by selectively inhibiting the reuptake of serotonin (SSRIs). Through that process, there is more serotonin available to improve the transition of messages between neurons. Many psychedelics work by agonising, binding to serotonin receptors, especially in neocortical pyramidal cells, and through that mechanism changing how the serotonergic system works. The complex effects of serotonin are mediated through 7 receptor types and at least 14 subtypes. Psychedelics usually influence either the 5-HT2a or 5-HT1a receptors.

Indole alkaloid

An alkaloid is a naturally occurring, organic, nitrogen-containing compound found in more than 4,000 species of plants, which has diverse physiological effects on humans. An indole alkaloid is a particular classification of alkaloid that has a chemical structure containing a ring system called indole. Examples of indole alkaloids include serotonin, and psychedelics such as psilocybin mushrooms, iboga, LSD and tryptamines such as DMT (dimethyltryptamine). Codeine and morphine (as well as nicotine) are well-known commonplace examples of pharmaceuticals derived from plant alkaloids.

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Psychedelics

Psychedelics, or hallucinogens, are psychoactive substances that powerfully alter perception, mood, and a host of cognitive processes. They are considered physiologically safe and do not produce dependence or addiction. Psychedelics can cause changes in perception, thought and feeling, ranging from visual distortions (illusions) to imagining things that are not there (hallucinations). Psychedelics heighten sensory inputs (bottom-up) and lower the influence of preconceived ideas (top-down). Most psychedelics profiled in this report are serotonergic psychedelics, exerting their influence via the serotonergic pathways in the brain. MDMA (an empathogen), ibogaine, ketamine, and salvinorin A being notable exceptions that mainly work via changing other systems.

Psilocybin ('magic' mushrooms)

Psilocybin is a psychoactive substance derived from psilocybe mushrooms (such as Psilocybe Mexicana). It is an indole alkaloid that, when converted to psilocin, has psychedelic properties. It is thought that psilocin acts mainly by activating the 5-HT2a receptors. Psilocybin can be synthetically manufactured and was first isolated in a laboratory in the 1950s. The mental health care company COMPASS Pathways has successfully patented a synthetically derived psilocybin derivative known as COMP360.

Ibogaine

Ibogaine is a psychoactive substance extracted from the bark of the root of an African rainforest shrub called Tabernanthe Iboga. Ibogaine is an indole alkaloid that has psychedelic properties. Ibogaine was isolated from the plant in 1901 and was synthesised in 1966. In small doses, it acts as a general stimulant. A synthetically derived substance similar to ibogaine, called 18-MC, is also being investigated for its anti-addictive properties.

Mescaline (peyote)

Mescaline is a naturally occurring psychoactive substance derived from the flowering heads of the peyote cactus and is found in Mexico and in southwestern United States. San Pedro and Peruvian Torch are examples of other cacti that contain mescaline. Mescaline is an alkaloid that has psychedelic properties. The mescaline molecule is of similar structure to two hormones produced in the human adrenal gland, adrenaline and noradrenaline. Mescaline can also be synthetically manufactured. It was first isolated from the peyote plant in 1896.

Ayahuasca

Ayahuasca is a brew made from a blend of different plants, primarily the Banisteriopsis caapi (ayahuasca or yagé) vine and Psychotria viridis (chacruna) shrub, which contains DMT. So, unlike DMT, which is most commonly smoked, ayahuasca is a liquid preparation, consumed orally as a 'tea'. Ayahuasca contains chemicals (MAOIs - monoamine oxidase inhibitors) that prevent the stomach from breaking down DMT and which prolong the effect of DMT. If ayahuasca is synthesised it is sometimes named pharmahuasca.

DMT

DMT (dimethyltryptamine) is a naturally occurring chemical found at low concentrations in many plants, animals and humans. When taken in concentrated doses, it is a powerful psychedelic. It is ordinarily the central active ingredient in ayahuasca. DMT is thought to act by activating 5-HT2a receptors. It can also be synthetically manufactured.

5-MeO-DMT

5-MeO-DMT is a tryptamine alkaloid that was first synthesised in 1936. The compound is found in both plant and animal sources, including high concentrations in the parotid gland secretions of the Colorado River toad, Bufo alvarius. The psychedelic effects of oral ingestion are both fast-acting and short-lived. A UK-based company, Beckley Psytech, is exploring the use of 5-MeO-DMT for the treatment of a variety of neuropsychiatric disorders.

LSD

LSD belongs to a chemical group named lysergamides, which have both phenethylamine and tryptamine (such as psilocybin) groups embedded within their structure.

MDMA

MDMA is a synthetic stimulant of the central nervous system (CNS) derived from amphetamine. It is closely related in structure to another stimulant, methamphetamine. MDMA shares a similar chemical structure to mescaline, which is found in the peyote cactus and is referred to as an 'entactogen' (this translates as 'touching within') and as an 'empathogen' (which means it can generate empathy).

Ketamine

Ketamine was first synthesised in 1962 and is used most commonly in veterinary practice as an animal tranquilliser. However, it has practical medical applications as a general anaesthetic and sedative in human patients, especially in children and in patients who have compromised respiratory systems. Ketamine is also a powerful psychoactive substance and antidepressant. It is available in liquid-soluble form as ketamine hydrochloride and is marketed in both Europe and North America by numerous companies, including Endo Pharmaceuticals and Pfizer, under the brand names Ketalar/Ketanest.

Esketamine

Esketamine is the S(+) enantiomer of ketamine, which is one half of the two mirror images that make up (racemic) ketamine. It is currently unknown if esketamine is superior to ketamine or arketamine (R(-) enantiomer) for the treatment of depression. A subsidiary of Johnson & Johnson has received FDA (Food and Drug Administration) approval to manufacture a nasal spray to treat treatment-resistant depression (TRD) under the brand name Spravato.

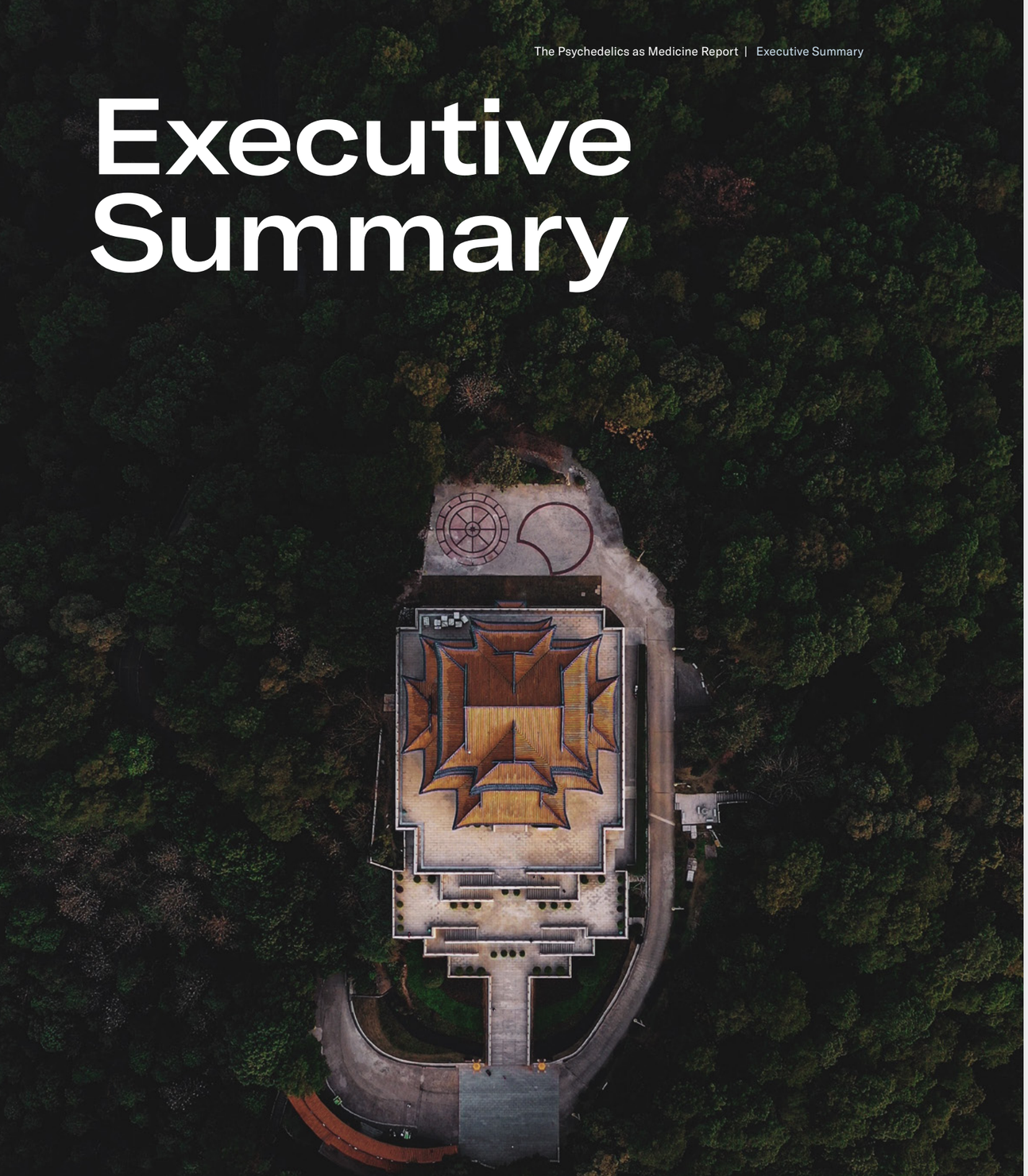
Salvia divinorum

Salvia divinorum is a species of plant native to Mexico. Little is known about the toxicology, adverse events, and safety, as little clinical research has been undertaken with salvia. It has psychedelic effects when consumed by chewing, smoking, or when drunk as tea. The chemical structure of salvia is distinct from other psychedelics, and it is a potent k-opioid receptor, so not a serotonin receptor agonist. Revixia Life Sciences, an entity of clinical-stage biopharmaceutical company atai Life Sciences, is developing a proprietary formulation of Salvinorin A, RLS-01, as a medication for TRD.

Breakthrough Therapy Designation

If the United States FDA awards a substance/treatment Breakthrough Therapy designation (BTD), this means the FDA will expedite the substance's development and review process because clinical evidence has shown that it may offer a substantial improvement over existing therapies. BTD has been given to COMPASS Pathways and Usona Institute to develop psilocybin to treat depression, to the Multidisciplinary Association for Psychedelic Studies (MAPS) which is developing MDMA to treat post-traumatic stress disorder (PTSD), and to Janssen & Janssen for the treatment of TRD with Spravato.

Executive Summary



Psychedelics as medicine are at a crucial inflexion point. A growing number of studies are adding evidence to the astounding effectiveness of psychedelics to treat mental health and substance use disorders. Tireless work by daring researchers and relentless non-government organisations (NGOs) have made possible the renaissance of psychedelic research that we find ourselves in.

Exactly 50 years ago, most psychedelics were classified as controlled substances (Schedule I) under the Convention on Psychotropic Substances. The backlash against the 'hippie' culture also made it nearly impossible to study psychedelics, which showed initial successes in the treatment of alcoholism, anxiety, and other mental health disorders.

Forward-thinking investors and entrepreneurs now recognise the growing body of academic research. They, often with scientists advising them, are laying the groundwork for psychedelic-assisted therapy (PAT) at scale. As you will learn in this report, there are many areas where psychedelics are showing promise. Psychedelics are on course to become the next major paradigm shift. This blossoming industry marks the first significant innovation in mental healthcare since 1987 when antidepressants were first introduced.

This report examines six psychedelic substances in depth. These are: psilocybin ('magic' mushrooms), LSD, MDMA, ketamine, ayahuasca and ibogaine. The report includes sections dedicated to profiling each substance and identifying its legality around the world, as well as clinical trials or academic research underway to ascertain the potential benefits of these substances for treating a broad list of mental health conditions.

a Psilocybin, the psychoactive substance (when metabolised as psilocin) in over 200 species of fungi, has shown promise, when combined with psychological support such as talk therapy, in the treatment of a variety of mental health disorders. Most research has been done to treat so-called treatment-resistant depression or TRD (depression that does not respond to conventional antidepressants - estimated to affect 77 million people worldwide). Two separate providers, COMPASS Pathways and the Usona Institute have received Breakthrough Therapy designation (BTD) from the US Food and Drug Administration (FDA) for synthetic versions of psilocybin for use as part of psychedelic-assisted psychotherapy for TRD and major depressive disorder (MDD), respectively. COMPASS Pathways recently finished its phase IIb trial and will publish results later in 2021. The FDA designation is a step closer to licensing approval for this therapy in the US, which may be granted as early as 2025.

b LSD has shown tremendous early potential in treating depression, anxiety, PTSD, attention deficit hyperactivity disorder (ADHD), and cluster headaches, among

others. Although less intensely studied since the turn of the century, LSD has played a pivotal role in early research and even discovering serotonin (a neurotransmitter) in the brain. The practise of microdosing psychedelics (taking regular, sub-perceptual doses of a psychedelic, in fractional quantities not strong enough to result in hallucinations), which, anecdotally, is believed by many to enhance productivity and stimulate creativity, is beyond the scope of this report, due to a lack of scientific evidence proving its efficacy.

c MDMA-assisted psychotherapy is showing incredible promise for the treatment of PTSD; so much so that it is expected to receive FDA approval by 2023, having received BTD in 2017. The therapy has been so effective that a phase III clinical trial conducted by the Multidisciplinary Association for Psychedelic Studies (MAPS) found that two-thirds of the study participants who completed a course of MDMA-assisted psychotherapy no longer met the criteria for a PTSD diagnosis. Earlier studies showed that these effects held for up to 12 months after treatment. MDMA could be treating patients within six months after approval in the US and Israel, with European Medicines Agency (EMA) approval following a phase III trial in Europe.

d Ketamine is the only psychedelic profiled in this report that features on the World Health Organisation (WHO) List of Essential Medicines. Ketamine is widely available as a general anaesthetic. It can also be used 'off-label' (for purposes other than anaesthesia, which have not been approved) to treat conditions as varied as depression, anxiety, suicide ideation (SI), chronic pain and fibromyalgia. It is currently available in clinics throughout the US for these purposes and is starting to be offered in Europe. Ketamine clinicsmay prove to be a successful prototype for other psychedelic-assisted therapies for patients once approval has been granted to psilocybin or MDMA, for example. Esketamine, one half of the ketamine molecule, is the primary ingredient in a nasal spray patented by Johnson & Johnson under the name Spravato - the only FDA and EMA approved psychedelic medicine for the treatment of TRD.

e Ibogaine, which originates from West Africa, has been used for decades to treat substance use disorders (SUDs) in countries such as Mexico. It has shown efficacy in reducing a patient's misuse of stimulants, opiates and alcohol, and reducing symptoms of withdrawal (from opiates) after administering a single dose. Several 'second generation' (novel compounds based on existing psychedelics) psychedelics are being developed to harness the anti-addictive effect of ibogaine without the relatively high health risks, specifically heart rhythm disturbances, associated with the substance.

f Ayahuasca, which has been in use for millennia, is a psychoactive brew that combines several ingredients, DMT and MAOIs, that one consumes as tea. Although less well studied in clinical trials, the mixture and the isolated psychedelic DMT show promise in treating depression, anxiety, eating disorders, and could even help those with strokes to recover better. Many have sought ayahuasca experiences through partaking in ayahuasca retreats - particularly common across South and Central America.

Other psychedelics also show promise in the treatment of mental health and substance use disorders. These include Salvia Divinorum, mescaline (from the peyote cactus), DMT, 5-MeO-DMT, kratom, 2C-X, nitrous oxide and novel compounds (also called 'second generation' psychedelics). The future approval of the major psychedelics will probably clear a path for further clinical research and development of these other psychedelics into medicines.

There is significant support among sections of society to allow researchers to examine the potential benefits of psychedelics. PSYCH & Blossom's proprietary consumer data shows that 69% of adults in the US, the UK, Canada,

France and Germany would consider psychedelic-assisted therapy. Two-thirds support the legalisation of psychedelics for research purposes. Six out of ten participants from a representative sample in each country (3,050 respondents total) were curious to learn more about psychedelics as medicines.

To date, conventional pharmaceuticals have had limited success in treating certain conditions such as TRD, which does not respond to typical courses of antidepressants, or SUDs, most starkly illustrated by the opioid epidemic in the US. Pharmaceutical companies are now looking elsewhere for solutions, and there is a growing appetite for new plant-based medicines. Psychedelic substances, more than any other substance explored in the past 50 years, have the potential to address this crisis.

The psychedelics industry is a blossoming market that is on an exponential path, with investments quintupling, on average, in each of the last four years. With depression on the rise, fuelled even more by the COVID-19 pandemic, increasing awareness of the detrimental impact of mental health disorders, and the emergence of new treatment therapies, the global market for alternatives to conventional antidepressants is sizable.

The prospect of 'one-and-done' psychedelic options, such as ibogaine, to provide medium- to long-term relief from addictive substances, with a considerable reduction in the likelihood of relapse; or one-to-two doses of psilocybin for the effective treatment of TRD within a short course of treatment (six-to-eight sessions) will radically disrupt the existing market for conventional treatments. To get an idea of how valuable these drugs could be to our societies, we have calculated their potential to relieve some of the economic burdens of treating the conditions for which they are showing promise. We estimate that psychedelic-assisted therapies could provide relief in costs to society in the region of US$230 billion in relation to SUDs (opioid and alcohol), US$330 billion in relation to depression, and US$120 billion in relation to PTSD, for just the US and the European Union (EU).

These figures, highlighting the total addressable market, are an attempt to broadly illustrate the potential economic and societal benefits that could be wrought from psychedelic drugs if the success in preliminary clinical studies was replicated on the medicinal market once legalised and scaled up. The precision of these calculations is necessarily limited due to the preliminary nature of the clinical data.

The majority of psychedelics are classified as controlled substances under the United Nations (UN) Convention on Psychotropic Substances. However, with the recent approval of esketamine on both sides of the Atlantic and the likely approval of MDMA, and psilocybin-assisted psychotherapies in the next three to five years, it is likely that the status of these substances will come under review. Regulatory changes are already happening at the local level, particularly in the US; for example, the recent decriminalisation of psilocybin in six cities and the start of a legal and regulatory framework in Oregon. Other states such as California and over 100 cities are advancing regulatory changes.

The massive market potential of psychedelics has led to a flurry of investments into this space. Many investors and entrepreneurs from pharmaceuticals, cannabis and general investment groups are getting involved. The ones who will be successful in offering psychedelic-assisted therapy (PAT), along with the key infrastructure solutions to enable the industry, at scale, will reap the rewards and fuel the impactful healthcare businesses of the future. Some companies are already generating revenues by offering ketamine in clinics, often without much therapeutic guidance. Johnson & Johnson has capitalised on the rapid approval of Esketamine, though it is also finding stiff competition from private ketamine clinics.

The converging trends of digital therapeutics and psychedelics have enticed some groups to make significant investments in technology to bring about the best therapeutic outcomes. Atai has built a portfolio of a dozen companies that promise to both offer psychedelic-assisted therapy and collect data that will improve the therapeutic process. Many of the companies positioning themselves as the 'go-to' providers of psychedelic-assisted therapy are already opening ketamine clinics to sharpen their protocols and grow their customer base.

Not more than 18 months after MindMed became the first publicly listed psychedelic-focused pharmaceutical company, there are now over 40 companies listed on stock exchanges, from the innovative Candian Stock Exchange (CSE) to the well-respected National Association of Securities Dealers and Automated Quotations (Nasdaq). The biggest listed company, atai, currently trades around US$16 a share and is valued at US$2.4 billion (as of September 2021). We expect this number to keep growing into 2022 as more investors and companies position themselves in the right places for when psychedelics as medicines become available at scale.

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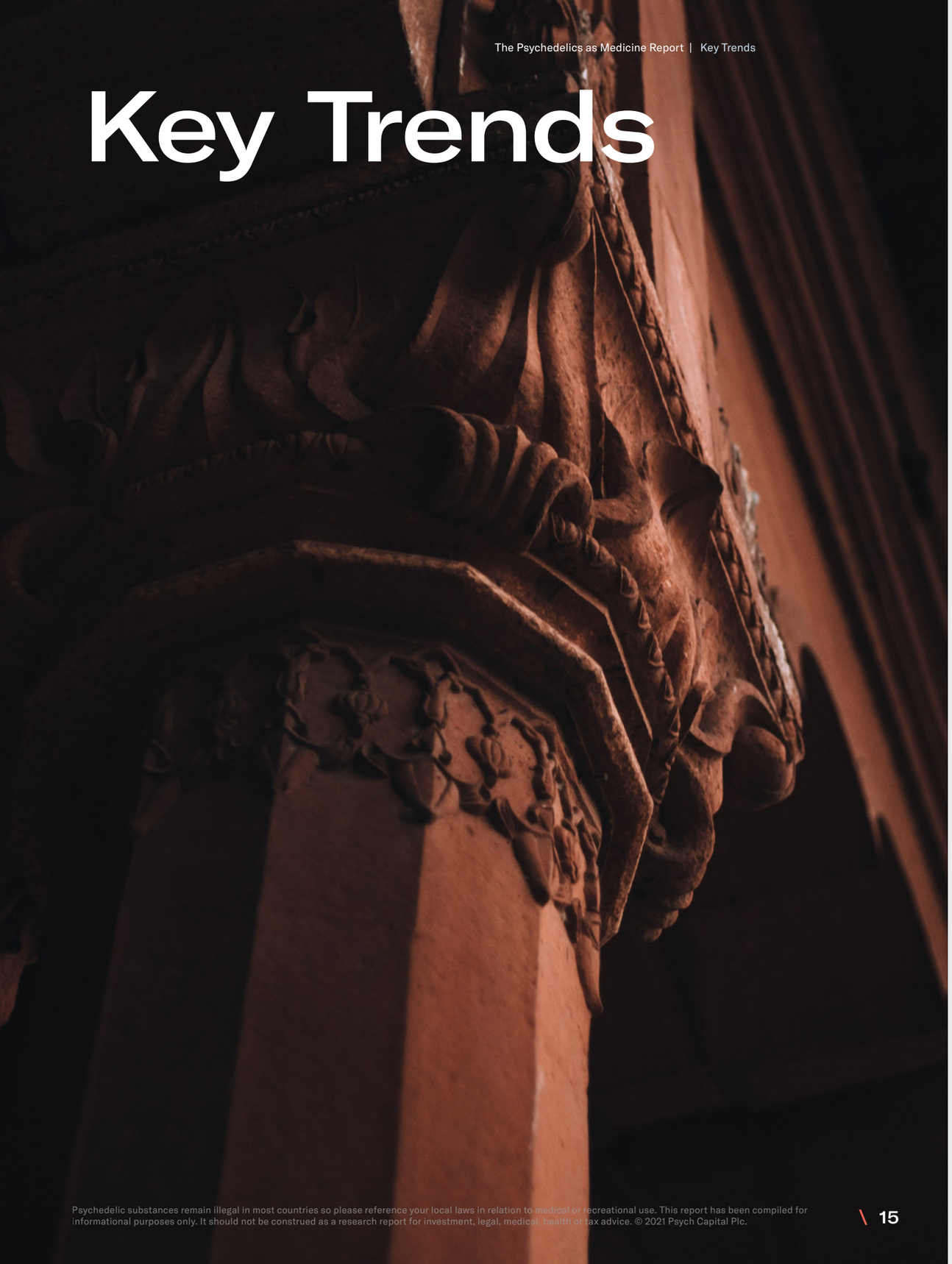

Key Trends

Research is at a tipping point

Clinical evidence is accumulating at an increasing rate. Not only is academic research into psychedelics going through a renaissance presently, but dozens of companies are also now sponsoring research to bring psychedelics as medicines to market. With several companies boasting valuations in the hundreds of millions or even billions, the research budget has grown exponentially in the last few years.

Whereas in the early 2000s it was near-impossible to do psychedelic research with humans, there are currently more than 50 ongoing clinical trials. Studies are happening at prestigious universities with several opening psychedelic research centres at Johns Hopkins, Imperial College London (ICL), Harvard and Massachusetts General Hospital. These trials have progressed from phase I studies that proved the safety of psychedelics to phase III; the final step before FDA approval, and beyond. One psychedelic, ketamine, is being employed to treat a variety of mental health disorders. It will soon be joined by many other psychedelics in the coming ten years, of which MDMA will be the first.

Psychedelics poised to treat many disorders

Mental health and substance use disorders affect more than 900 million people around the globe. Somewhat paradoxically, the more affluent countries are the ones who are dealing with the most immense burden. The costs associated with mental health care and the lives lost from substance use disorders are enormous. Making a sizable dent in this market by improving the mental health of millions is where the opportunity for psychedelics exists.

Watching my best friend and business partner suffer, being let down by existing treatments and finally finding comfort in psychedelic therapies, was all the inspiration I needed to commit my life to this cause.

Florian Brand,
Co-founder & CEO of atai Life Sciences

Psychedelics are being investigated and explored to treat many significant disorders; from various forms of depression to alcoholism. What sets psychedelics aside from conventional treatments is that a few sessions with a high dose of a psychedelic can usually lead to long- term effects measured in months or years. The upfront costs of psychedelic-assisted therapy (PAT) will need them to be treated differently from current medications which may cost less but are turning out to be ineffective for the majority of patients.

Instead of numbing someone to their circumstances, psychedelics offer the possibility to engender long-lasting changes in behaviour and mental health. Not only will this save money for insurers, hospitals and caretakers, and handsomely reward those who will bring these medicines to market, it will also give back valuable qualitative years of life to those helped by psychedelics.

Therapy will be the name of the game

Therapy is an integral part of how psychedelics lead to improvements. As will be detailed later in this report, psychedelics enable active coping through which patients are able to resolve past trauma or addiction. Psychedelics have also been described as 'non-specific amplifiers' enhancing the effectiveness of therapy.

Types of talk therapy which work best for psychedelic and mental health disorders are currently being investigated. Most published studies have used either cognitive behavioural therapy (CBT), acceptance and commitment therapy (ACT) or forms specifically adapted to PAT.

MAPS, COMPASS Pathways, California Institute of Integral Studies (CIIS), MIND Foundation, and many others are currently training therapists to give PAT. The number of qualified therapists, excluding those who provide ketamine, sits at no more than a few hundred. The expectation is that this will scale up to more than 50,000 therapists within the next ten years.

Legislation and regulation moving in the right direction

Six states and six cities in the United States have moved to decriminalise psychedelics; 100 more cities and several states are working on similar legislation. Public opinion favours psychedelics, and legislators are, for the first time in 50 years, loudly speaking out against restrictions on research and the freedom to take psychedelics for recreational use.

Psychedelic research will initially have to complete more phase III trials for approval as medicines. This is expected as early as 2023 for MDMA regarding PTSD and within two years after that for psilocybin regarding TRD; both designated as breakthrough therapies by the FDA. If the decriminalisation efforts continue at a similar pace as in the last few years, more than a dozen states are expected to stop the enforcement of laws against psychedelic use.

Patients and doctors are ready for change

More than two-thirds of medical professionals support the easing of restrictions on research barriers. If approved by a governing medical body, six out of ten would like to provide PAT to their patients. Doctors and nurses are ready to accept PAT as an option in their toolbox. Many are closely following the research, with psychiatrists being most aware of recent developments.

Patients are similarly ready for change; two-thirds of the people we've surveyed strongly supported personal consideration for psychedelic medicine where it is shown to be safe and effective. When we presented them with information about the level of scientific research conducted, the support numbers increased further.

Psychedelics have moved from the fringes of society to the front page of the New York Times, and it will not be long before they become an accepted treatment for a wide variety of mental health and substance use disorders.

Market Value

The Psychedelics as Medicine Report | Market Value

KEY TAKEAWAYS

1. **Medical psychedelics companies are valued at over US$10 billion.**
2. **The market value of medical psychedelics is valued at US$190 million and expected to exceed US$2.4 billion by 2026.**
3. **The pandemic has great potential to rattle the mental health landscape, and psychedelic therapy offers another tool to support the alleviation of a growing global epidemic.**

Note to the reader:
The value estimates contained within this report are top-level and for information purposes only. For a more detailed market value forecast, please contact our team at info@psych.global.

A GROWING MARKET

The market opportunity in the nascent and growing psychedelics' space is being harnessed by a growing base of institutional investors seeking to establish and scale businesses in a landscape showing scientific and commercial promise.

While capital invested in psychedelic companies is over US$2 billion, the current value of medical businesses surpasses US$10 billion, with atai Life Sciences' initial public offering (IPO) earlier this year making it the most valuable publicly-traded business among the 47 publicly-traded businesses in the sector, currently valued at US$2.4 billion (as of September 2021).

Biotech and pharmaceutical companies continue to dominate businesses within the sector, though there is a growing base - and appetite for - research clinics, therapy providers and software infrastructure. Canada's capital markets remain a popular choice for psychedelic companies.

There are over 100 ketamine clinics in operation in the USA with many more in the pipeline. Despite gaining regulatory approval in the UK, Johnson &Johnson's Spravato (esketamine) did not receive approval by NICE (National Institute for Health and Care Excellence, which approves drugs for use by the National Health Service) twice, citing the cost-effectiveness estimates for esketamine to be much higher than the cost-effective use of National Health Service (NHS) re-

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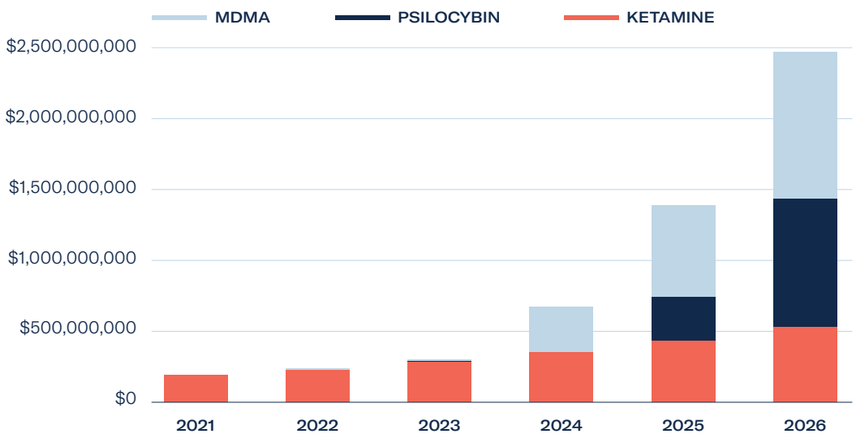
sources, and would like to better understand the long-term use of esketamine in patients, and whether the improvement in symptoms and quality of life can be sustained following treatment. Spravato costs about £10,000 (US$14,000) per course of therapy. In the USA, it was suggested that the price of Spravato needs to be reduced by 40% in order to be cost-effective for the management of treatment-resistant depression (TRD).

Approval landscape

While ketamine has been available as an off-label drug for depression for many years, it wasn't until 2019 when Spravato (esketamine, a ketamine derivative) got FDA approval, and the following year approval by the European Medicines Agency (EMA), for TRD, or for use in psychiatric emergencies. Currently, MAPS' MDMA-assisted therapy for PTSD is the only psychedelic therapy undergoing phase III trials with commercialisation goals; globally, there are 82 active phase II trials with psychedelics, of which 45% are completed. Among the phase II trials with commercialisation goals, Usona and COMPASS Pathways are investigating psilocybin therapy for the treatment of depression. The research path for many aspirational researchers will take years to go through the various stages of clinical trials, analysis and reviews, and as such, we have focused primarily on ketamine, psilocybin and MDMA, as these compounds are either being used for treatment already or are close to being reviewed for widespread therapeutic purposes.

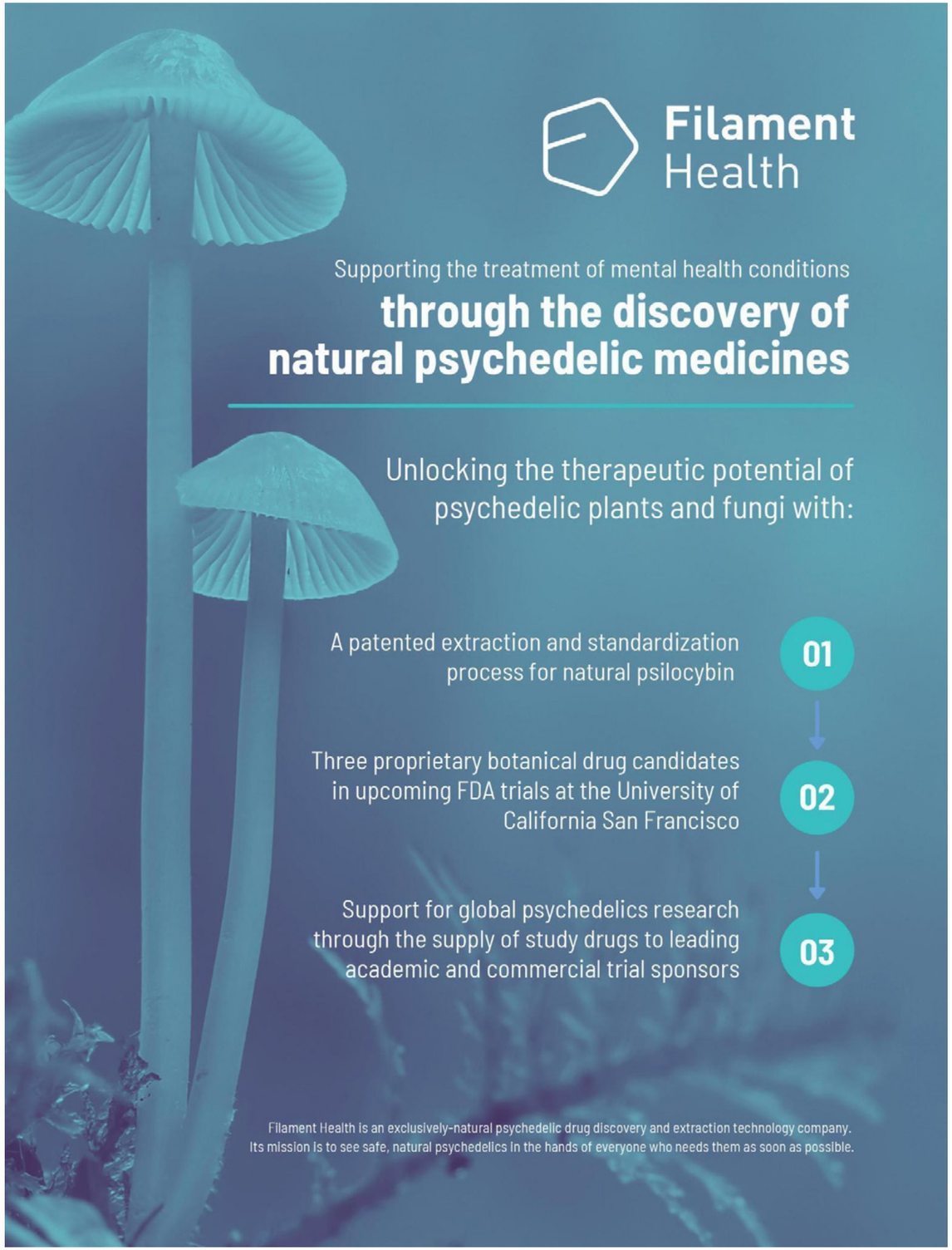
Based on estimates around MAPS' therapy goals during their data exclusivity period from 2023-2029, we forecast total healthcare savings to be rather substantial for patients - at least US$18 billion, and revenue gains from providing therapy and training to be in the region of $7 billion. Assuming a linear growth rate for ketamine clinics, at US$600 per course of treatment, the revenue of ketamine clinics could be upwards of US$3 billion over the same period, with healthcare cost savings on a par with revenue gains.

Projected growth of medical psychedelics market revenues



Source: Blossom

Note: The above is an estimated, forecasted value of psychedelics as medicine sales in Europe and North America, subject to regulatory changes. MDMA- and psilocybin-assisted therapies are undergoing clinical trials and our model assumes approval with implementation within six months of approval. It should be noted that approval in Europe will take longer and may be subject to further study requirements.



Projected growth of medical psychedelics market

In modelling the medical psychedelics market, we focused on therapy training and services, to encapsulate the current market condition. In 2021, with ketamine the only compound used off-label widely for the treatment of mental health conditions, and esketamine for TRD, ketamine-assisted-therapy dominates the market. We expect compassionate use to increasingly include psilocybin and MDMA, with policy and health advocates being strong proponents of such therapies. MDMA is currently available for compassionate use in Israel, Switzerland and Canada. Compassionate use exception is expected in 2022 for psilocybin-assisted therapy in Europe, with Canada's section 56 exceptions being another route to early access before Health Canada's consideration.

Our model is dependent on the exact dates of approval by the FDA or equivalents in other countries. Nonetheless, the model incorporates data on therapists' availability (both who is trained and how many patients they can serve), consumer willingness, and adjacent revenues such as therapist training and other complementary therapy services (e.g. Wavepaths' music service). Underground and non-medicinal revenues are not modelled.

Psilocybin therapy (and specific training protocols) will grow in sales through clinical access being granted to practitioners (beginning in early 2023) - and we expect this to be a key driver in societal education and contributor to wider reforms across America. We predict MDMA-assisted therapy to take a strong market share from 2024, owing in large part to the later trial stage, plans to create therapy opportunities, and MAPS' head start to therapist training

There are many companies researching best practice for the training of psychedelic therapists, who have distilled these into training programmes, such as the MIND Foundation and COMPASS Pathway. Diversity in the offerings provides aspiring therapists with options from which they could choose training most aligned to their goals, though it will be encouraging to see more government subsidies and universities embed psychedelic therapy training, to increase access - both in terms of knowledge and resources - and widen therapist potential for the growing demand, with more PATs expected to be approved in the near future.

The cost of illness

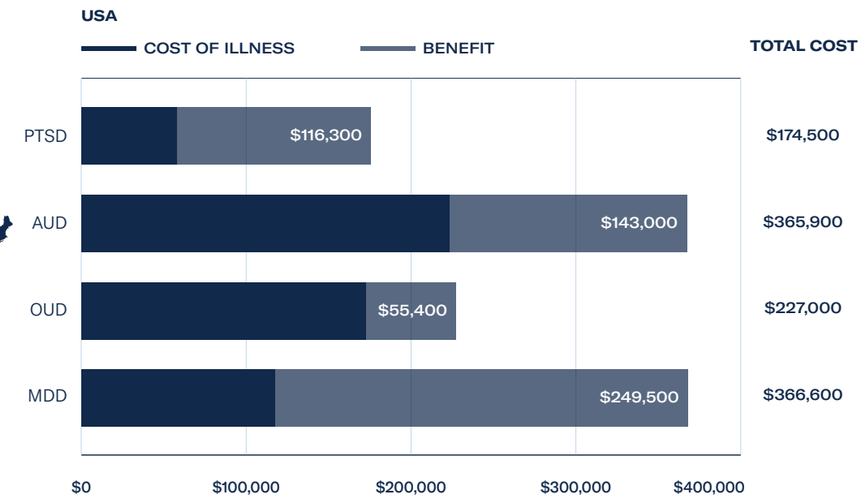
Mental health conditions are very costly and wide-ranging for society, affecting the quality of life for patients and their support networks, as well as the economy at large. Outside of healthcare spending, economic losses are primarily caused by impaired levels of labour participation from those affected by mental health conditions. Mental health innovation can impact society at all levels - socially and economically.

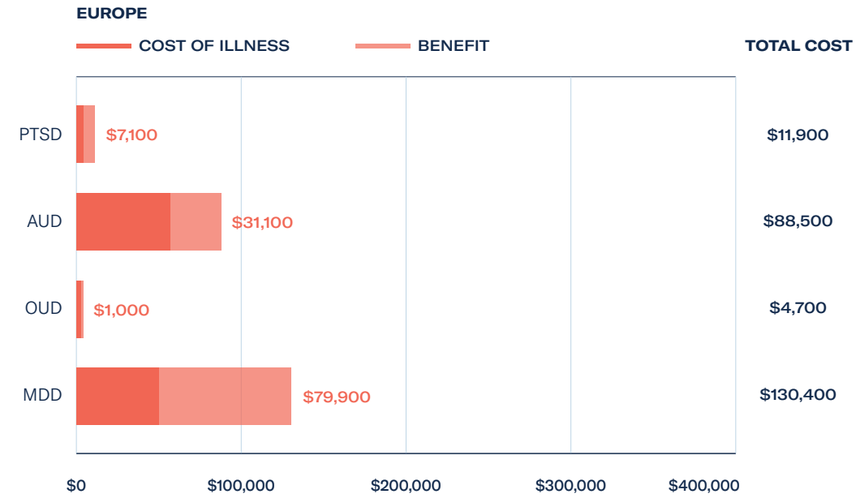
The burden of mental health conditions across Europe and America was quantified through understanding the healthcare costs - direct and indirect - that are being used to treat these conditions; together with the economic loss which ensues from impaired productivity levels, affecting businesses and the economy at large. By investing in new, effective treatment tools, we explore the extent to which these costs can be alleviated through modelling current trial efficacies (and the likelihood of these trials successfully gaining approval), together with the interest consumers have in receiving such treatments. The potential of PAT, as shown in the graph on the next page, are vast and promising.

In particular, the cost-saving to employers (such as through gaining back sick days or employer productivity), has the potential to provide US$64 billion to European countries, and US$270 billion to America - where costs are attributed at a greater expense to healthcare (more than 4-times for opioid use disorder (OUD) - a national epidemic in America - and over 6-times for major depressive disorder (MDD)).

ECONOMIC HEALTH MODEL

Potential savings on costs brought about by psychedelic-assisted therapies compared with costs of mental health conditions to society in the US and EU, in millions





Source: Blossom / Our World in Data / YouGov / Marseille et al. 2020

Mental health during the COVID-19 pandemic

While symptoms of depression and anxiety were particularly heightened at the start of the pandemic, the uncertainty surrounding future restrictive measures and the medium-/long-term effects of the conditions in which people lived during this period is yet to be understood. Using data modelled by the UK's National Health Service, we could extrapolate expectations of new or additional mental health support that could be required for patients with depression and PTSD. In Europe, this could mean 139% more cases of depression and 21% more patients being treated with PTSD - costing Europe's healthcare system an additional US$41 billion to treat. Similarly, the healthcare costs in America could amount to US$185 billion for new and additional mental health support for depression, and US$33 billion for PTSD patients - a total of 29 million people.

I believe that psychedelics represent one of the best shots we have in combatting the mental health crisis. So now it's all about execution, transforming the prior evidence we have on psychedelic compounds into FDA compliant, modern, rigorous scientific data, so that we can bring new treatments to the people who really need them.

Christian Angermayer,
Founder and Chairman of atai Life Sciences

There has been much discussion around the scale of the trauma caused by the pandemic; an event that imposed lengthy restrictions upon people's ability to travel, interact with one another, and experience life in ways to which they were accustomed. Parallels have been drawn between the two most traumatic events that Americans have recently faced: the COVID-19 pandemic, and the 9/11 terrorist attack, where with the latter, the repercussions on people's wellbeing is still being felt. Unlike the targeted experience of the terrorist attack, the COVID-19 pandemic has permeated all homes, across geographies and at varying severities. Far more than a health crisis, the pandemic has exacerbated socio-economic inequalities, and the extent to which this will continue is strongly dependent upon global responses to health, economic and social mobilisation of support. A longitudinal study found that those who had worked on the scene of the 9/11 attack, and those who had physically witnessed it, had the highest rates of PTSD and depression for 15 years following the event. However, residents of the area were also similarly affected, and in order to exemplify the pervasive nature in which the pandemic's trauma could influence new mental health conditions following a traumatic incident, we applied the research to our model. It was revealed that PTSD cases could rise by 28 million, and depression cases by 29 million, among Americans; totalling over US$1 trillion in illness costs.

The Psychedelics as Medicine Report | Market Value

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Legislation and Regulation: An Overview

The United Nations (UN) Convention on Psychotropic Substances framework for the international control of psychotropic substances (those which affect how the brain works and cause changes in mood, awareness, thoughts, feelings, or behaviour) lists the substances in one of four Schedules (I to IV) or leaves them unlisted if no harm is perceived (e.g. for caffeine). The ones perceived as least harmful and with a medical application, such as midazolam, are listed in Schedule IV. The ones where the UN perceived no medical benefits and the greatest harm, were listed in Schedule I.

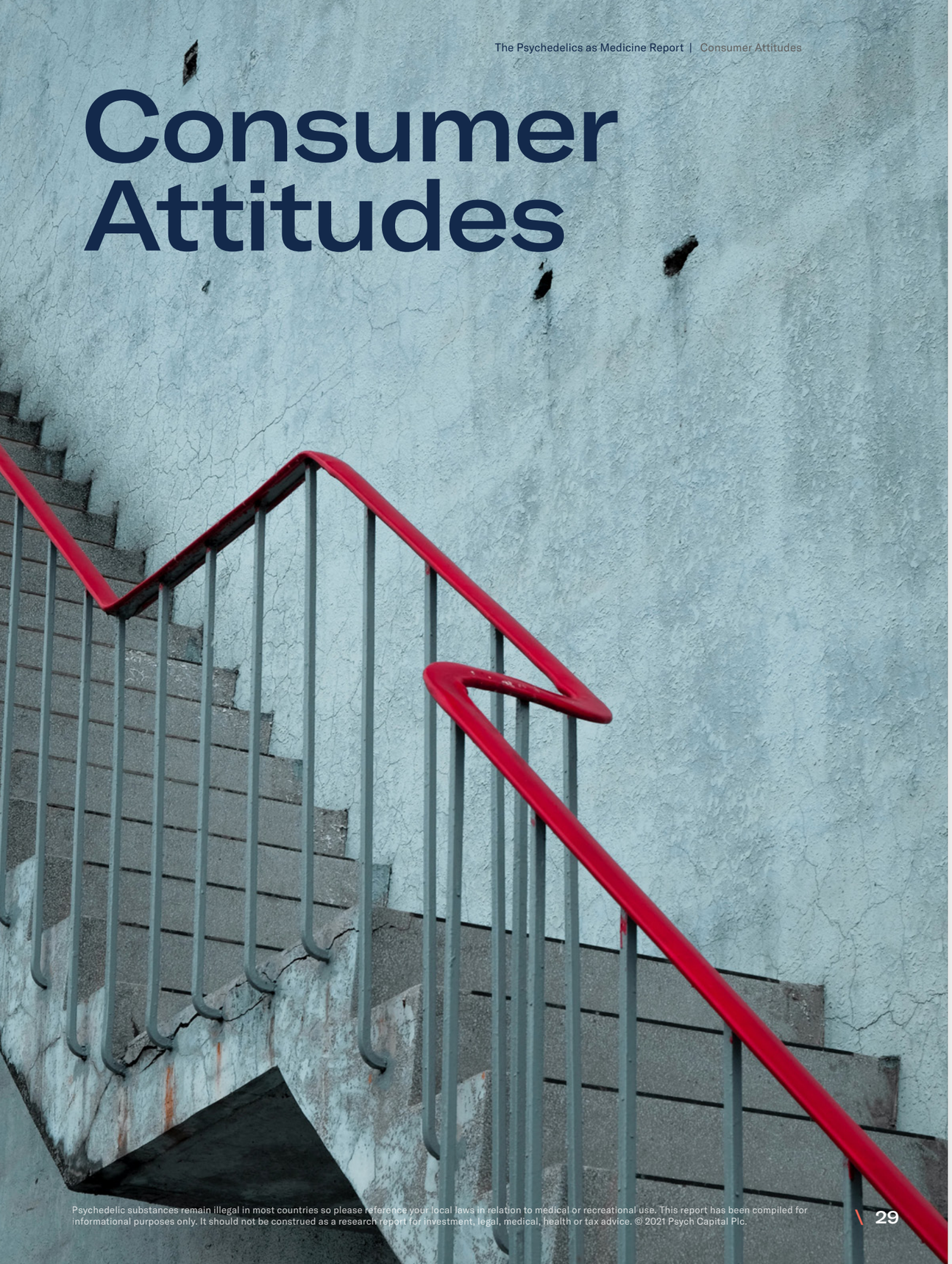
Psilocybin, MDMA, DMT and LSD are listed as Schedule I substances under the convention. Ketamine, which is on the WHO List of Essential Medicines, is not a controlled substance. Ayahuasca is not specifically controlled, although the individual components that make up the brew are controlled, including DMT, which sits in Schedule I. Individual countries have also placed restrictions on some, or all, of these substances.

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

Source: Blossom
**A small number of UN member states are not party, or acceded, to the treaty with conditions such as provisions for the rights of indigenous peoples to make use of traditionally used substances.*

Consumer Attitudes



KEY TAKEAWAYS

1. **We discovered that approximately two thirds of Europeans and Americans support legalisation of psychedelics for medicinal use.**

2. **Two in three individuals are aware of the use of psychedelics for mental health conditions and would consider psychedelics for therapeutic use.**

3. **Consumer knowledge about specific psychedelics varies, presenting an opportunity for education from trusted sources.**

4. **Results show that 38% of consumers know of someone who could benefit from psychedelic-assisted therapy.**

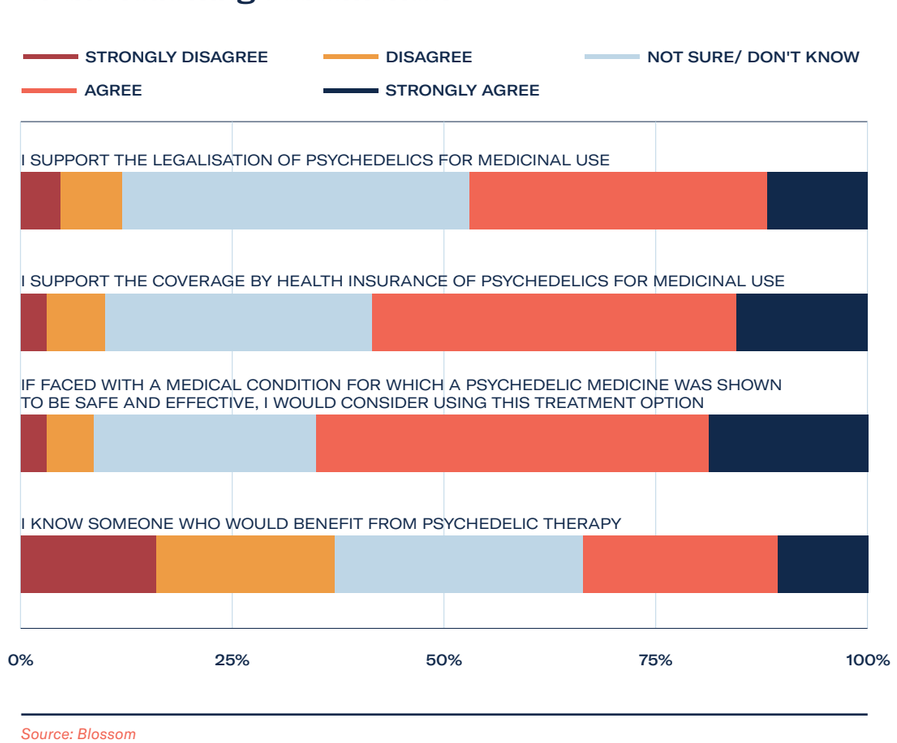
In June 2021, PSYCH and Blossom conducted a nationally representative consumer survey in five countries. The aim of which was to gauge awareness of, and attitudes towards, the potential use of psychedelics for the treatment of a variety of mental health conditions. The survey was conducted between 10 and 17 June, among 3,050 adults living in the US, Canada, the UK, France and Germany. Each sample consisted of at least 600 responses which were proportionally filled out, by age group and sex, representative of each individual country. This section offers a topline analysis of the survey results. Raw data cuts and a more detailed analysis of the consumer sentiment towards psychedelic therapies are available on request via info@blossomact.com.

CONSUMER'S TAKE ON PSYCHEDELICS AS MEDICINE

Consumers were asked about their views on several statements relating to the use of psychedelic-assisted therapy to treat mental health conditions. Five out of ten respondents were in favour of medical legalisation, with four out of ten unsure, and one in ten who disagreed with legalisation. The majority of consumers surveyed were in agreement with seeing psychedelic therapy covered by insurance providers (59%), and they strongly supported personal consideration for psychedelic medicine where it is shown to be safe and effective (65%). A third of respondents knew of someone who could benefit from psychedelic-assisted therapy (PAT).

Last year's survey encompassed only 18-66 year olds, so for the purpose of the following comparison, we focused on those aged between 18-64. Support for legalisation reduced in 2021 among Americans by 6% (to 50%) for the legalisation of psychedelics for medical use. Similarly, fewer Americans knew someone who could benefit from psychedelics in 2021, though as you can see from the diagram below, contextual information makes a difference. UK respondents in 2021, on the other hand, were more supportive of legalisation for medical use (increase of 7% to 43%), and more were aware of someone who could benefit from PAT (increase of 9% to 53%).

Considering the use of PAT to treat mental health conditions, to what extent do you agree with each of the following statements?

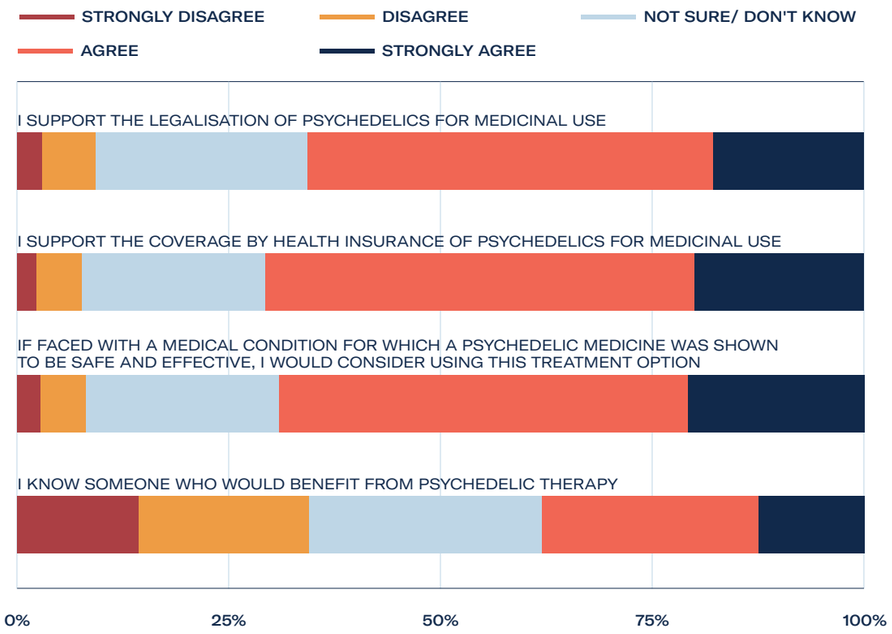


Source: Blossom

When presented with a scenario in which psychedelics were shown to be safe and effective in the treatment of certain mental health conditions such as PTSD and depression, where their respective country's drug regulators approved certain psychedelics as medicines (in conjunction with talk therapy), we observed a noticeable increase in agreement across all four questions. This result shows us that consumers are in favour of safe and effective treatment options – regardless of the associated stigma which psychedelic compounds have faced in previous years.

French consumers showed the least agreement across all the geographies surveyed, with regard to all four questions. After being given more context on psychedelic medicines, there was a stark increase in agreement - with the highest increase being seen (versus the other countries) with regard to health insurance support in the case of knowing someone who could benefit from PAT. This strongly demonstrates that people are amenable to trusting new treatment options in circumstances where drug regulators and evidence demonstrates efficacy and safety.

After being presented with a scenario where PAT was shown to be safe and effective to treat mental health conditions



Source: Blossom

The education opportunity

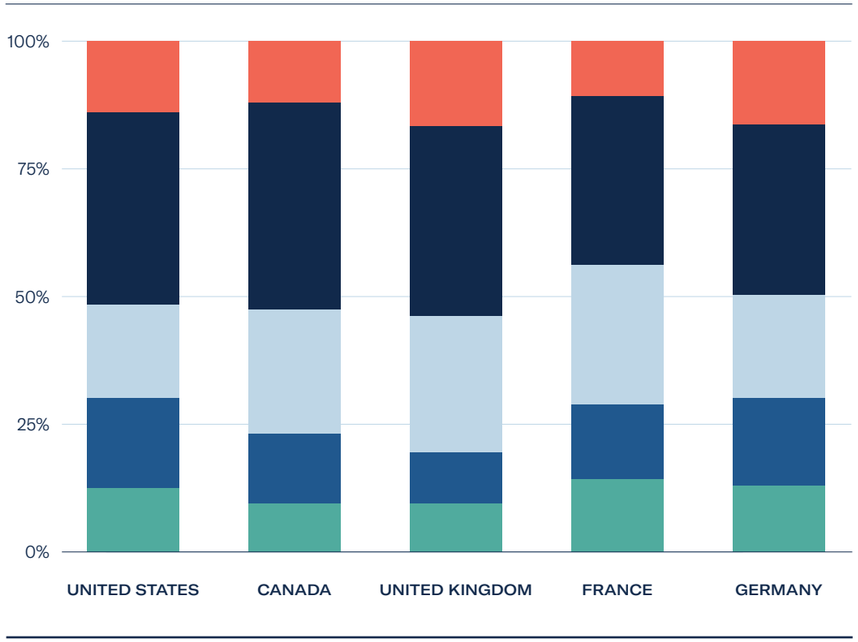
Familiarity with psychedelics for the treatment of mental health conditions was the highest among those aged between 18 and 44. Despite the 45+ cohort being less knowledgeable on the topic, support for legalisation for medical use, health insurance, and treatment consideration for themselves (if faced with a mental health condition where psychedelic therapy has shown to be effective) remained high among all age groups – even prior to being given more context on psychedelic treatments. However, those aged

over 65 were the least likely to agree on these issues, particularly with regard to legalisation (where only 34% agreed), and the majority did not have an opinion. When given more contextual information, opinions were further cast, and 59% of this cohort were in favour.

Considering the extent to which mental health conditions have been experienced – either directly or indirectly – by the large majority during the pandemic, and with the greater focus on mental health in the media and general culture, the openness to supporting new forms of treatment comes as no surprise, posing an opportunity for the medical psychedelics industry to use this momentum.

When we look at the differences between the different countries surveyed, Germany had the most people informed about psychedelics, as well as the most who claimed to be well-educated (along with the UK) about the treatment potential of psychedelics. The familiarity of medical psychedelics was the lowest in France, where respondents also expressed the least interest in learning more. There are also fewer research groups and clinical trials ongoing in France than in some of the surveyed counterparts, which could also be contributing to the initially lower rates of support given to insurance coverage, legalisation and personal therapeutic use. Overall, women and men were broadly aligned with both their curiosity in psychedelics, and knowledge on the topic.

Which statement best describes your awareness of the use of psychedelics for the treatment of mental health conditions?



Source: Blossom

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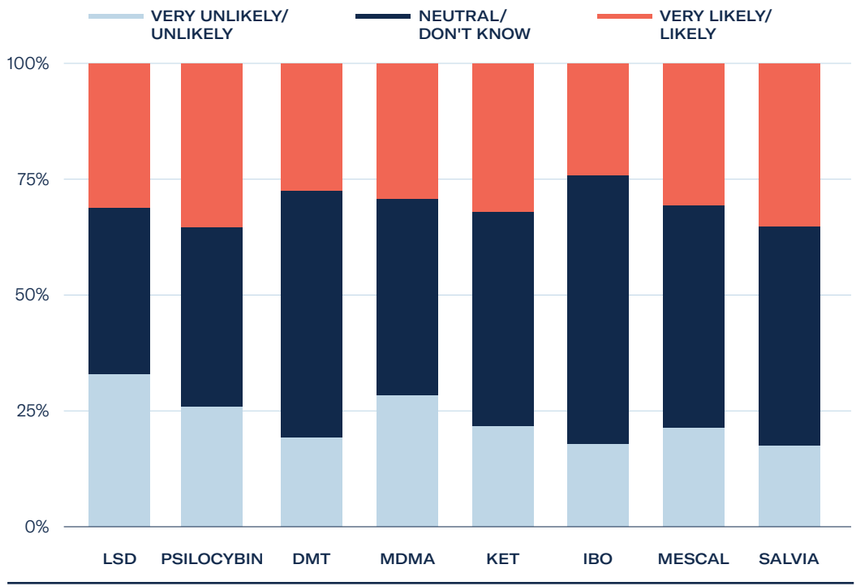
Psychedelics of choice

Consumers were given the opportunity to select each psychedelic compound which they would be willing to consider during PAT - should it be shown to be safe and effective, and be approved by drug regulators. The most popular options were psilocybin and salvia – where 35% of respondents expressed an interest. Psilocybin, in particular, has been at the forefront of consumer's minds, in part due to strong media coverage - reflecting clinical trial results in the treatment of mental conditions, cultural discourse around microdosing for cognitive enhancement or creativity, and its use in psychedelic-assisted retreats in locations such as the Netherlands and Central American countries. In November 2020, Oregon was the first state to decriminalise psilocybin and approve it for therapeutic purposes. Interestingly, while salvia has not been at the forefront of news reporting or clinical research, to the same degree as many of the other psychedelics, those who were inclined to try salvia were people who had used psychedelics in the past.

While 31% of respondents stated that they were likely or very likely to try LSD, it was also the drug that was the least popular among respondents (with 33% stating they were unlikely to try it) - illustrating quite a mixed view among respondents. Consumers ranked physicians and scientists as the topmost trusted sources surrounding the benefits of medical psychedelics (with religious leaders and politicians ranking the lowest). By participating in consultations with physicians to understand personalised treatment options, and further media coverage of clinical trial results, use cases and reviews of various psychedelic therapies, decision-making around treatments will become clearer for those interested in understanding their options.

How likely would you consider using the following psychedelics as a treatment option if you could benefit from PAT?



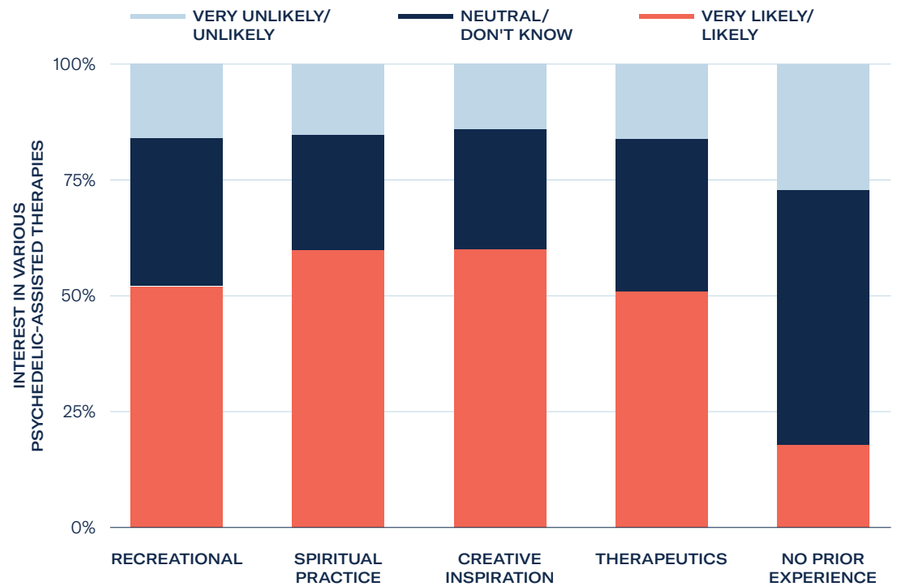
Source: Blossom

INFLUENCE OF PRIOR DRUG USE ON OPENNESS TO PSYCHEDELIC-ASSISTED THERAPIES

Respondents who had previously tried psychedelic drugs for recreational, creative, or therapeutic purposes, were more likely to demonstrate openness to trying psychedelics as a treatment option, alongside talk therapy, should they receive approval from their respective country's drug administration. This finding demonstrates that prior experience yields further interest in psychedelics – particularly among those who have used psychedelics for spiritual or creative reasons.

While those who have had no prior experience with psychedelic drugs were less likely to demonstrate the same strong levels of interest, they weren't entirely opposed either – with 54% stating that they were neutral or didn't know, and 27% expressing that they were unlikely or very unlikely to demonstrate interest.

Psychedelic experience and interest in various PATs



Source: Blossom

It's interesting to see the large curiosity and familiarity exhibited by consumers towards psychedelics for the treatment of mental health conditions. We see this as being really important in driving legalisation of these treatments and in receptiveness toward businesses emerging to be part of the wider wellness solution. 'The mental health revolution that we are currently in is long overdue', commented Dr Reid Robison, Director and Chief Medical Officer at Novamind. 'The pandemic has further highlighted the urgent need for better solutions. We're starting to see less stigma towards mental health and more widespread acceptance of psychedelics as a therapeutic option.' Psychedelics have borne the brunt of adverse media coverage for years, and our findings suggest the importance in appropriately communicating with the wider public, to drive a better awareness of this emerging market.

EXPERT INTERVIEW

Dr Reid Robison

Chief Medical Officer, Novamind

Can you tell us how you got on the path of psychedelic medicine?

Early in my career as a psychiatrist, I was discouraged by the limitations of available treatment options, and it became my quest to find better solutions. Many conventional medicines work slowly with potentially little to no therapeutic effect. And unfortunately, funding for research and innovation in this space has not kept pace with the increasing need for effective treatment options. Today mental illness is one of the world's leading causes of disability and over a million lives are lost each year to suicide.

I studied and ran clinical trials for ketamine around the time it started gaining attention in the psychiatry community in 2011. It was a paradigm shift in treating mental health conditions because of its anti-depressant capabilities, psychedelic properties and what it could mean for therapeutic practice. I haven't looked back. Since 2016, we've administered over 7,000 ketamine treatments.

Where does Novamind fit in the industry?

Novamind is on a mission to bring innovative mental health treatments to market and to expand access to those treatments for all people. Psychedelic-assisted therapy, in particular, is a departure from the current standard of mental healthcare. It requires a specialized infrastructure that most mental health practitioners don't have. Add to that an explosion of new therapeutic candidates in the pipeline that require research sites, patients and people who have specialized training to deliver psychedelic therapy.

Novamind is operating a unique and successful business model focused on our growing network of psychiatry clinics and our contract research organization that serves leading drug developers. Our clinics deliver both mainstream and newer treatment modalities like ketamine-assisted psychotherapy and transcranial magnetic stimulation. Our research sites are co-located with our clinics to enable patient recruitment from a large, diverse population. Patients benefit from access to new treatments options and a highly skilled, multidisciplinary clinical and research team. We are currently scaling our network of clinics and research sites with a multi-state expansion plan across the United States. In anticipation of FDA-approvals for MDMA and psilocybin, we are uniquely positioned with our clinical infrastructure and research expertise to provide those treatments to our clients.

What are some Novamind innovations that are solving problems in the sector?

Our model enables us to create cost-effective treatment options that address specific needs within unique patient populations, then use our research capabilities to study outcomes in real-time. A great example that hits home for me is our clinical pilot for frontline healthcare workers (Frontline Ketamine Assisted-Psychotherapy). The risk of burnout in healthcare professions is high, especially as mental health needs have become even more urgent in the pandemic. I've also personally seen some of the most severe cases of PTSD in this population. In this pilot, we are delivering ketamine-assisted psychotherapy in a group setting that uses the power of social connection.

The Psychedelics as Medicine Report | Expert Interview

Another innovation I'm especially looking forward to is our Park City location in Utah. It will offer unique intensive treatment programs outside daily routines and environments, which can contribute significantly to positive outcomes.

How do psychotherapy and ketamine work together?

Ketamine-assisted psychotherapy generally consists of three sessions. The preparatory session involves screening, consent, discussion of treatment goals, and education about the medicine. Dosing begins with intention setting and ends with processing of the experience. When administered, psychedelics act on the serotonin receptors that are linked to cognitive flexibility, enhanced imagination and creative thinking. It provides a window of opportunity to disrupt patterns in the brain. The integration session is where we can make lasting change. It allows individuals to explore their psychedelic experience and discover insights and meaning that can be incorporated into day-to-day life.

What has surprised you about the mental health revolution to date?

The mental health revolution that we are currently in is long overdue. The pandemic has further highlighted the urgent need for better solutions. We're starting to see less stigma towards mental health and more widespread acceptance of psychedelics as a therapeutic option. There's an inextinguishable light in everyone, no matter where they are on their journey or struggle. Everyone has the potential to heal and recover, and we see our role at Novamind as being that doorway to a transformative healing path. The significant growth in demand for mental health services can be seen at our clinics: we are forecasting 65,000 visits to our clinics in 2021, a 225% increase from 2020.

What excites you about the future of psychedelics?

I'm excited to see the mainstream adoption of psychedelic medicine. The momentum of the public saying this is something we want and believe in, is powerful. We're seeing positive policy shifts towards greater access. And the field is starting to embrace new therapies as potentially game changing. We can start to address root causes of mental illness, not just the symptoms, supported by evidence-based medicine. We're proud to be hosting clinical trials that will help to bring those medicines to market. Novamind has been selected as a key research site for neuropsychiatric clinical trials with leading drug developers like Merck, Otsuka, Bionomics, and our pipeline of clinical trials continues to grow.

The opportunity before us at Novamind and in fact, the entire industry, is to responsibly shape this new era. Novamind's contributions are focused on developing the clinical infrastructure required to safely administer MDMA and psilocybin following FDA-approval. Novamind is leveraging its years of experience treating thousands of patients to deliver best-in-class treatments. Every day I get to help expand access to mental health treatments and create a new standard of care.

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NOVAMIND

CSE: NM | OTCQB: NVMDF | FSE: HN2

Treating people today Positioned for tomorrow

Ketamine-Assisted Psychotherapy • Spravato • Talk Therapy

Psychedelic Medicine • Transcranial Magnetic Stimulation

Contract Clinical Trials • Research Services

Novamind.ca →

Rapidly expanding access to psychedelic medicine across the United States

At our growing network of psychiatry clinics and research sites, we're studying the next generation of life changing mental health treatments and preparing for the future FDA approval of MDMA, psilocybin and more. We're treating people today using innovative therapies including ketamine-assisted psychotherapy.

Psychedelic medicines anticipated to receive US FDA approval

MDMA
Phase III trial, PTSD
2023

Psilocybin
Phase IIb trial, depression
2025

LSD, DMT & others
Late 2020s

Contact us to learn more about our mission | ir@novamind.ca

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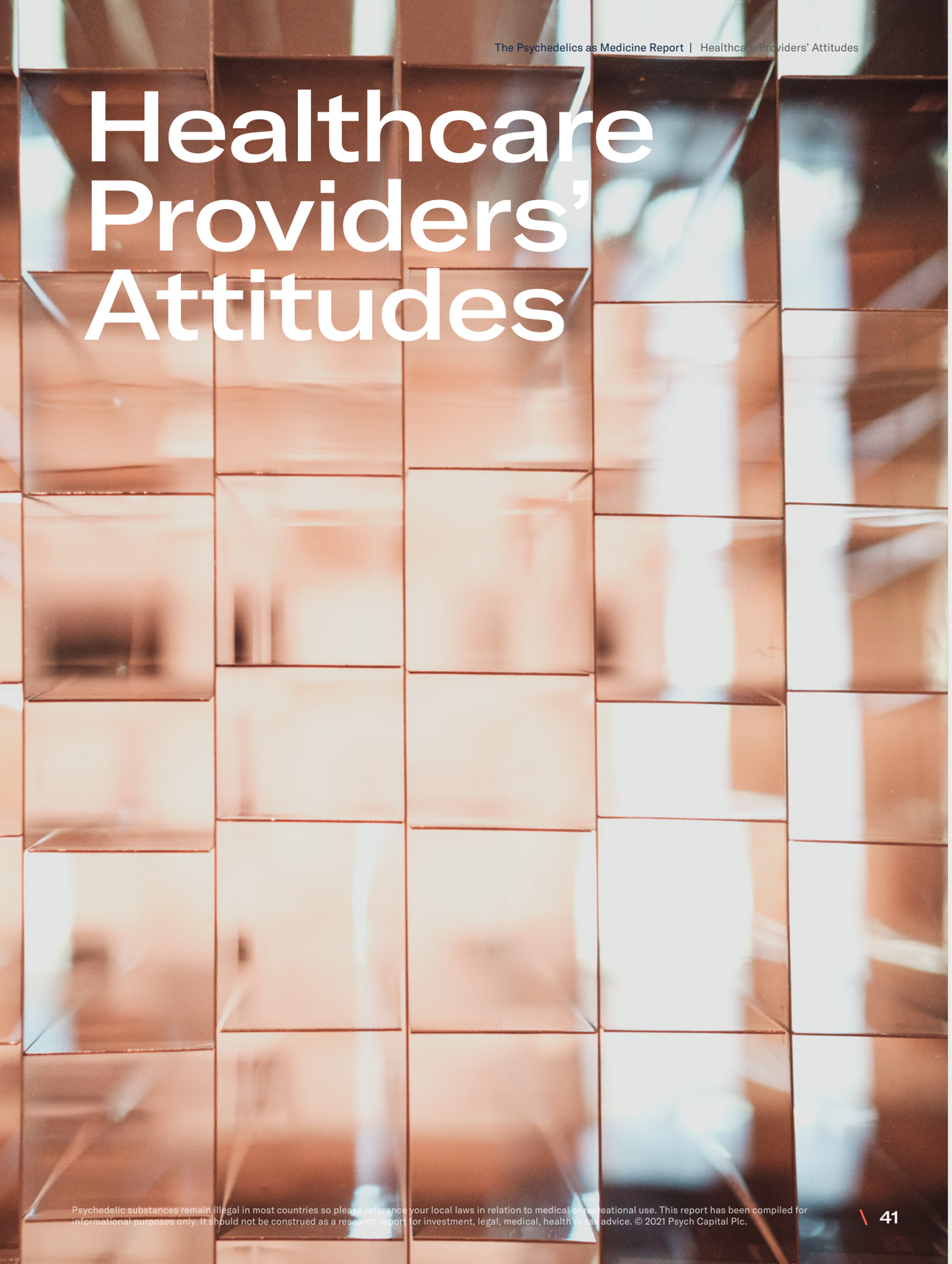

Healthcare Providers' Attitudes

The Psychedelics as Medicine Report | Healthcare Providers' Attitudes

KEY TAKEAWAYS

1. **Healthcare professionals are well-informed on research surrounding psychedelics for mental health, speaking from personal experience - with four out of ten having used psychedelic drugs, and over half having experienced mental health conditions.**

2. **There is strong agreement about the therapeutic benefits of psychedelics, along with receptiveness for the challenges psychedelic experiences pose.**

3. **Two-thirds of healthcare providers are excited about the prospect of psychedelics as medicines.**

Given that healthcare professionals, in the coming years, will be working with patients undergoing psychedelic-assisted therapy (PAT), we conducted a survey measuring UK health professionals' views around mental health solutions, and their understanding and opinions of psychedelics. The 440 respondents were comprised of; nurses (55%), doctors (24%) and various other healthcare workers (21%) – 79% of the cohort were females, 20% male and 1% non-binary. The survey captured quite a diverse set of healthcare workers, including those who work in general practice (16%), surgery (12%), psychiatry (8%), public health and policy (6%), paediatrics (6%), anaesthesia (5%), among others – with two thirds who have been practising for under ten years.

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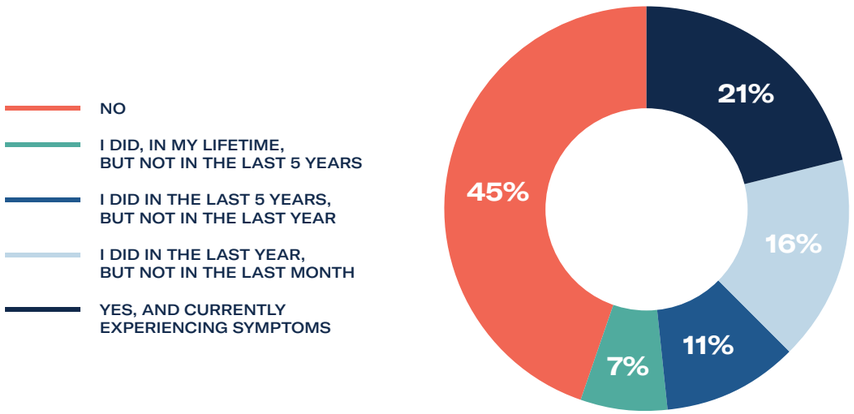
STATE OF MENTAL HEALTH: HEALTHCARE WORKERS

More than half of the healthcare workers have been affected by a mental health condition and are intimately familiar with the impact these experiences have had on their lives. Of our respondents, 21% are currently exhibiting symptoms, 16% within the last year (but not currently) and 11% within the last five years, with a further 7% who have had a pre-existing mental condition at some other point in their lifetimes.

Do you have a pre-existing mental health condition?



Source: Blossom

Healthcare workers' attitudes towards current mental health and substance use disorder treatments

When asked about their views on the efficacy of current treatments for various mental conditions, most healthcare professionals stated that they believe the current treatment options for PTSD, depression, eating disorders and drug and alcohol addiction are 'somewhat effective'.

Interestingly, more healthcare professionals believed our current treatment options are 'somewhat effective' for depression, higher than of any of the other conditions (45%). Drug and alcohol addictions scored the lowest in terms of their perceived treatment efficacies, which could be due to the high relapse rates and complex layers of other mental health disorders which underlie reasons for addiction. Common treatment options for depression currently include talk therapy, antidepressant medications (such as serotonin reuptake inhibitors (SSRIs)/serotonin and norepinephrine reuptake inhibitors (SNRIs)), and for PTSD could consist of antidepressants, cognitive behavioural therapy and eye movement desensitisation and reprocessing.

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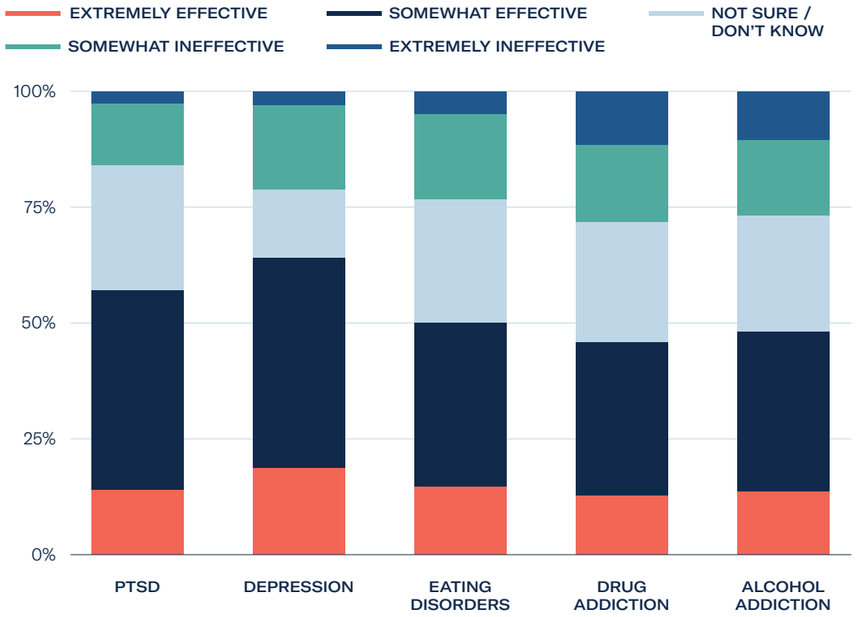
How effective do you perceive the current treatment options for the following mental health disorders?



Source: Blossom

PSYCHEDELIC EXPERTISE OF HEALTHCARE WORKERS

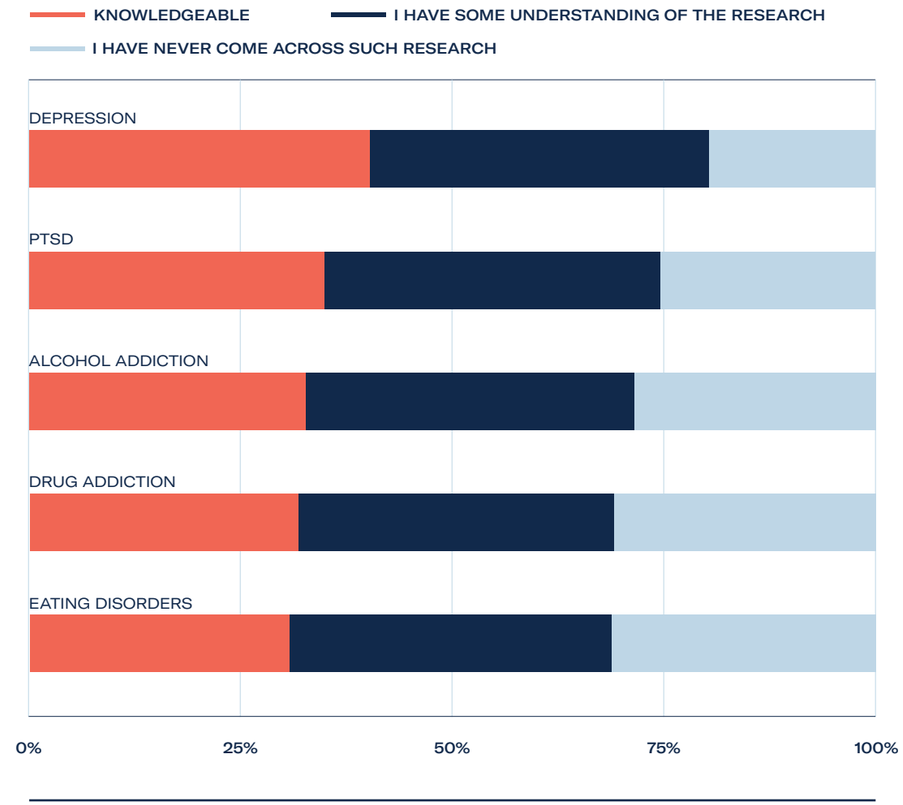
To gauge the current level of knowledge healthcare workers had of PAT, we asked them how familiar they were with research regarding PAT for the treatment of PTSD, depression, eating disorders, drug addiction and alcohol addiction.

Overall, familiarity was the greatest with research regarding depression and PTSD, followed by alcohol addiction – which is in alignment with recent advancements in clinical trials surrounding these conditions. Strong knowledge regarding developments into the research of depression involving psychedelics could be attributed to the high prevalence of the condition; the treatment of which has not seen similar innovative advancements for decades. The least recognised research areas were around eating disorders and drug addiction – areas in which we expect more targeted clinical research in forthcoming years.

Doctors were the most informed profession surveyed, where on average, eight out of ten were familiar with psychedelic research surrounding mental health disorders, and just under half self-reported to be 'knowledgeable' in contrast with seven out of ten nurses expressing familiarity, and three out of ten identifying themselves as 'knowledgeable'. While doctors were the most knowledgeable about research on PTSD and drug addiction, nurses were the most informed about PTSD and depression. Those working in psychiatry were more knowledgeable about research on drug addiction and eating disorders, though it is worth noting that they only formed a small cohort in our study group.

To what extent do you agree with the following statements?

I am familiar with research regarding psychedelic-assisted therapy for the treatment of ...



Source: Blossom

THERAPY: THE BENEFITS AND CHALLENGES

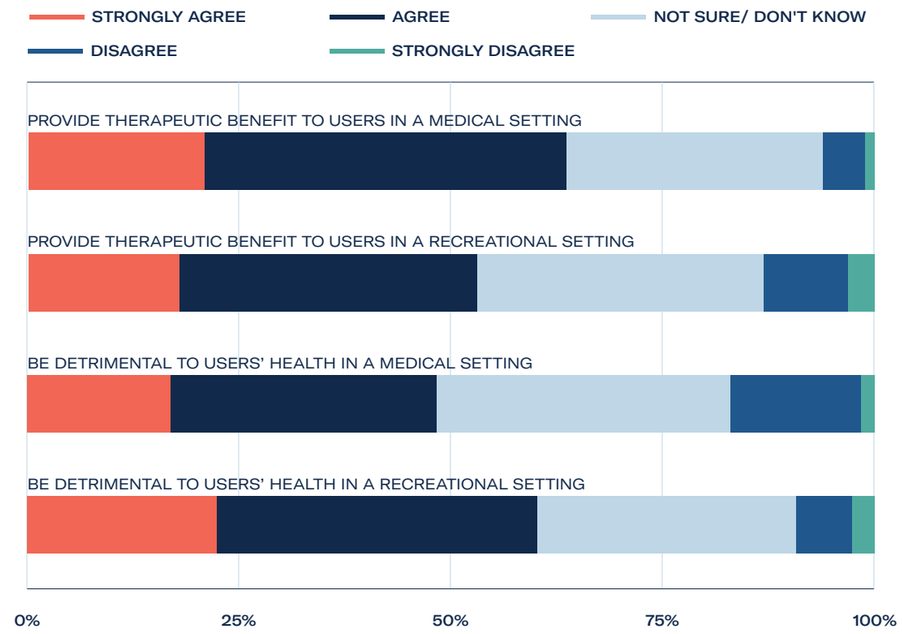
Responses to statements around whether psychedelics can provide therapeutic benefits, or be detrimental toward users was surveyed, and the results were rather mixed – signifying an opportunity for healthcare professionals to be provided with more resources and training to inform their views, which will of course be further bolstered with growing research and clinical trials, use cases and training initiatives. The most popularly held view was that psychedelics provide therapeutic benefit to users in a medical setting, followed by a strong view claiming that psychedelics can be detrimental to users' health in a recreational setting – illustrating that healthcare professionals are in agreement around the therapeutic benefits available to patients in a controlled setting, with trained professionals.

Interestingly, more than half of the respondents agreed that users can receive therapeutic benefits of psychedelics in a recreational setting, 48% also agreed that this could, in fact, be detrimental to users' health (while 17% disagreed with this statement). Broadly a third remained unsure about their views. While research has shown psychedelic compounds to have lower addictive and physiological risks to users, versus other commonly used recreational drugs, harm reduction still remains top priority, and in particular, with regard to psychological risks (commonly stemmed from lack of preparedness, and nonconstructive 'set' and 'setting').

As more states look to decriminalise and legalise psychedelic compounds in the USA, earlier this year the Psychedelic Peer Support Line was launched by the Fireside Project. It is a hotline which psychedelic users (or their accompanying friends) can call to receive guidance from trained facilitators around the holistic psychedelic experience – from preparation through to integration.

Healthcare workers' views on medical and recreational psychedelics

Psychedelics can provide therapeutic benefit to users/be detrimental to users' health in a medical/ recreational setting



Source: Blossom

INFLUENCE OF PSYCHEDELIC USE ON PRACTITIONER VIEWS

Healthcare professionals who had used psychedelics for therapeutic and spiritual reasons, were the strongest supporters of the therapeutic benefits of psychedelics for medical (with 83% of both groups agreeing) and recreational use (73% and 70%, respectively). This could be due to the more intentional approach these groups had to their psychedelic practice. Those who had tried psychedelics recreationally and for creative inspiration also agreed with the benefits far more than those who had no experience with psychedelics – in which only 55% agreed with therapeutic benefits in a medical setting, and 45% agreed with therapeutic benefits, recreationally.

Stronger opinions were once again seen with those who had tried psychedelics therapeutically or for spiritual reasons, with the majority (63% and 57%, respectively) agreeing on the detrimental effects psychedelics can have in a medical setting. Only 44% of those with no prior experience agreed with this statement, and 41% weren't sure. In fact, those with no prior psychedelic experience were understandably the most uncertain about these statements. Majority agreement around the detrimental effects of psychedelics taken both recreationally and medically among all cohorts – and particularly among those who have tried psychedelics – speaks toward the appreciation of both the challenges and benefits which could be experienced.

Practitioner experience is clearly important in facilitating the understanding and exposing the stronger viewpoints around the therapeutic benefit and challenges of these drugs, something which MAPS has been vocal in driving among their MDMA therapy providers.

Treatment and research support

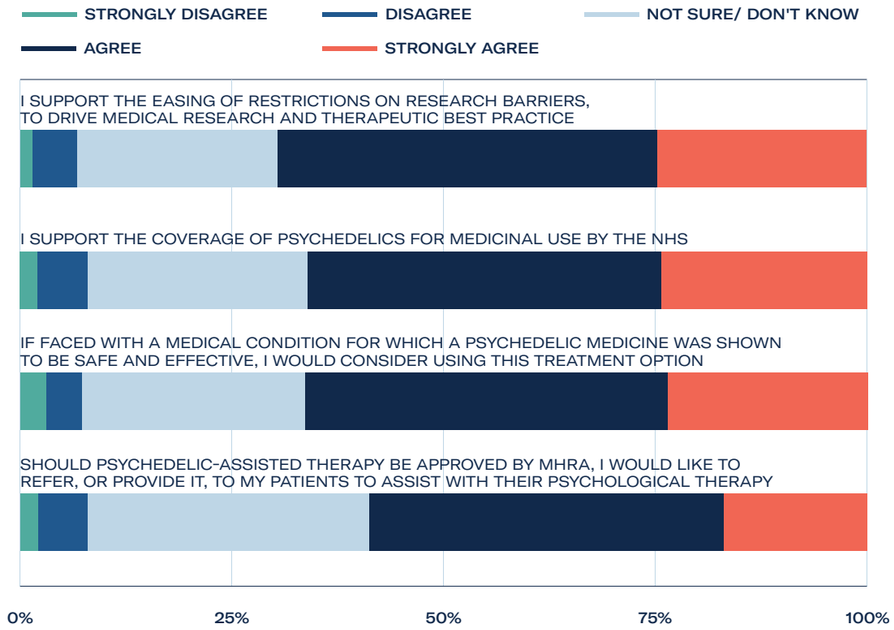
We questioned mental health providers regarding their support for psychedelics as medicines, with some questions similar to those posed earlier to consumers, in order to get a sense of the variety of perspectives.

Medical professionals were asked: 'Considering the use of psychedelic-assisted therapy to treat mental health conditions, to what extent do you agree with each of the following statements?' These statements centred around 1) easing restrictions on research barriers, 2) coverage by healthcare services, 3) openness to personal use of PAT, and 4) desire to refer or provide patients for PAT.

Medical professionals strongly supported the easing of restrictions on research barriers, to drive medical research, with 70% agreeing. While not directly comparable, we asked healthcare workers if they would like to refer or provide PAT to their patients, and we asked consumers if they would know someone who could benefit from PAT. Six out of ten medical professionals were open to providing or referring patients to PAT, whilst only a third of consumers knew someone who could benefit from PAT. We attribute the stronger support by healthcare providers to them being closer to larger cohorts suffering from mental health conditions, as well as the ongoing research, and empathy, towards the various implications for their patients and their ability to support them.

Similarly high interest was found among both groups when asked if faced with a medical condition for which a psychedelic medicine was shown to be safe and effective, whether they would consider using this treatment option. About two-thirds of both groups responded positively, showing again that, even at this stage with research predominantly in phase II trials, people are receptive to PAT.

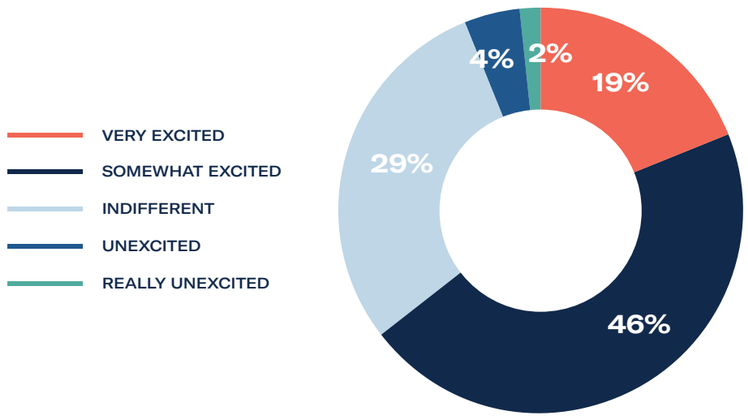
Considering the use of psychedelic-assisted therapy to treat mental health conditions ...



Source: Blossom

THE SHARED SENTIMENT: EXCITEMENT

How excited are you about the prospect of psychedelics as medicines?



Source: Blossom

Two-thirds of medical professionals are excited about psychedelics as medicines - which is unsurprising given their strong inclination to provide, or refer, patients to receive PAT, when possible. It has been interesting to see the high levels of familiarity among healthcare professionals regarding psychedelic therapy for mental health disorders, and more so, to note their shared positive outlook for the future. As the ones who will be intimately involved in the delivery of PAT, this level of support is fundamental to the scaling up of psychedelics as medicines.

Spotlight on Health

The Psychedelics as Medicine Report | Spotlight on Health

KEY TAKEAWAYS

1. According to Our World in Data, the share of the population with mental health and substance use disorders stands at nearly 1 billion people, or 15% of the world population, a proportion that has been stable or rising since 1990.

2. There have been no significant changes in mental health treatments in the last 30 years; up to a third of those suffering from depression do not respond adequately to a course of appropriate antidepressant medication.

3. The societal burden of depression amounts to more than US$490 billion per year for the US alone, eclipsing the societal costs of cancer or diabetes.

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PSYCHEDELICS COMING OUT OF THE CLOSET

Psychedelics have long been something that one only spoke about, in intimate circles, with reference to alternative healing and traditional medicine. The banishing of psychedelics as medicines, after they became synonymous with the counterculture of the 1960s, has led to collective amnesia, with many people today unaware of the rich history of psychedelics prior to their ostracism. Not only were psychedelics the focus of more than 1,000 studies, but they were also used by psychiatrists and relationship councillors with great success.

Now, over 50 years after psychedelics have left the public consciousness, they are rejoining the conversation. That is the medical conversation; psychedelics have never left the public arena. In the US alone, 32 million people, which is nearly 10% of the population, have used a psychedelic in their lifetime. Among those aged 30 to 34, 20% have tried a psychedelic. It is not only that psychedelic use is commonplace, but large scale surveys have also shown that classic psychedelic use is associated with reduced psychological distress.

In 2009, the young, eager researcher, now Dr Robin Carhart-Harris, told his colleagues he wanted to focus his research on psychedelics and study them using functional magnetic resonance imaging (fMRI). Many advised him against this path. In the 40 years prior, no other researcher had administered psychedelics in the UK. Yet, he persisted and under the guidance of Professor David Nutt and building on the work by the Beckley Foundation, their team at Imperial College London became the first to study psychedelics in the UK.

Now just 12 years later, there are more than a hundred psychedelic studies being conducted each month. Established drug researchers such as Matthew Johnson and Roland Griffiths at Johns Hopkins Medicine are joined by a slew of younger researchers from all over the world. Psychedelic research centres are growing like mycelium across the world and from what was originally perceived to be 'career suicide', psychedelic researchers are now making it to the front page of the New York Times.

NOVEL WAY OF TREATING PERSISTENT PROBLEMS

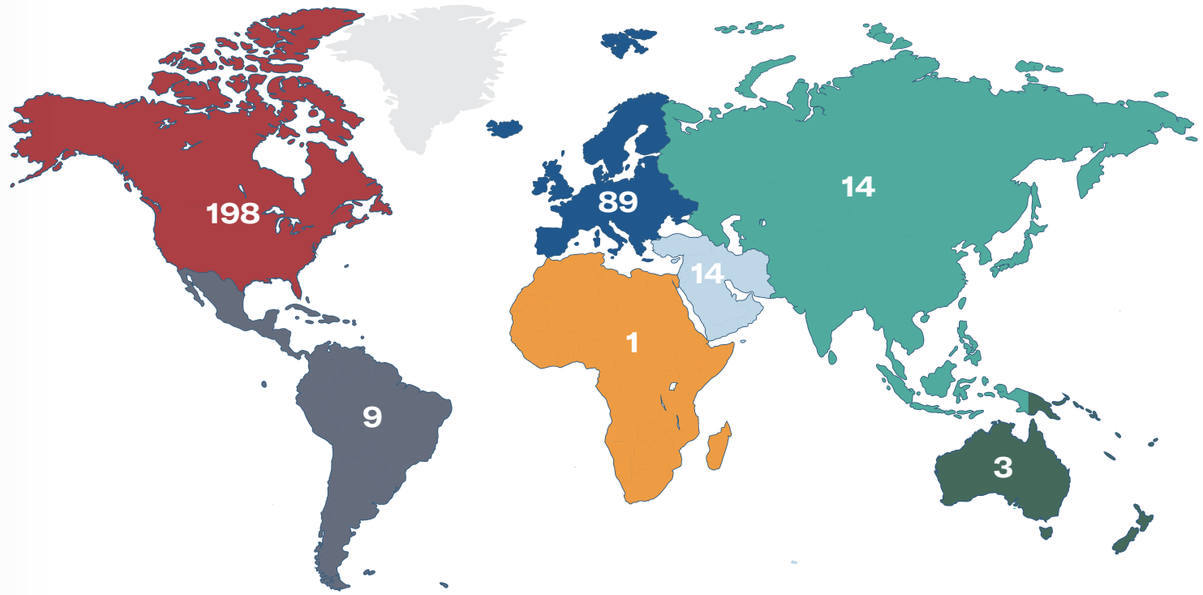
Psychedelics belong to a category of substances (mainly plant-based) that possess powerful psychoactive properties, meaning that they change someone's state of consciousness. Most psychedelics, especially the classic psychedelics, LSD and psilocybin, achieve their mind-altering effects through interaction with the serotonergic system. By changing how serotonin, dopamine, and other neurotransmitters are either released or absorbed, psychedelics change activation patterns in the brain.

These neurological changes also emerge at the psychological level where this altered state allows one to tackle old problems with renewed vigour. One way psychedelics can be viewed is that they allow someone to break free from old patterns or tracks. Imagine a ski slope where, after an intense day of skiing, your next run down the mountain is already predetermined. The grooves are deep and small moguls force you to take one, of only a few routes, down. Wait a night and for some fresh snow to fall, and novel ways down the mountain become available again. A fresh ski slope, just like a brain influenced by psychedelics, offers a mountain of possibilities.

It is this process that happens both at the neurological and psychological level. Psychedelics by themselves do not solve any problems, they only allow one to take action and broaden the options available, especially in combination with psychotherapy. Where traditional medications such as antidepressants aim to relieve the symptoms of the suffering one experiences (passive coping), psychedelics allow one to see problems with a fresh set of eyes (active coping).

Even after more than 300 clinical trials, we are still discovering the many processes through which psychedelics work. Classical psychedelics work by binding to a receptor

Total number of clinical trials (since 2000)



NORTH AMERICA	
MDD	83
TRD	31
PTSD	27
ANXIETY	9
SUD	10
EATING DISORDERS	4

LATIN AMERICA	
MDD	3
TRD	6
SUD	1

EUROPE	
MDD	23
TRD	16
PTSD	5
ANXIETY	2
SUD	5
EATING DISORDERS	1

AFRICA	
TRD	1

MIDDLE EAST	
MDD	8
TRD	1
PTSD	3

ASIA	
MDD	11
TRD	1

OCEANIA	
MDD	2
TRD	1

Source: Blossom/Clinicaltrials.gov

that normally detects serotonin (antagonising the 5-HT2a receptors). Ketamine, on the other hand, works by activating AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors and strengthening synaptic connections. MDMA increases the activity of at least three neurotransmitters; serotonin, dopamine and norepinephrine. We are still discovering the different ways in which psychedelics work in the brain. Recent research by Awakn Life Sciences points towards previously unknown receptor activation by MDMA.

What we do know is that the mental health outcomes are significant and promising. The most prominent study to date has been done

by the Multidisciplinary Association for Psychedelic Studies (MAPS). The latest data from their phase III clinical trial, the last step before Food and Drug Administration (FDA) approval, is showing that 67% of the participants in the MDMA group no longer met the diagnostic criteria for post-traumatic stress disorder (PTSD); participants who had previously been suffering for 15 years on average.

The promising results before prohibition, combined with the resurgence of research, show the untapped potential that psychedelics offer. This is not only as a replacement of often ineffective and life-long conventional therapies, but as a curative model when combined with psychotherapy. The next step that is required is validation by the FDA and the implementation of psychedelic-assisted therapy at scale. Psychedelic medicines, both naturally occurring and those synthesised, have the potential to redefine how mental health conditions will be treated.

KEY CONDITIONS

Psychedelics as medicines are being investigated for the treatment of a wide range of mental health disorders such as depression (MDD, TRD), suicidal ideation, PTSD, eating disorders, anxiety and substance use disorders (SUD), such as addiction to alcohol, opioids and nicotine.

This is needed now, more than ever before, as, according to Our World in Data, 1 billion people are suffering from mental health and substance use disorders. This amounts to 15% of the world population, a number that has surely risen during the COVID-19 pandemic. For every year that is lost due to early death or disability (DALYs - disability-adjusted life year), 7% is caused by mental health and substance use disorders. The cost to society of depression has surpassed that of cancer and doesn't look to be going down without finding new solutions.

Up to 30% of people with depression are treatment-resistant (TRD), meaning their condition has not responded positively to at least

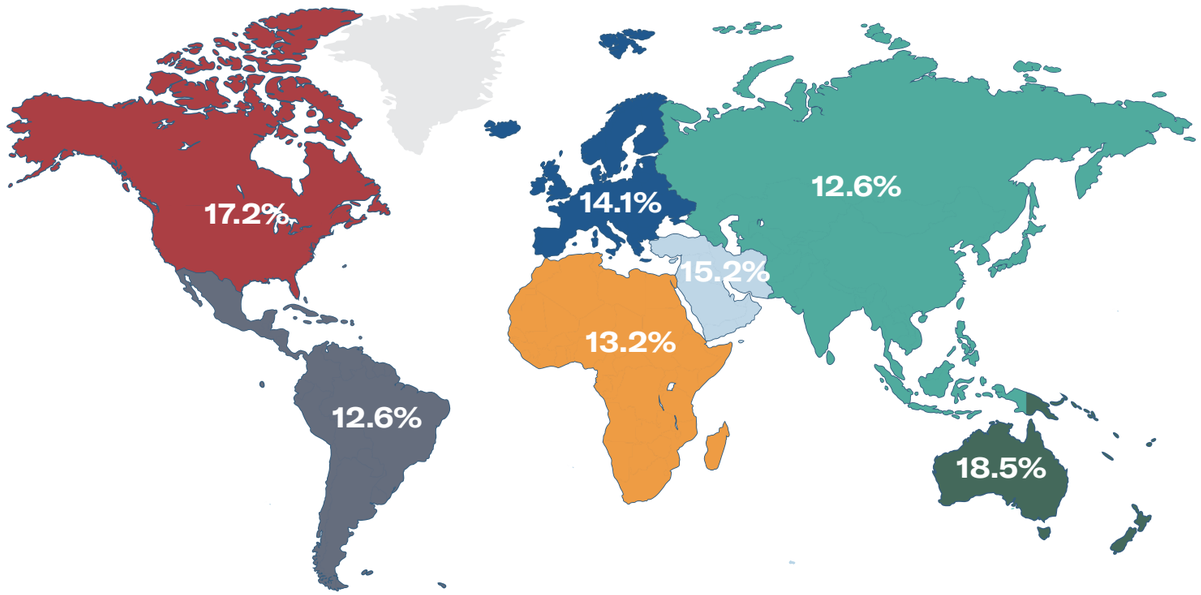
two courses of antidepressant treatment. This equates to roughly 77 million people suffering from TRD worldwide. It is likely that this figure is a conservative estimate given that many people suffering from mental health problems, such as depression, choose not to seek help for their condition.

Substance use disorders (SUDs), including dependence on opioids, for conditions such as chronic pain, have reached epidemic proportions, particularly in North America, where even conservative estimates place the cost to the US economy at tens of billions of dollars in lost earnings every year. The US stands out from the global average of 1% of the population with SUDs with 3.5% of the population being addicted, and almost 1 in 10 people between 20 and 30 addicted to various substances. In 2019, 50,000 people in the US alone overdosed on opioids, either from prescribed medications or their street alternatives. Other substance misuse conditions, such as alcoholism and nicotine addiction, exacerbate the problem. Conventional pharmaceuticals, prescribed for these and other mental health conditions, have had varying success to date and companies are now looking elsewhere for solutions.

The widespread and long-term use of traditional antidepressants has been dubbed as a 'public health experiment on a large scale' according to Dr Daniel Engle, as nobody truly knows what the impact will be on public health or on those individuals who have spent many years on antidepressants. Already we are seeing many conventional pharmaceutical products experience a backlash from the negative side effects of long-term usage and/or addiction, with opioids – the bedrock of the pharmaceutical industry – being a key example of this. There is a definite appetite for alternatives to conventional medicines among patients.

Mental health disorders also lead to a significant number of indirect deaths through suicide and self-harm. Our World in Data finds that up to 90% of suicides in high-income countries can be attributed to underlying mental health or substance use disorders.

Percentage of mental health and substance use disorders (2017)



NORTH AMERICA

MDD	4.8%
TRD	1.6%
ANXIETY (including PTSD)	6.5%
SUD	5.4%
EATING DISORDERS	0.5%

LATIN AMERICA

MDD	2.8%
TRD	0.9%
ANXIETY (including PTSD)	4.6%
SUD	3.1%
EATING DISORDERS	0.3%

EUROPE

MDD	4.0%
TRD	1.3%
ANXIETY (including PTSD)	6.6%
SUD	2.8%
EATING DISORDERS	0.6%

AFRICA

MDD	3.8%
TRD	1.3%
ANXIETY (including PTSD)	4.3%
SUD	1.6%
EATING DISORDERS	0.2%

MIDDLE EAST

MDD	4.2%
TRD	1.4%
ANXIETY (including PTSD)	5.1%
SUD	1.8%
EATING DISORDERS	0.3%

ASIA

MDD	3.4%
TRD	1.1%
ANXIETY (including PTSD)	3.2%
SUD	1.8%
EATING DISORDERS	0.2%

OCEANIA

MDD	4.5%
TRD	1.5%
ANXIETY (including PTSD)	6.8%
SUD	3.8%
EATING DISORDERS	0.9%

Source: Blossom/Our World in Data

In addition, those suffering from mental health disorders face double the chance of dying from cardiovascular diseases. The risk of dying at an early age is highest for those suffering from eating disorders, such as anorexia.

In a world that is spinning around ever faster, the health care system isn't able to keep up. Spending on medical care has gone up 6-fold in the United States over the past 50 years. In that time, the rate of depression and other mental health disorders hasn't budged or has slightly risen. It is time for a new way forward.

Facts about mental health conditions:

NUMBERS (millions)	MENTAL HEALTH CONDITIONS
970	Number of people with mental health or substance abuse disorders
282	Number of people with anxiety disorders
258	Number of people with major depressive disorder (MDD)
77	Number of people with a treatment-resistant form of depression (TRD)
269	Number of people with post-traumatic stress disorder (PTSD)
105	Number of people with alcohol use disorder (AUD)
70	Number of people with other substance use disorder (SUD)

Source: Blossom/Our World in Data/WHO

PSYCHEDELIC HISTORY AND FUTURE

Using psychedelics to treat mental health conditions is a new development in Western and industrialised countries. After briefly being used in the 1960s and 70s, psychedelics have not had a place in modern-day health care. But, their role in society and their potential to heal, has been documented over millennia and is recognised by many diverse indigenous communities around the world.

Psilocybin mushrooms have a long history of traditional use – from indigenous Australians over 10,000 years ago, to the ancient native peoples of Central America (particularly in Mexico), who believed that psilocybe mushrooms were sacred. The Aztec people referred to mushrooms as teonanácatl or 'flesh of the gods'. Healing ceremonies are still held in Mexico today, led by native shamans known as curandera.

In West and Central Africa, ibogaine has traditionally been used by the Bantu and Pygmy communities of Gabon, specifically in Bwiti religious ceremonies and as an aide to healing. Certain peoples of Gabon and the Congo region have also used iboga extracts, or chewed the root of the plant, in order to remain calm, but alert, whilst hunting animals.

The word 'peyote', the name given to the cactus from which the psychedelic substance mescaline is derived, comes from an ancient Aztec word, which translates as 'Divine Messenger'. Under the Native American Religious Freedom Act, 1994, Native American peoples living in the US have a legal right to use peyote as part of religious ceremonies. One Native American congregation successfully petitioned the US Supreme Court in 2006, to allow its members to use ayahuasca as part of its religious sacraments.

DMT, one of the main components of ayahuasca, can also be found in cohoba, a hallucinogenic snuff used by the Indians of Trinidad

and by the Llanos in northern South America during the earliest explorations of the continent by the Spanish. DMT has been dubbed 'the spirit molecule', a nickname taken from the popular book of the same title, by Dr Rick Strassman, who examined how DMT produced mystical and near-death experiences in study volunteers in the early to mid-1990s.

The Centre for Psychedelic and Consciousness Research at Johns Hopkins University has also undertaken research to examine the importance of spirituality among participants in psychedelic studies. A number of these studies have found that subjective mystical experiences (for example during monitored sessions while using psilocybin) were an accurate predictor of sustained positive responses among participants. Currently, a debate is ongoing within the scientific community, to understand in what ways mystical experiences contribute to the positive long-term effects that psychedelics engender. Where some researchers argue that such experiences of awe are the key driver of mental health benefits, others are researching ways to separate the mental health and anti-addictive effects from the mind-altering perceptions.

The latter group is also investigating if we can separate the hallucinogenic and therapeutic effects of psychedelics. Blasphemy to some; separating these effects could lead to a wider acceptance of psychedelics as medicines and for them to be used by those who would rather not experience changes in their consciousness. If found to work in humans, as studies with non-hallucinogenic analogues have only been completed in mice, these could also save costs where a qualified medical professional does not have to sit with a patient for several hours anymore.

The challenge going forward will be to utilise the healing properties of psychedelics, something indigenous communities have been doing for hundreds, if not thousands of years, to develop modern psychedelic-assisted therapies and medicines, while also scaling up the process to meet global demand. Psychedelics as medicine should benefit a new generation of patients suffering from a broad range of mental health conditions, while also respecting the cultural, spiritual and historical importance of these substances to indigenous communities.

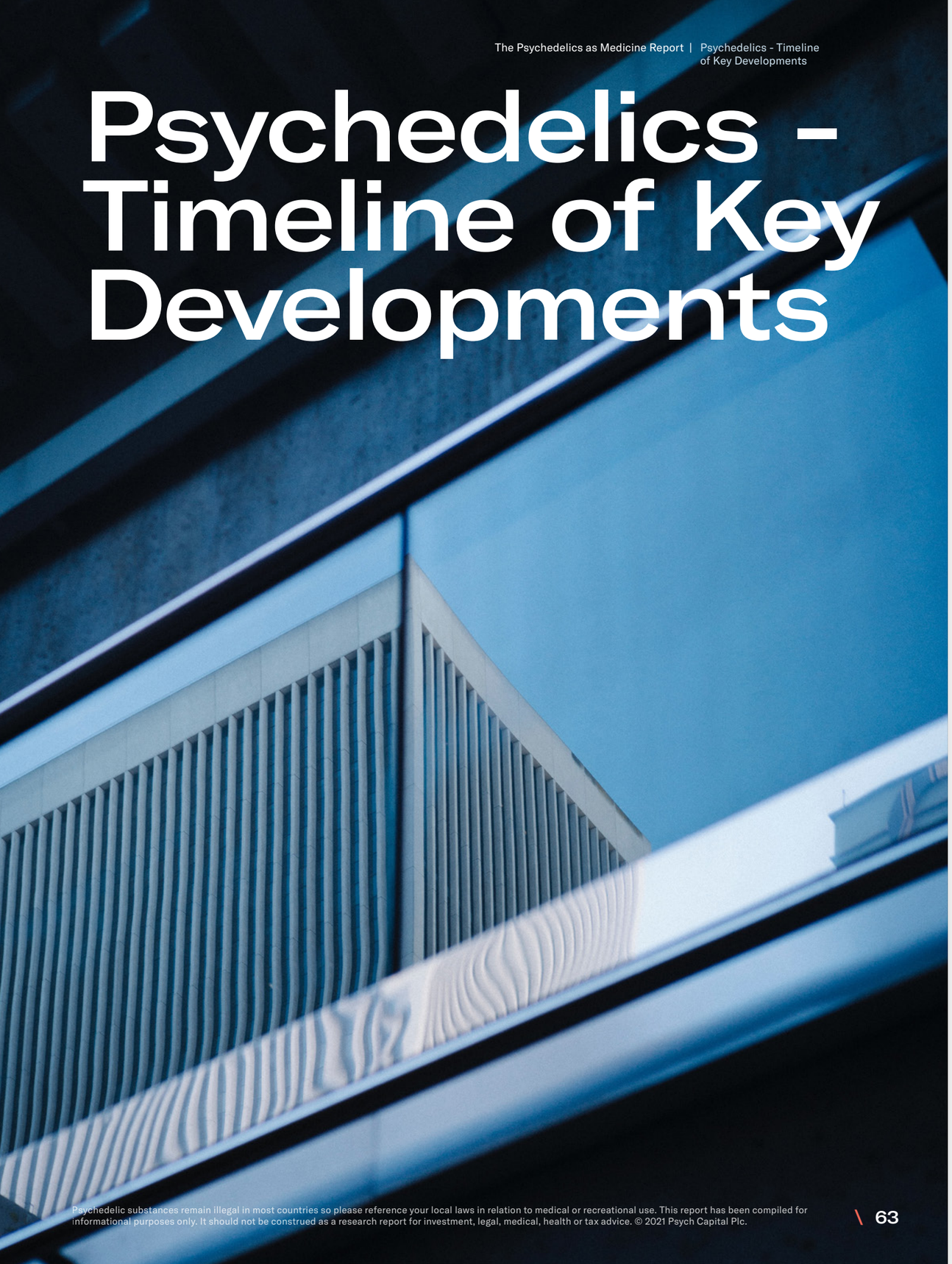
WHY PSYCHEDELICS ARE DIFFERENT

The jury is still out on how effective psychedelics will be in the treatment of mental health and substance use disorders. Early studies on everything from smoking cessation to PTSD show the significant and often lasting impact of psychedelics. But, not in all cases does depression stay away and without changing their environment, how long can we expect treatment effects to last? What will prevent psychedelics from becoming the next ineffective treatment?

The key difference between psychedelics and other treatments is that the methods and goals are completely different . Whereas many treatments are aimed at helping someone live with a condition and making life liveable again, psychedelics aim to cure. Psychedelics are activating and can help, in combination with psychotherapy, someone to 'face the music'.

This also means that psychedelic therapies are not a pill or treatment that someone has to take every day for the rest of their life. Some early psychedelic studies have shown that participants were free from anxiety for up to five years. More studies will have to show if these effects are sustained or whether psychedelic treatments need to be repeated months or years later.

These effects have been found in early clinical trials and for the classical psychedelics that are detailed in this report, but this is not for all psychedelics, such as ketamine. The cost-effectiveness to society needs to be carefully examined, as the upfront costs of psychedelic treatments are often much higher than that of other therapies. Only if PAT is able to help a large proportion of those treated, and for a long period of time, can we expect them to find widespread adoption.



Psychedelics - Timeline of Key Developments

The Psychedelics as Medicine Report | Psychedelics - Timeline of Key Developments

Year	Month	Event	Location
1896		Arthur Heffter isolates mescaline for the first time	Germany
1901		Dybowsky and Landrin isolate ibogaine for the first time	France
1912		Anton Köllisch synthesises MDMA for the first time	Germany
1938	November	Albert Hofmann synthesises LSD for the first time	Switzerland
1947		LSD is introduced as a commercial medication to psychiatrists under the trade-name Delysid	Global
1958		Albert Hofmann isolates psilocybin for the first time	Switzerland
1962		Calvin Stevens synthesises ketamine for the first time	US
1962	April	Walter Pahnke and colleagues conduct the Good Friday Experiment	US
1966	May	California bans LSD	US
1968	October	Staggers-Dodd Bill passes, banning possession of LSD and other stimulants and depressants without a prescription	US
1971	February	UN publishes the Convention on Psychotropic Substances; psychedelics including LSD, DMT and MDMA are now internationally controlled substances	Global
1971	May	US Controlled Substances Act comes into effect moving most major psychedelic drugs to Schedule I	US
1971	May	UK passes Misuse of Drugs Act 1971, placing controls on most known psychedelics	UK
1977		MDMA will be used by a small group of psychotherapists for the next eight years	US

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Year	Month	Event	Location
1985	June	MDMA joins other psychedelics and is added to Schedule I under an emergency ban by the Drug Enforcement Agency (DEA)	US
1996	June	Canada moves many psychedelics, including LSD and psilocybin, to Schedule III	Canada
2000	November	World's first clinical trial of MDMA-assisted psychotherapy begins in Madrid; it will be shut down before completion - Spain	Spain
2001	July	Personal possession of all drugs decriminalised in Portugal	Portugal
2014	September	The results from an open-label pilot study show 80% of participant smoking-free 6 months after psilocybin-assisted therapy	US
2017	August	MDMA-assisted psychotherapy granted Breakthrough Therapy designation (BTD) from US FDA	US
2018	October	COMPASS Pathways receives BTDfrom US, FDA for psilocybin synthetic derivative, COMP360	US
2019	March	Esketamine approved in the form of Spravato by FDA, followed by European Commission approval in December	Global
2019	May	Denver, Colorado votes to decriminalise psilocybin mushrooms	US
2019	June	Oakland, California votes to decriminalise psilocybin mushrooms	US
2019	November	Usona Institute receives US FDA BTD for psilocybin treatment for MDD	US
2020	January	COMPASS Pathways announces US patent approval of COMP360, its synthetically derived psilocybin for the treatment of TRD	US
2020	February	Santa Cruz, California votes to decriminalise psychedelic substances including psilocybin, ayahuasca and peyote	US
2020	March	MindMed becomes the first publicly listed psychedelics company	Canada

Year	Month	Event	Location
2020	April	A number of ballot initiatives to decriminalise / legalise psychedelics in states in the US are impeded by the spread of COVID-19 - US	US
2020	May	MAPS preparing for FDA approval after positive interim analysis of phase III trials of MDMA for PTSD	US
2020	July	Oregon Psilocybin Service Initiative (IP34) succeeds in placing legal psilocybin for treatment in a medical setting on the state ballot for November 2020	US
2020	August	Health Canada grants four exemptions for use of psilocybin in palliative care	Canada
2020	September	Ann Arbor, Michigan becomes third US city to decriminalise psychedelic substances including psilocybin, ayahuasca and peyote	US
2020	October	Numinus Wellness harvests Canada's first legal psilocybin mushrooms	Canada
2020	November	Washington DC decriminalises psychedelic substances including psilocybin, ayahuasca and peyote	US
2020	November	Oregon decriminalises psychedelics and creates psilocybin-assisted therapy framework with the passing of Measures 109 and 110	US
2020	December	UK approves clinical trial for DMT to treat depression	UK
2021	March	UK's first ketamine-assisted psychotherapy clinic opens in Bristol	UK
2021	March	Australian government invests AU$15 million into research of psychedelic medicines - Australia	Australia
2021	May	MAPS publishes results from phase IIIa clinical trial, showing potential for MDMA to combat PTSD	US
2021	June	California Senate approves bill to legalise possession of psychedelics	US
2021	June	COMPASS Pathways completes phase IIb clinical trial for psilocybin derivative to treat TRD	UK
2021	July	Health Canada approves real-world open-label trials for MDMA-assisted therapy to treat PTSD	Canada

Countries to Watch

The Psychedelics as Medicine Report | Countries to Watch

KEY TAKEAWAYS

1. Canada has resisted the harsh classification of drugs and was the first G8 country to legalise cannabis. The same route through which cannabis found medical use, Section 56 exemptions, is now also being explored with psychedelics.

2. The Canadian Securities Exchange has become the place for forward-thinking companies that work with psychedelics to list, with over US$330 million being raised on the exchange, in the first half of 2021.

3. China has historically been averse to psychedelics and has even tried to add ketamine to the list of controlled substances. Yet, in the last few years, a dozen studies have been done to generate evidence for ketamine's effectiveness in this country of 1.4 billion people.

4. Switzerland has allowed psychedelic-assisted therapy through compassionate use exemptions and has also had an outside impact on psychedelic research with 35 clinical trials being conducted in the country, surpassing any other country, bar the US.

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CANADA

Canada has a history of embracing novel healthcare policies, as an early adopter of assisted dying and medicinal cannabis. In 2020, the federal regulator, Health Canada, granted over 20 exemptions to access psilocybin and this year approved a clinical trial to combat treatment-resistant PTSD with MDMA. The study within the patient population hopes to identify best practices for its medical application, and obtain safety and efficacy data for its regulatory approval.

Politicians in Canada have long supported drug decriminalisation, even when it put the country at odds with the international community. At the same time as the UN published the Convention on Psychotropic Substances, the US passed the US Controlled Substances Act and the UK enacted the Misuse of Drugs Act 1971, Canada's Le Dain Commission were recommending that regulations be loosened and that drugs be gradually decriminalised.

Alas, in 1996 the Controlled Drugs and Substances Act was passed, which classified drugs into eight schedules, I to VIII, similar to the US framework. In 2018, Canada federally legalised cannabis, the first G8 country to do so, setting a trend that resulted in a UN Commission voting to declassify the drug in 2020. As the world caught up with Canada's progressive drug policy, Health Canada granted over 20 exemptions from the Controlled Drug and Substances Act for researchers, drug developers, medical practitioners and patients to access psilocybin.

The four initial Section 56 exemptions were permitted to palliative care patients to ease end-of-life distress, with studies having demonstrated psilocybin's potential to treat depression and anxiety for this patient population. Since the landmark decision, the reasons for Section 56 exemptions have been expanded, enabling for-profit and non-profit companies to cultivate, harvest, process and study psilocybin producing fungi. If these exemptions show exceptional results, it is hoped psilocybin's therapeutic use may be recognised and legalised.

In October 2020, Numinus Wellness harvested Canada's first legal flush of psilocybe mushrooms, with the favourable regulatory climate encouraging the relocation of burgeoning psychedelic companies abroad. The Canadian Securities Exchange became the 'de facto' trading platform for US cannabis operators to connect with investors. Psychedelic companies, such as Braxia Scientific, are following a similar route, with over US$330 million being raised on the exchange in the first half of 2021 alone.

In addition to significant steps towards the regulation of psilocybin, in 2021, Health Canada made a momentous decision on MDMA-assisted therapy, approving a clinical trial to investigate the compound's safety and efficacy in combating treatment-resistant PTSD. The study not only hopes to identify MDMA's suitability for regulation but also opportunities to streamline treatments to reduce costs and promote their adoption. The demand for novel treatments and restricted drugs is so high that Health Canada has restored its Special Access Programme, to make it easier for researchers and healthcare professionals to obtain banned compounds for treatment-resistant disorders.

With a history of embracing progressive health policies, and by demonstrating support for psychedelic medicines by providing legal exemptions for patients and through the revival of the Special Access Programme, many psychedelic companies and investors are venturing that Canada may be the first country to enact federal legislation authorising psychedelic medicines. If correct, this could provide these stakeholders with a crucial first-mover advantage.

CHINA

Although the vast majority of research and development of psychedelic medicines has taken place in North America and Europe, China has conducted a dozen clinical trials to investigate the potential of ketamine and more recently psilocybin. These are critical to global adoption with studies in China recruiting participants of ethnicities underrepresented in the western hemisphere.

China has strict illicit drugs laws, with death sentences handed out in severe cases. The country has also repeatedly asked the UN to add ketamine to the Convention on Psychotropic Substances of 1971 Act; thereby removing its designation as an essential medicine.

However, China is also running clinical trials to explore the benefits of the same compounds that it rigorously denounces. In tightly controlled environments, the country has conducted as many clinical trials with psychedelics as Israel and nearly as many as the UK, with ketamine being the principal focus of its investigations, alongside a solitary study into psilocybin.

The results of these studies have wide-reaching implications for researchers and regulators, as they have been conducted outside the western hemisphere with local patient populations. This is important as patient diversity in clinical trials is essential, as a better representation of society globally, with researchers being able to access a wider data set and to therefore better generalise the outcomes.

China has hosted clinical trials to observe the long-term safety of ketamine in the treatment of depression. A 2015 study involved over 120 patients dependent on the drug, to identify correlations with psychotic and depressive disorders and the concerns raised. In 2018, research was published by neuroscientists at the Zhejiang Chinese Medical University, who detected instances where ketamine impacted on brain activity and as a result identified molecular targets to manufacture ketamine-based antidepressants with greater safety and efficacy.

In an effort to develop medicines for treatment-resistant depression, Wuhan General Group is exploring the therapeutic potential of psilocybin through its subsidiary M2BIO. The subsidiary looks to create new therapies for mental disorders, including anxiety, PTSD, and addiction, by disrupting neuroactivity. The company is well-positioned to collaborate with legislative bodies and once created, these novel treatments could be regulated in China and further afield, for large patient populations, with the healthcare policies of many Asian countries echoing the regional superpower.

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SWITZERLAND

Switzerland became synonymous with psychedelic research following Albert Hofmann's synthesis of LSD and isolation of psilocybin. Despite its small size, the country has conducted the second largest number of clinical trials into psychedelic medicines. Home to a number of prestigious scientific organisations, studies have been conducted on a wide range of psychoactive substances including ayahuasca, DMT and mescaline.

Swiss chemist, Albert Hofmann, first synthesised LSD in 1938 and was the first to consume the compound five years later. Fifteen years later he isolated psilocybin and psilocin, cementing himself in the foundations of psychedelic research.

In 1951, Switzerland passed the Narcotic Drugs and Psychotropic Substances Act, to prevent unauthorised consumption and to regulate the availability of psychedelics for medical and scientific purposes. In 1972, Zurich recorded its first fatal heroin overdose, leading the government to adopt a progressive public health approach to drug policy, centred around harm reduction.

Switzerland legalised psychedelic-assisted therapy in 1988, with medical practitioners authorised to prescribe LSD and MDMA. A group setting approach was applied to the therapy, which would reduce the resources associated with the treatment, to increase its accessibility and adoption. Between 1988 and 1993, when the programme ended, almost 200 patients had been seen in a group setting, in studies that would inform trials in future populations.

From 2007, Switzerland restarted examination of the potential of LSD-assisted therapy, under an expanded compassionate use programme, and in 2012 conducted a study with MDMA to combat treatment-resistant PTSD. Subsequent studies investigated optimal dosages in therapeutic settings and the benefits of LSD in palliative care; sponsored by the Swiss National Science Foundation.

On the back of these results, the Swiss regulator has granted authorisations for over a dozen patients to access MDMA and LSD in a therapeutic setting. Initially, protocols were developed for individual therapy, to promote regulatory approval, however, group therapy trials were also approved in 2017, enabling researchers to benefit from the data collected nearly thirty years earlier.

In 2018, Switzerland conducted fMRI scans on subjects to observe changes in brain activity - pioneering research into how LSD impacts neuron activity to disrupt mental disorders. Decreased functional connectivity was observed within the default mode network with between-network connectivity intensifying, particularly in the thalamus and cerebral cortex.

In 2020, MindMed acquired data and patent rights for research into psychedelic medicines conducted at the University Hospital Basel over a 10 year period. Later that year, Switzerland approved MindMed's phase IIa clinical trial into LSD's efficacy to treat ADHD and a phase I trial into the application of LSD and MDMA in combination. The firstever clinical trial, using both together, started in 2021, with the results expected to be published in 2022.

With an extensive history of research into psychedelic-assisted therapy, Switzerland has developed the framework, institutions and expertise to continue pioneering new treatments. Over 35 clinical trials have been conducted in the nation, with a conducive regulatory environment attracting drug developers to establish and invest in future studies.

The Psychedelics as Medicine Report | Countries to Watch

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Psychedelic Profiles

The Psychedelics as Medicine Report | Psychedelic Profiles

This section provides detailed profiles of each psychedelic and the mental health and substance use disorders for which they can offer compelling novel treatments. Each combination is either being studied in a clinical trial, usually in combination with psychotherapy, or it is soon to be studied.

List of 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 Disorder	✓		✓	✓		✓			

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HEALTH CONDITION	PSYCHEDELIC SUBSTANCE								
	Psilocybin	LSD	MDMA	Ketamine	Ibogaine	Ayahuasca	DMT/5-MeO-DMT	Mescaline/ Peyote	Salvinorin A/Salvia
Opioid Use Disorder				✓	✓	✓			
Chronic Pain			✓	✓					
ADHD		✓							
Cluster Headaches	✓	✓							
Stroke							✓		
OCD	✓			✓					
Inflammation		✓		✓				✓	

Note: This is an indicative list for illustrative purposes only and should not be regarded as exhaustive.
Source: Blossom/Clinicaltrials.gov

The Psychedelics as Medicine Report | Psychedelic Profiles

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EXPERT INTERVIEW

George Goldsmith
CEO and Co-founder, COMPASS Pathways

What is psilocybin therapy and why is everyone talking about it?
Psilocybin therapy is one of the most promising innovations in psychiatry today and has the potential to transform the lives of millions of people suffering with mental health challenges.

We are in the middle of a global mental health crisis. One person dies from suicide every 40 seconds and in that same timeframe another 20 attempt it. More than 320 million people of all ages around the world suffer with depression and up to a third of them are diagnosed with "treatment-resistant depression" (TRD) and not helped by current treatments.

Psilocybin is an active ingredient in some species of mushrooms, often referred to as "magic mushrooms". Early studies have shown that a single high dose of psilocybin could improve outcomes for patients with depression, anxiety, addiction and other mental health illnesses, when administered with psychological support from specially trained therapists.

So we have a therapy that could make a difference in areas of significant unmet medical need. That's why people are talking about it.

What is COMPASS's part in this?
I co-founded COMPASS Pathways with my wife, Ekaterina Malievskaia, after we experienced the pain of mental health illness in our own family. Our son became very ill when he went to college. We thought it would be easy to fix – it wasn't. Each new medication made him worse and the mental health care system did not provide the care he so desperately needed.

Along our journey we talked to many, many people who told similar stories of feeling helpless and frustrated by the inability to access effective mental health care. Some of these were people we had known for years, who were opening up to us for the first time. We realised that "everyone has a story" – and we started COMPASS so that we could do something to bring innovation and help to patients.

In 2018 we received Breakthrough Therapy designation from the FDA for COMP360, our proprietary formulation of synthetic psilocybin. And we are currently in the final stages of a large-scale, randomised, controlled phase IIb study of psilocybin therapy for TRD, taking place in 22 sites across 10 countries. This is the world's largest psilocybin therapy trial. Data is expected by the end of 2021 and if all goes well, we'll begin phase III next year and hope to apply for regulatory approval after that.

If this therapy gets approved, how will people access it? What does your business model look like?
Access is central to our mission at COMPASS. We are in active discussions with regulators, payers and insurers about the data we need to generate in order to ensure that this therapy is reimbursed and made available to patients in need, regardless of their ability to pay.

If COMP360 psilocybin therapy is approved, we plan to target public and private healthcare providers and clinic networks directly; we will not be building our own clinic network. Any business model will have to include digital solutions to complement and augment our psilocybin therapy protocol. Digital technologies can help to collect and measure behavioural information that will enable us to provide personalised care pathways that could help predict and prevent deterioration and relapse.

What else is in your portfolio?
We work with leading academic institutions and researchers around the world, and provide our COMP360 psilocybin, free of charge, to selected investigator-initiated studies (IISs) in areas of high unmet need. These are signal-generating, exploratory studies covering indications such as anorexia nervosa, bipolar disorder II, body dysmorphic disorder, depression in cancer, and PTSD. If these studies provide signals that merit further investigation, we will consider moving them into late stage trials.

We also have an active preclinical research programme. The hub of this is our Discovery Center, anchored at University of the Sciences in Philadelphia, and with a network around the US. The teams here are developing many new, optimised psychedelic compounds that target the 5HT2A receptor, which is believed to mediate the potential therapeutic effects of psychedelics. We plan to have a couple of these enter clinical trials over the next 18 months to two years.

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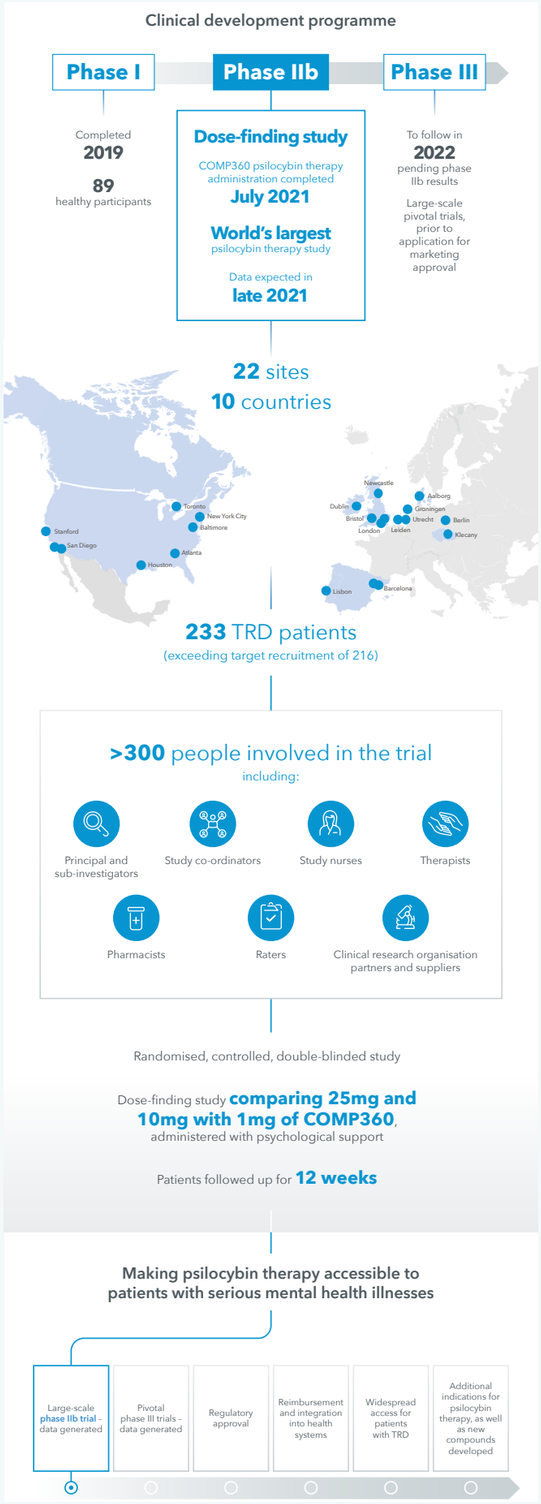

How have you seen this field change over the last few years?

There are been growing excitement around psychedelic therapies in recent years, with much talk of the "psychedelic renaissance", numerous psychedelic companies and retreats emerging, and a rising interest from politicians in legalising substances including psilocybin.

We are a mental health care company, which means our priority is to help people with serious mental health challenges. Developing psychedelic therapies is, for us, a way of achieving this goal, it is not the goal.

This means that evidence is our friend. We need to generate data, through rigorous clinical trials, that demonstrate quality, safety and efficacy of psilocybin therapy. Only then can it be approved by regulators, reimbursed, and made available to as many as possible who might benefit.

What progress do you anticipate making in the next 12 months?

Data from our phase IIb trial will be shared in late 2021; if all goes well, we aim to move into phase III in 2022. We will also be expanding our portfolio with studies in new indications, based on the signals we see from our IIS partners.

We are building a strong digital team, with experts from Mindstrong, Tesla, Stanford, and Google-sister company Verily, working together to build apps and tools that will be able to quickly measure and track behavioural change, and improve patient outcomes.

The promise of psilocybin therapy is significant. To make sure we realise this promise, we need to generate data that will demonstrate the safety and efficacy of psilocybin therapy and enable its widespread rollout and accessibility to all. The promise is big but we must be patient for a little while longer.

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Key Psychedelic Deep Dives

The Psychedelics as Medicine Report | Key Psychedelic Deep Dives

The psychedelic deep dives presented here offer detailed information on clinical trials and research being conducted and the legal framework surrounding the following psychedelics, as well as a breakdown of conditions for which each substance has potential curative properties. Featured in the key psychedelic deep dives are:

- Psilocybin
- LSD
- MDMA
- Ketamine
- Ibogaine
- Ayahuasca

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PSILOCYBIN

The Psychedelics as Medicine Report | Key Psychedelic Deep Dives

KEY TAKEAWAYS

1. Psilocybin-assisted therapy for depression (MDD and TRD) is finishing phase II clinical trials and may become a licensed therapy as early as 2025.

2. Academic studies conducted around the world using psilocybin with accompanying psychological support (PAT) are demonstrating rapid and long-lasting positive effects on patients suffering from depression and anxiety. In one study the positive effects were still evident up to four and a half years later.

3. Next to health care reimbursed therapies, decriminalisation efforts are opening another avenue through which psilocybin, ‘magic mushrooms’, can become a tool for the improvement of mental well-being.

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Psilocybin is a psychedelic that can be derived from over 200 varieties of fungi. Since its isolation in 1958 by Albert Hofmann, a variety of synthetic methods for producing psilocybin have been found. A human body quickly metabolises psilocybin into psilocin which is the pharmacologically active agent which interacts with several serotonin receptors in the brain. Specifically, it is best known for being a 5-HT2a agonist, meaning it can change serotonin activity in the human brain and disrupt dysfunctional brain connectivity. Through these and other mechanisms, psilocybin thus offers a potent new alternative for the treatment of a wide variety of mental health conditions.

Clinical trials and research

Psilocybin is, after ketamine, the second most studied psychedelics to date. There have been 64 clinical trials to date of which 26 are phase II studies. The trials with psilocybin are for the widest range of mental health disorders. The following is a list of conditions for which psilocybin has potential therapeutic benefits based on clinical trials and academic studies conducted to date:

- Depression (MDD, TRD, and bipolar);
- Anxiety and depression in patients with life-threatening disease;
- Social anxiety for those with autism;
- Substance misuse, including alcohol, opioid and nicotine dependence;
- Eating disorders such as anorexia nervosa;
- Demoralisation in long-term AIDS survivors;
- Cluster headaches/migraines; and
- Symptoms of obsessive-compulsive disorder (OCD).

In these 64 clinical trials, nearly 2,100 patients have been enrolled, as of July 2021. Among the active trials are those investigating psilocybin for the treatment of migraine headache, psilocybin for the treatment of OCD, and psilocybin-assisted treatment of alcohol dependence. Most of these studies are either taking place in the US or Europe, as is the case for the other key psychedelics.

North America

Several studies with psilocybin for relieving anxiety in those suffering from life-threatening diseases were the impetus for studying psilocybin in the US. This is also where, in 2020, a long-term follow-up study was done with participants from the New York University School of Medicine study. The researchers found that among 15 cancer patients who participated, up to 80% were still feeling the positive effects from one dose of psilocybin, up to four and a half years later.

Several studies carried out by researchers from the Centre for Psychedelics and Consciousness Research at Johns Hopkins University have concluded that not only does psilocybin have long-term, positive effects on the depression and anxiety scores of study participants and on the relapse rates of participants suffering from substance misuse conditions, but also the abuse potential of psilocybin compares favourably with other substances such as opioids. In other words, patients are at minimal risk of developing a dependence on psilocybin relative to other drugs which are used as medicines.

Researchers at the University of New Mexico Health Sciences Centre have instigated a pilot study for the treatment of alcohol dependence with psilocybin. The study with ten participants showed that up to nine months later they had significantly reduced their alcohol intake after two high dose psychedelic treatment sessions.

Also widely reported is another pilot study from Matthew Johnson and colleagues at Johns Hopkins that found that 12 of the 15 participants in a smoking cessation trial were not smoking up to six months later. A follow-up study 2.5 years after the trials showed that 60% were still smoking abstinent. These numbers compare favourably versus other, often much longer, treatments that achieve up to 35% smoking abstinence.

> I have smoked for a number of years, and I have attempted to quit on numerous occasions, and I always would go through withdrawal. I didn't with psilocybin.

Study participant, *Johns Hopkins University, psilocybin for smoking cessation trial*

Europe

In 2017, Imperial College London conducted a psilocybin study with 16 patients suffering from TRD, using fMRI technology to measure changes in brain function in the subjects before and after doses of psilocybin were administered. The study found that psilocybin, with accompanying psychological support, produced rapid and sustained antidepressant effects, with the potential to 'reset' the brain, offering a potential new treatment for TRD. The College's Centre for Psychedelic Research is positioning itself to serve as a model research clinic that serves as a prototype for the licensed psychedelic care facilities set to be a feature of mental health services in the future.

The Centre for Affective Disorders at King's College London established a psychedelic trials group, which received funding from the National Institute for Health Research (NIHR) in 2017, to investigate the safety and efficacy of psilocybin for patients with TRD, coupled with a suite of psychological supports and medical supervision, through a randomised, placebo-controlled trial. The centre, which is headed up by Professor Allan Young, is currently involved in trials sponsored by mental health care company COMPASS Pathways, which began in 2019.

The phase II study, which was also conducted at 21 other sites in Europe and North America, of psilocybin-assisted therapy for TRD, was completed in June 2021. COMPASS Pathways will publish the results of this trial in late 2021. The trial is the largest of its kind to date and has treated 216 patients. At this time, COMPASS Pathways is furthest along with making psilocybin, specifically their proprietary COMP360, into a medicine.

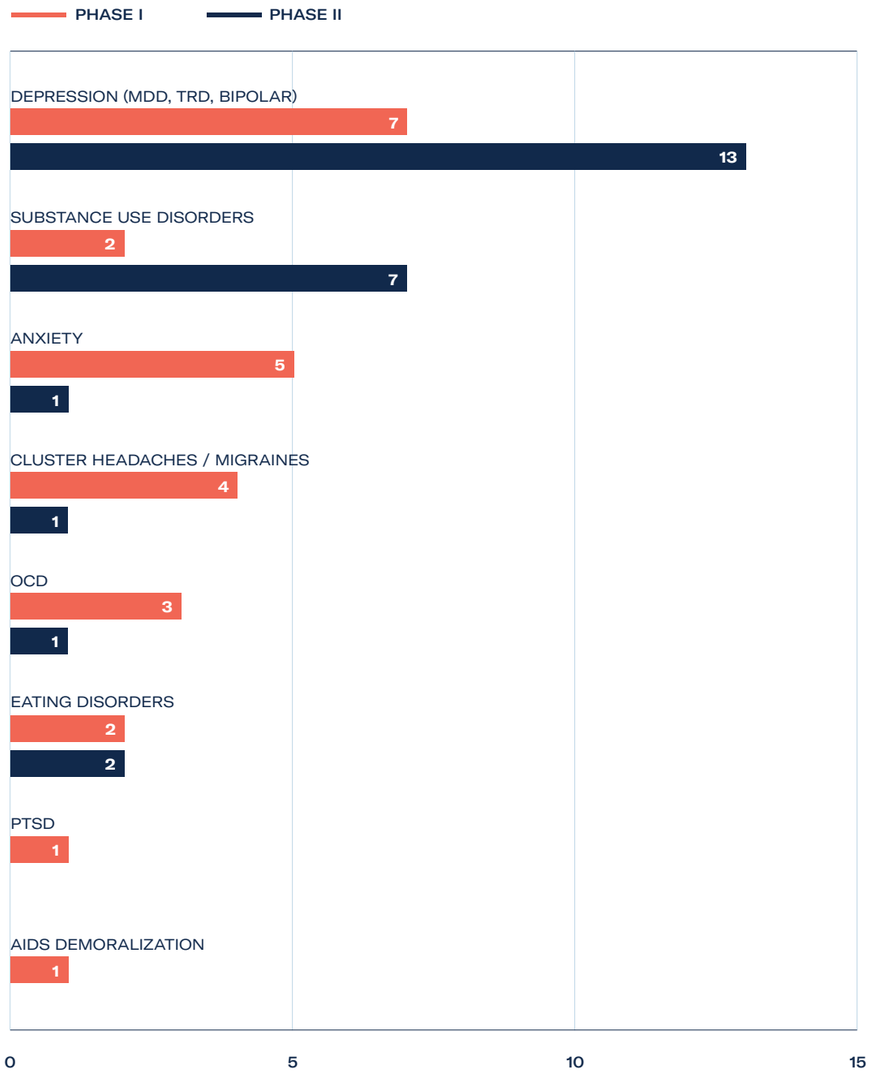
In continental Europe, the MIND Foundation has set up a comparable study. Since March 2021 they have been recruiting 144 patients to study the effects of one or two psilocybin doses on TRD. The EPIsoDE study is funded by the Federal Ministry of Education and Research, marking the first time direct federal funding has been allocated to such a study in Germany.

Oceania

In Australia, Mind Medicine Australia (MMA) and St Vincent's Hospital, Melbourne, are co-operating on a psilocybin study on anxiety in terminally ill cancer patients. MMA is a registered charity that aims to support safe and effective psychedelic-assisted treatments, via clinical research. MMA focuses specifically on the clinical application of medicinal psilocybin and medicinal MDMA for mental health conditions, such as PTSD and anxiety.

This effort is greatly assisted by the recent AU$15 million competitive grant that was launched in March 2021, only weeks after the Therapeutic Goods Administration (TGA) had rejected access for mental health professionals to use psychedelics. The money will be used to fund clinical trials in Australia with psilocybin, MDMA and other psychedelics.

Number of clinical trials to date, using psilocybin as an intervention, by condition treated



**Studies with healthy participants (usually phase I studies, are excluded from this overview, thus the total number of studies is lower than the total number of clinical trials conducted.*
Source: ClinicalTrials.Gov / Blossom (correct as of 01/07/2021)

Legality of psilocybin mushrooms worldwide

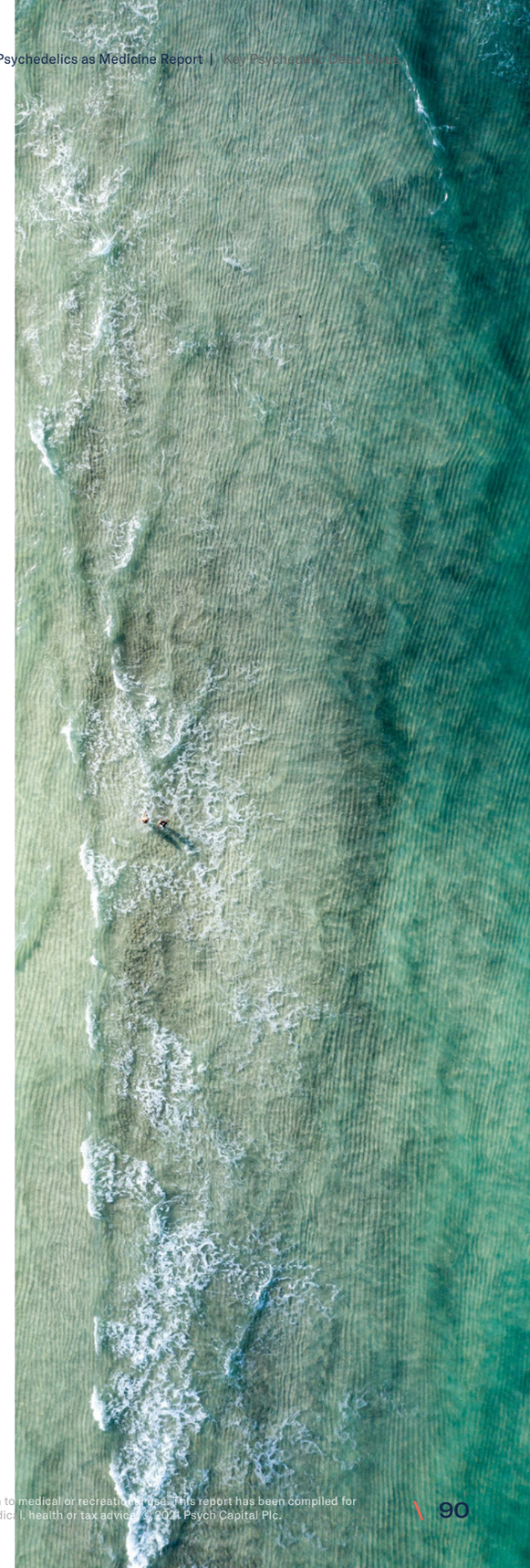
The UN Convention on Psychotropic Substances (the 'Vienna' Convention), 1971, identifies psilocybin as a Schedule I substance, a category of illicit drugs deemed to offer no medical benefit and with a high potential for abuse.

The Vienna Convention lacks clarity in relation to the legal status of organic materials containing psilocybin (i.e. so-called 'magic' mushrooms). The result is that not all countries have adopted a strict interpretation of the convention rules governing psilocybin mushrooms. The Netherlands is one example of a country that has created exemptions for its cultivation, sale and supply.

North America

The Controlled Substances Act, 1971, which provides a legal framework for the US federal drugs policy, prohibits the manufacture, sale, possession or use of psilocybin in the US. While this may be the case at the federal level, a number of initiatives at the state level have resulted in the decriminalisation of the substance. Some cities in Colorado and California approved the decriminalisation of psilocybin in 2019, with the citizens of Denver becoming the first in the country to vote to decriminalise psilocybin mushrooms on 7 May 2019. The city council of Oakland, in the state of California, followed a month later, on 5 June. In January 2020, Santa Cruz, also in the state of California, became the third city in the country to decriminalise psychedelic mushrooms. As of July 2021, more than seven cities and as many states, have implemented legislation surrounding the decriminalisation of psilocybin.

According to the grassroots movement, Decriminalise Nature, there are as many as 100 other initiatives at various stages of development in cities across the US. On 6 July 2020, activists in Washington DC seeking to decriminalise psychedelics submitted a sufficient number of signatures to successfully petition for inclusion on the November ballot. The Psilocybin Service Initiative of Oregon (PSI Oregon 2020) is a 2020 ballot initiative that led Oregon to become the first state to legalise



psilocybin-assisted therapies and to decriminalise personal possession of drugs (Measures 109 and 110). A two-year development process is currently ongoing to establish rules and regulations. The start of 2023 is the earliest date when applications related to the manufacture, sale and purchase of psilocybin products and services is set to commence in Oregon.

California, the most populous state in the US, has been working on decriminalisation legislation since Oakland's victory. Senator Scott Weiner is leading this charge and has successfully secured the decriminalisation of several psychedelics (notably excluding peyote for conservation reasons) through the Senate and several committees. A vote on the Assembly floor and the Governor's desk awaits.

Finally, a federal bill was introduced to US Congress to decriminalise drug possession in June 2021. The Bill is still in the early stages and will go through several revisions that will take at least several months. Still, this marks the first significant signal of change for drug policy at the federal level.

In Canada, an advocacy group made up of healthcare professionals, called TheraPsil, was established in 2017; its mission being to promote compassionate use of psychedelics. The group successfully challenged the illegality of psilocybin by petitioning Health Canada to allow access to mushrooms in a medical setting for those patients in palliative care who were experiencing psychological distress due to their terminal diagnoses. On 4 August 2020, in a landmark case, the Health Minister of Canada, Patty Hajdu, approved the use of psilocybin therapy for four patients with anxiety resulting from terminal cancer. It is the first exemption for the use of a psychedelic treatment in Canada since 1974.

Since then, 17 healthcare professionals have also been granted exceptions to possess and ingest psilocybin themselves in training to learn what processes their patients go through. After the initial four patients, 24 more have been granted section 56 exemptions. Still, these approvals are sometimes taking more than 100 days to be granted and as of July 2021 TheraPsil is urging, via their lawyers, the Minister of Health to respond within 14 days.

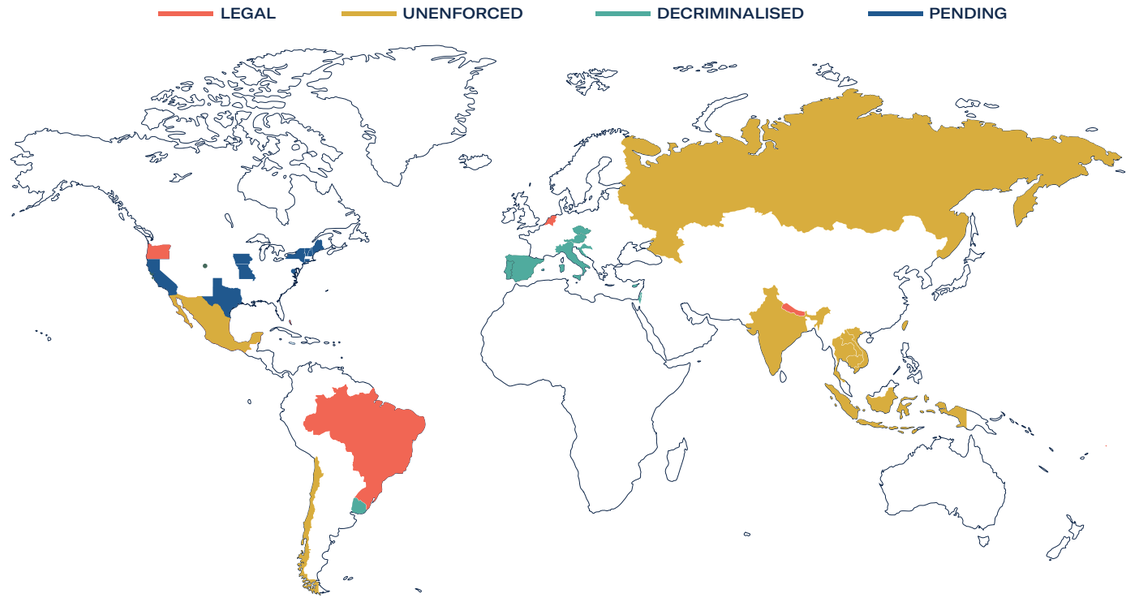
Europe

In 1976, the Netherlands was one of the first countries to decriminalise possession of 'small amounts' of any drug for personal use. In December 2008, the government of the Netherlands specified threshold limits on the amount of fresh and dried psychoactive mushrooms a person could be in possession of, for personal use. To date, it is legal to possess up to 5 grams of fresh mushroom or 0.5 grams of dried mushroom for personal use, but not for the purpose of sale or supply. Psilocybin truffles can be cultivated legally for these purposes because of a legislative loophole as the truffle is a different part of the mushroom, which grows beneath the earth rather than above ground. The production, possession and sale of truffles in 'smart shops' are legal in the Netherlands.

Oceania

In August 2020, the Green Party in the Australian Capital Territory (ACT) committed to supporting the introduction of regulated psychedelic therapies as part of its drug law reform election platform. Although the changes to the Therapeutic Goods Administration (TGA) at the start of the year were not honoured, more money is going towards research that could provide evidence for allowing the therapeutic use of psilocybin in Australia.

Map of cities, states and countries where psilocybin-containing mushrooms are legal or decriminalised for personal possession and use.



LEGAL	UNENFORCED	DECRIMINALISED	PENDING
NEPAL	CAMBODIA	PORTUGAL	CALIFORNIA
BRAZIL	CHILE	CZECH REPUBLIC	TEXAS
NETHERLANDS**	INDIA	AUSTRIA	MISSOURI
BAHAMAS	INDONESIA	CROATIA	IOWA
BRITTISH VIRGIN ISLAND	LAOS	CYPRUS	NEW YORK
SAMOA	MEXICO*	ISRAEL	VERMONT
OREGON	RUSSIA	ITALY	NEW HAMPSHIRE
	TAIWAN	SPAIN	CONNECTICUT
	THAILAND	URUGUAY	MAINE
	VIETNAM	ANN ARBOR	DENVER
		DISTRICT OF COLUMBIA	
		SOMERVILLE	
		OAKLAND	
		SANTA CRUZ	

Mushroom spores are not included in this list
**In Mexico, mushrooms are tolerated by authorities for use in religious rituals only.*
***In the Netherlands, magic mushrooms are illegal, but, due to a legal loophole, magic truffles are not.*
Source: Blossom/Psilocybin Alpha/Talking Drugs

LSD

The Psychedelics as Medicine Report | Key Psychedelic Deep Dives

KEY TAKEAWAYS

1. LSD was widely studied in the 1960s and generated over 1000 scientific papers. These studies showed positive developments in reducing anxiety during 'end-of-life' care, depression and alcoholism.

2. Modern-day studies using fMRI are enlightening researchers about the way everyday consciousness functions and how the hierarchy of the brain is 'flattened' or 'segregated' under the influence of LSD.

3. The duration of an LSD trip makes it a less likely candidate to be developed as a medicine. Its microscopic effective dose and widespread use in recreational microdosing do still show opportunities for the further study of this psychedelic.

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Lysergic acid diethylamide (LSD, LSD-25, acid) is a serotonergic psychedelic. LSD binds to serotonin receptors, specifically the 5-HT2a receptor, as well as dopamine receptors (which psilocybin doesn't bind to). The effects of LSD are noticeable at dosages measured in the millionths of a gram. Research studies use between 50 and 200 micrograms, which can produce effects for upwards of 12 hours. The study of LSD played a pivotal role in the discovery of the function of serotonin in the brain. Although widely studied in the 1960s, LSD is trailing behind psilocybin in terms of scientific interest.

Clinical trials and research

LSD was the most studied psychedelic around 60 years ago. Trials were conducted to study the effect of LSD on mood, alcohol dependence and, unfortunately also on patient populations with schizophrenia or autism, who hadn't given consent to being administered a psychedelic. These questionable practices, in a time before ethics review boards, and the lack of any control groups who were given a placebo, means that much of the research was not up to today's standards. The promising results from that time were also swept under the carpet when the counterculture adopted LSD as a recreational drug. The freeze on research has held back our understanding of mental health disorders for decades.

In the current era of research, 19 clinical trials have been conducted with LSD. Of those, four are phase II studies. The trials with LSD not only focus on mental health disorders but also serve a purpose for better understanding how our brains work. For instance, one study investigated the role of dopamine and serotonin after LSD administration and how this affected emotional processing. Studies like this can then inform those which more directly study mental health disorders in which emotional processing is disturbed.

The following is a list of conditions for which LSD has potential therapeutic benefits based on clinical trials and academic studies conducted to date:

- Depression (MDD);
- Anxiety and depression in patients with life-threatening disease;
- Substance misuse, including alcohol, opioid and nicotine dependence;
- Alzheimer's disease (low-dose LSD);
- Cluster headaches/migraines; and
- Symptoms of OCD.

In the 19 clinical trials, 530 patients have been enrolled as of July 2021. Among the active trials are those investigating LSD for the treatment of anxiety, LSD for the treatment of depression, and LSD as a treatment for cluster headaches.

Europe

Researchers in Basel, the city in which Albert Hofmann discovered LSD, are now testing the effects of this psychedelic on the human fear response. Researchers have shown that 100 micrograms of LSD are sufficient to reduce the fear response in healthy subjects who are shown pictures of others in a fearful state. They observed reduced activity in the amygdala (emotional centre), which was mirrored by the subjects' reports that those who received the LSD dose experienced less fear than those who did not.

How LSD specifically, and psychedelics in general, are metabolised in the body has a direct influence on the intensity of the 'lived' experience. Researchers found that people who lacked copies of the CYP (Cytochrome P450) gene, which codes for an enzyme that breaks down LSD, had up to 75% more exposure, as measured by their blood plasma levels, of LSD. These participants had more intense and longer-lasting trips. Information on genetic differences could lead to the development of more personalised medicines or to more personalised dosing.

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Another study in Switzerland, one of the few double-blind, placebo-controlled studies with LSD in patients, was conducted with 11 people who were suffering from life-threatening diseases. The patients underwent two sessions with either 200 microgram or 20 microgram (active placebo) LSD. The study found a significant decrease in anxiety and a trend towards lower scores on a measure of depression.

In 2019, the Beckley Foundation, in collaboration with Maastricht University, concluded one of the first double-blind, placebo-controlled studies on microdosing LSD and its effects on pain management, mood and cognitive function. Currently, the foundation is researching the impact that a fixed microdose of LSD can have on amplifying brain plasticity. It is hoped that the results of these studies will lead to LSD becoming a possible treatment for a range of conditions such as mood disorders, age-related cognitive decline/mild impairment, chronic pain, brain rehabilitation and addiction.

The present data suggests low doses of LSD could constitute a useful pain management treatment option that is not only effective in patients but is also devoid of the problematic consequences associated with current mainstay drugs, such as opioids.

Amanda Feilding, *Beckley Foundation, on LSD microdosing for pain trial*

A neuro-pharmaceutical company, MindMed, is also funding research into the effects of microdosing LSD and its impact on creativity and focus, with a view to developing a new treatment for the symptoms of ADHD. In April 2020, MindMed filed a patent in the US (preserving worldwide rights) for a neutraliser technology intended to shorten or eliminate the effects of an LSD trip during a therapy session. If sufficiently developed, this technology could effectively act as an 'off-switch' to an LSD trip. This research is a collaboration between MindMed and the University of Basel's Liechti Laboratories.

At Imperial College London (ICL), the Centre for Psychedelic Research (CPR) was set up last year, backed by five founding investors who contributed £3 million to get the project off the ground. The stated purpose of this research centre is two-fold: to investigate the potential of psychedelics in treating mental health disorders and secondly to probe the basis of human consciousness using the most modern imaging techniques available. One of the first studies conducted by the Psychedelic Research Group at ICL, prior to the establishment of the CPR, was a study on the effects of LSD on brain activity, using brain imaging techniques.

North America

Researchers at the Eleusis Benefit Corporation in New York are seeking to leverage the anti-inflammatory activity of low doses of LSD to stave off Alzheimer's disease. The company so far has been successful in stage I clinical trials, which demonstrated the safety of doses up to 20 micrograms in geriatric populations. Next, the researchers will investigate whether the anti-inflammatory activity of LSD is neuroprotective against Alzheimer's.

In June 2020, MindMed announced a phase IIb commercial drug trial, for the treatment of anxiety disorders, officially known as Project Lucy. The trial will focus on experiential doses of LSD, administered by a therapist. The company's aim will be to submit an application for an investigational new drug (IND) with the US FDA.

Oceania

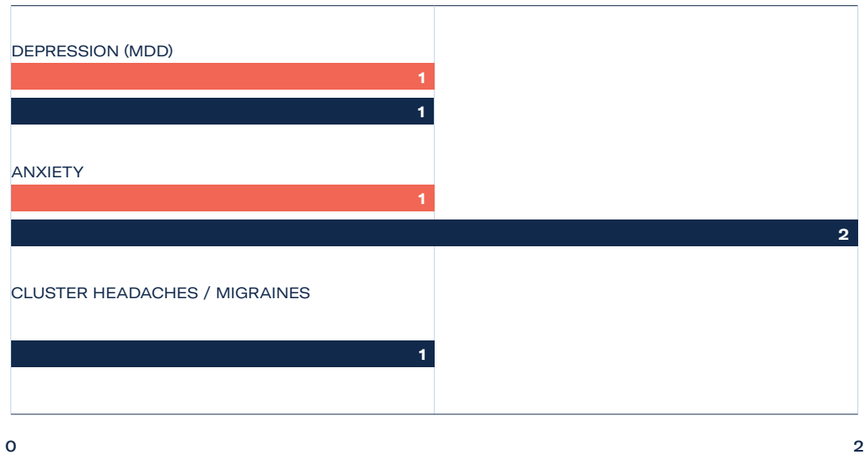
In January 2020, the Ministry of Health approved the first LSD microdosing study in New Zealand. Researchers at the Centre for Brain Research at the University of Auckland had previously engaged in other multidisciplinary research projects using LSD, including the same brain imaging study conducted by researchers from ICL.

Legality of LSD worldwide

The UN Convention on Psychotropic Substances (the 'Vienna' convention), 1971 identifies LSD as a Schedule I substance, a category of illicit drugs deemed to offer no medical benefit and with a high potential for abuse. The possession of LSD was made illegal in the US in 1968, but research continued until the late 1980s. Stringent government rules that prevented easy access for research purposes, in combination with less stellar results than hoped, ended any further research after that time.

The push for decriminalisation, as mentioned in our section on psilocybin, partly applies to LSD. The possession of small amounts of LSD (40 units or less) is decriminalised in Oregon as of February 2021. Some countries, including Mexico and Portugal, have decriminalised the possession of (small quantities) of drugs, including LSD.

Number of clinical trials to date, using LSD as an intervention, by condition treated



**Studies with healthy participants (usually phase I studies) are excluded from this overview, thus the total number of studies is lower than the total number of clinical trials conducted. This is especially true for LSD trials where healthy participants are often studied.*
Source: ClinicalTrials.Gov / Blossom (correct as of 01/07/2021)

MDMA

The Psychedelics as Medicine Report | Key Psychedelic Deep Dives

KEY TAKEAWAYS

1. MDMA is not regarded as a classic psychedelic; it is classified as an empathogen. It is an outlier among the other substances profiled in this report as there are no or fewer hallucinogenic effects. The potential for abuse in recreational use is also higher than with classical psychedelics.

2. MDMA-assisted psychotherapy for the treatment of PTSD has completed the first part of phase III clinical trials. After receiving Breakthrough Therapy designation from the US FDA in 2017 it is expected to get final approval in 2023.

3. It may then take up to six months after FDA approval for MDMA-assisted psychotherapy to be administered to the first patients. A real-world trial underway in Canada and other 'compassionate use' trials may give earlier access to a small number of patients.

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MDMA (3,4-Methylenedioxymethamphetamine, ecstasy) is a psychedelic that was first discovered in 1912, whilst finding a novel chemical route towards making another compound, by Merck. MDMA works primarily by increasing the availability of serotonin, dopamine and noradrenaline. A sense of general well-being and happiness, increased self-confidence, and increased empathy towards others are some of the subjective effects of MDMA. These effects are also what may facilitate psychotherapy efficacy.

Unlike with classical psychedelics, many recreational users experience a slump in their mood a few days after MDMA use. This negative side-effect has not been observed in clinical research where the dose is lower and patients are not dancing throughout the night; two factors that possibly contribute to the slump. Although most ecstasy tablets contain MDMA, it is not uncommon for them to contain adulterants. Similar to LSD, MDMA was used by therapists before it became illegal - particularly in couple therapy - and is still being used by underground practitioners to aid in the therapeutic process.

Clinical trials and research

MDMA is being researched as a potential treatment, in combination with talk therapy, for a variety of mental health disorders. There have been 47 clinical trials to date of which 19 are phase II studies and three phase III studies. The following is a list of conditions for which MDMA has potential therapeutic benefits based on clinical trials and academic studies conducted to date:

- PTSD;
- Depression, Major Depressive Disorder (MDD) and Treatment-resistant Depression (TRD).
- Anxiety;
- Social anxiety for those with autism;
- Substance misuse, specifically alcohol;
- Eating disorders, such as anorexia nervosa
- Chronic pain.

In these 47 clinical trials, nearly 1,900 patients have been enrolled as of July 2021. Among the active trials are several investigating MDMA for the treatment of PTSD, MDMA for the treatment of eating disorders, and MDMA for the treatment of alcoholism.

PTSD

PTSD is a stress-related, debilitating condition that may occur following a traumatic event such as war, disaster, sexual abuse, violence, terrorism, or from accidents resulting in traumatic brain injury (TBI). From the limited data available it has been suggested that up to 327 million adults may suffer from PTSD and/or major depression worldwide. In the US alone, an estimated 6.8% of the population will experience PTSD at some point in their lives (equates to over 22 million Americans). Currently, in the US approximately 870,000 veterans are in receipt of disability payments for PTSD from the Department of Veterans Affairs, which costs the US government an estimated US$17 billion a year.

MAPS

MAPS is a non-profit research and educational organisation established in the US in 1986 and it has raised over US$100 million for psychedelic therapy, medical cannabis research and education since its founding. Its sister organisation, MAPS Public Benefit Corporation (MAPS PBC) conducts the clinical trials and, as a wholly-owned subsidiary of MAPS, will aim to make MDMA-assisted therapy as widely available as possible whilst reinvesting profits to achieve this.

Worldwide

MAPS has led the effort towards making MDMA, when used in conjunction with psychotherapy, a medicine. This has culminated in the publication of the results of the successful phase III trial. The 90 participants received 12 therapy sessions of which three were with either placebo or MDMA. Of those who received MDMA, 67% no longer had PTSD,

compared to 32% in the placebo group. An additional 21% of those who received MDMA had a clinically meaningful response.

The data, which represents half of the participants that will be treated in the full phase III trial, mirrors that of earlier phase II trials. The results of the current cohort were only measured up to five weeks later. What earlier studies show is that, even 12 months later, those treated with MDMA were as likely, or even more likely, to not meet the diagnostic criteria for PTSD as they were at the point the study ended.

In August 2017, the FDA granted Breakthrough Therapy designation to MDMA-assisted psychotherapy for PTSD. The second half of the phase III trial is expected to be completed next year, in 2022. Full approval from the FDA is expected in 2023 and depending on the point in the year when this takes place, patients with PTSD may, during that same year, be able to get treated with MDMA. If treatment is approved, it will only be available following referral from a doctor and only in supervised therapeutic settings from certified clinicians.

The clinical trials have been conducted at more than 15 sites in the US, Canada and Israel. On 3 February 2019, the Department for the Treatment of Mental Trauma, housed within the Israeli Ministry of Health, announced the approval of the compassionate use for MDMA-assisted psychotherapy for PTSD, which will also allow 50 patients to receive the treatment. Patients with PTSD are eligible to receive treatment at four sites throughout Israel.

MAPS Europe is pursuing phase III trials on the continent which will allow MDMA-assisted therapy to also be approved by the European Medicines Agency (EMA). Money is currently being raised to get EMA approval as quickly as possible after FDA approval.

The resurgence of research into using drugs such as MDMA to catalyse psychotherapy is the most promising and exciting development I've seen in my psychiatric career.

Michael Mithoefer, *Acting Medical Director for MAPS PBC*

North America

In 2018, the University of California, Los Angeles (UCLA) conducted a small feasibility study (12 participants) on the impact of MDMA on the social anxiety of adults with autism. All of the participants in the study, even those who took a placebo, displayed some improvement, but patients who took the MDMA experienced a significant drop in their anxiety after the first session and another reduction after the second dose. Even six months after the treatment ended, they continued to feel considerably less anxious about social encounters.

Further north, at the Ryerson University in Toronto, researchers have conducted the first modern-day studies on MDMA and couple therapy. Of the six couples in the study, one of the partners was suffering from PTSD but both partners underwent cognitive behavioural conjoint therapy (CBCT). Both partners were happier, in a better relationship with each other, and the partner suffering from PTSD also felt relief regarding the symptoms related to PTSD.

MDMA has also been investigated as a treatment for anxiety and other psychological distress related to life-threatening illnesses. A small 2018 study at the Harbor-UCLA Medical Centre found improvements in scores of anxiety, but these results didn't reach significance. A larger trial, with more participants, may find that MDMA can be beneficial for this patient population too.

An ongoing study, that is recruiting patients, will investigate the safety and feasibility of treating eating disorders with MDMA-assisted therapy. Specifically, the study will investigate those with anorexia nervosa restricting subtype (AN-R) and binge-eating disorder (BED). This study is also being supported by MAPS and is a phase II study that will take place in the coming year in the US and Canada.

Europe

Researchers from Imperial College London (ICL), some of which are also associated with Awakn Life Sciences, have published the first results of MDMA-assisted therapy for those with alcohol use disorder (AUD). The study was an open-label trial, meaning all patients knew they were getting MDMA, and involved two sessions with MDMA and then eight further therapy sessions. Patients went from drinking an average of 131 to 19 units of alcohol per week from before the study to one year after completion. Although there was no head-on comparison, other treatments for AUD rarely, if ever, find results of this magnitude.

The Psychedelics as Medicine Report | Key Psychedelic Deep Dives

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Legality of MDMA worldwide

A number of countries worldwide have decriminalised the possession of small amounts of any drug, so long as it can be proven that the drug is intended for personal use. Some of these countries have explicitly legislated for threshold amounts of MDMA.

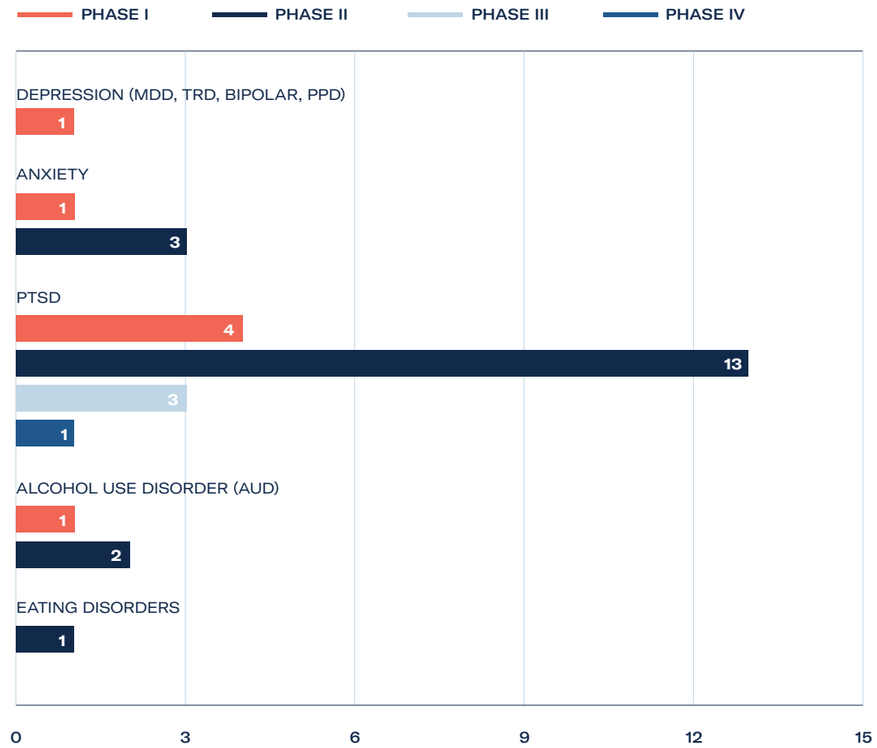
These countries vary greatly in terms of what constitutes acceptable threshold amounts. In Germany, for example, possession of up to five grams of MDMA for personal use is permitted. In Peru, on the other hand, possession of any amount greater than 0.25 grams of MDMA will result in sanctions. Furthermore, Peruvian national police continue to make arrests for drug possession, which, in 2018, accounted for almost half of all arrests for drug offences. Internationally, MDMA remains a Schedule I controlled substance, meaning it is considered to have a high potential for dependence and abuse.

Map of cities, states and countries with thresholds for MDMA possession

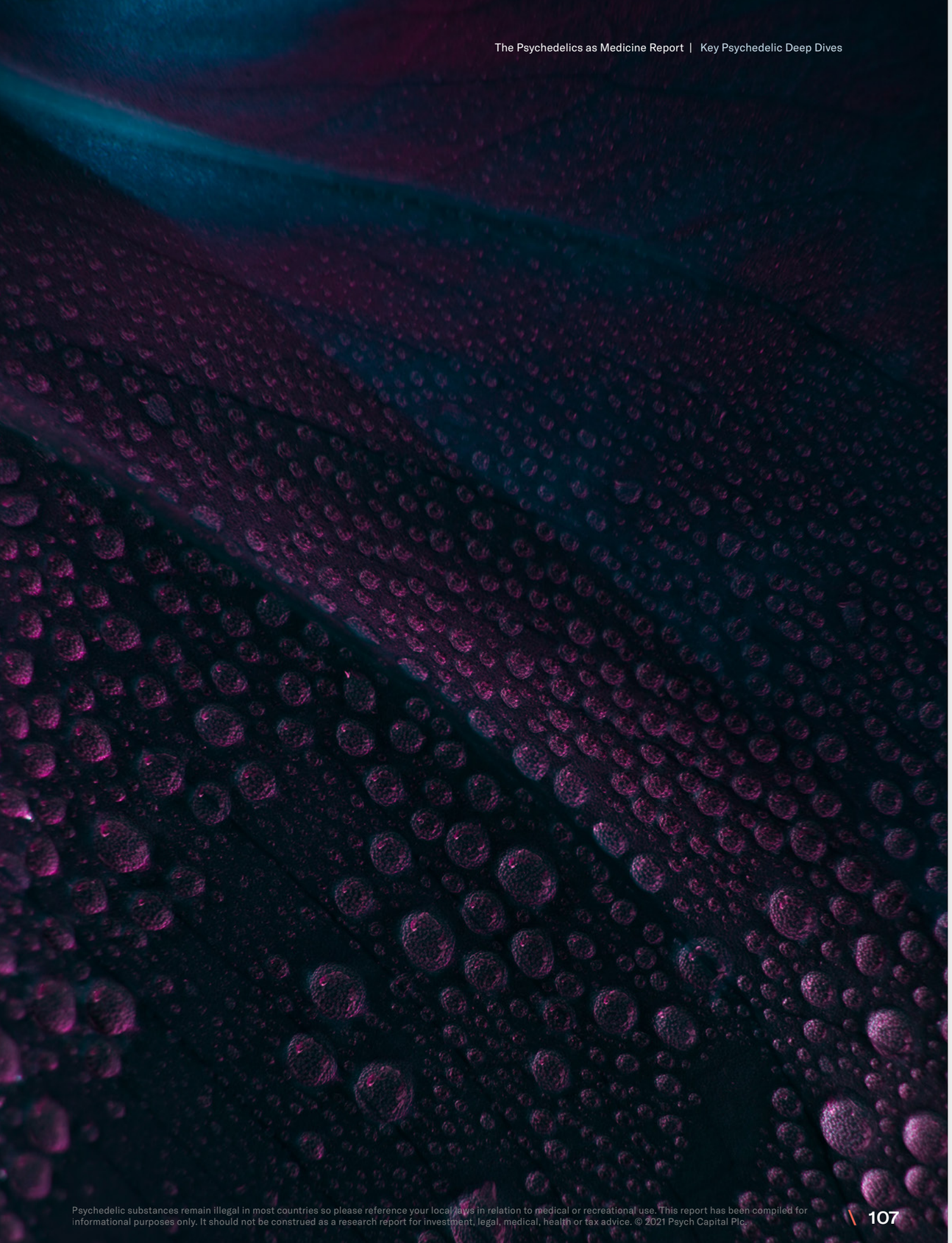
	COUNTRY / STATE / CITY	AMOUNTS OF MDMA PERMISSIBLE	YEAR DECRIMINALISED
<5g	GERMANY	5g	1992
	SPAIN	2.4g	1983
<2g	CZECH REPUBLIC	1.2g	1990
	PORTUGAL	1g	2001
	OREGON	1.2g	2021
<1g	NETHERLANDS	.5g	1976
<.5g	RUSSIA	.3g	2004
	PERU	.25g	1991
	MEXICO	40mg	2009

Source: talkingdrugs.org / Blossom

Number of clinical trials to date, using MDMA as an intervention, by condition treated



***Studies with healthy participants (usually phase I studies) are excluded from this overview, thus the total number of studies is lower than the total number of clinical trials conducted.*
Source: ClinicalTrials.Gov / Blossom (correct as of 01/07/2021)



Timeline: MDMA as Medicine

Year	Developments
2008	First MDMA-assisted psychotherapy open-label study for PTSD completed by MAPS
2013	Phase II trials begin
2017	MAPS applies to the US FDA for BTD for MDMA-assisted psychotherapy for PTSD
2017	FDA grants BTD for MDMA-assisted psychotherapy for PTSD
2019	The Ministry of Health in Israel approves compassionate use of MDMA for treatment-resistant PTSD
2020	MAPS receives approval from the US FDA for expanded access programme for MDMA-assisted psychotherapy for up to 50 patients across 10 sites in the US
2020	MAPS raises $30 million with the Capstone Challenge organized by Tim Ferriss and the Psychedelic Science Funders Collaborative (PSFC)
2021	Phase IIIa trials completed in the US
2022	Phase IIIb trials expected to be completed in the US
2023	MDMA-assisted psychotherapy is expected to receive FDA approval and to be available to patients in the US from certified clinicians, upon referral from a doctor
2024	MAPS expects EMA (Europe) and MHRA (UK) approval by the end of the year
2029	MAPS has the goal to treat 500,000 patients before the end of data exclusivity

Source: Blossom / MAPS

KETAMINE

The Psychedelics as Medicine Report | Key Psychedelic Deep Dives

KEY TAKEAWAYS

1. Unlike other psychedelics, ketamine has been available as a medicine (general anaesthetic) for decades. For this reason, it is on the World Health Organisation's List of Essential Medicines. It is also used as an 'off-label' treatment for depression, anxiety and suicidal ideation.

2. There has been a proliferation of ketamine therapy clinics throughout the US and to a lesser extent in Europe. These clinics may well become a prototype in the market, occupying a prime position to take advantage of future expansion into psilocybin and MDMA assisted-therapy, when these substances receive FDA and EMA approval. The sector is relatively unregulated and ketamine infusion therapy is often not administered in conjunction with talk therapy.

3. Esketamine, a subtype of ketamine, in the form of a nasal spray (Spravato) has been patented by Johnson & Johnson and has been approved for the treatment of TRD with accompanying suicidal ideation. The costs of Spravato are significantly higher than that of ketamine which has led the UK's National Institute for Health and Care Excellence (NICE) and Health Canada to not approve it as a medicine.

4. Ketamine is the only psychedelic substance, among those profiled in this report, to be the focus of clinical trials in Asia. In China, specifically, clinical trials are focused on ketamine as an intervention, to study the impact of ketamine on health conditions such as postnatal depression, autism in children and arthritis.

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Ketamine was first synthesised in 1956 and is used most commonly in veterinary practice as an animal tranquilliser. It is also a human anaesthetic and a powerful psychoactive substance and is available in liquid-soluble form as ketamine hydrochloride. Ketamine was granted US FDA approval for medical use as a general anaesthetic and sedative back in 1970 and has been classified as 'safe to use' as an anaesthetic because it does not reduce blood pressure or compromise a patient's respiratory system. Ketamine may be injected into the muscle (IM), passed through an intravenous (IV) drip, taken orally, or absorbed via an oromucosal (nasal) spray.

Clinical trials and research

Ketamine is the most widely studied psychedelic to date. Excluding studies that look at the anaesthetic effects of ketamine, there are 140 clinical trials of which 22 are phase III trials and 32 are phase IV trials. Phase IV trials observe the real-world application of approved medicines in large patient populations to monitor the effectiveness, after it has been approved. Ketamine has been shown to be effective, starting almost immediately and then for up to seven days or more, for a wide range of mental health disorders. The following is a list of conditions for which ketamine has potential therapeutic benefits based on clinical trials and academic studies conducted to date:

- Depression, major depressive disorder (MDD), treatment-resistant depression (TRD), and bipolar disorder;
- Suicidal ideation;
- Anxiety;
- Social anxiety for those with autism;
- Substance misuse, including alcohol, cocaine, and opioid dependence;
- Eating disorders such as anorexia nervosa;
- Chronic pain;
- Inflammation;
- Cluster headaches/migraines; and
- Symptoms of OCD.

In these 140 clinical trials, nearly 11,000 patients have been enrolled as of July 2021. Among the active trials are those investigating ketamine for the treatment of depression in veterans, ketamine for the treatment of depression in teenagers and late-life depression, and a head-to-head comparison of ketamine versus electroconvulsive therapy for depression. Some studies are taking place in China, Israel, the United Kingdom, Canada and Mexico; most studies however are being done in the US.

North America

More than 100 clinical trials have investigated the effectiveness of ketamine for the treatment of mental health disorders. The overwhelming conclusion states that ketamine is effective in the acute treatment of all forms of depression (MDD, TRD, bipolar disorder, postpartum depression (PPD)), suicidal ideation, and PTSD. The effects are usually noticeable in the first few hours and persist at a high level up to seven days later. The effectiveness of ketamine wears off in the days afterwards and some studies find that patients are back to baseline in 28 days. The lack of long-term effectiveness could be to do with the different way ketamine interacts with the brain, the lack of talk therapy in many trials, and other factors. However, ketamine's benefit also extends to those who require immediate relief, and may prefer to gain an alleviation of symptoms, without engaging in the process of talk therapy.

Two studies at the start of 2021 have added evidence for the long-term effectiveness of ketamine when administered repeatedly. The first study, from the Washington University School of Medicine, found that a 96-hour infusion of intravenous ketamine lowered depression scores for those with TRD, up to eight weeks later. The second study gave six weekly oral doses of ketamine for those suffering from suicidal ideation and found significant reductions up to four weeks after the end of the study.

A review of studies of ketamine in the treatment of depression in patients with a history of psychosis or current psychotic symptoms showed that the available literature does not support the assumption that ketamine exacerbates psychotic symptoms in those patients. The review was limited in sample size (41 patients) but it stands out because psychotic patients are excluded in nearly every other trial with psychedelics in order to limit risks.

Ketamine has been shown to be effective in the treatment of several substance use disorders. One double-blind, placebo-controlled study in December 2019 investigated the effects of ketamine in combination with motivational enhancement therapy to treat alcohol use disorder. A single administration of ketamine, in combination with talk therapy, improved the number of days the participants weren't drinking and also reduced the number of heavy drinking days.

In March 2020, a study from Louisiana State University examined the comparative efficacy of psilocybin and ketamine in rodent models. The study found that a single administration of psilocybin, or LSD, produced persistent antidepressant-like effects in the rodent model. In contrast, ketamine produced only a transient antidepressant-like effect. The results of the study indicate that classic psychedelics may have therapeutic efficacy that is more persistent than ketamine.

Europe

Several studies in Europe are comparing the effectiveness of ketamine with that of electroconvulsive therapy (ECT). ECT is a procedure whereby small electric currents are passed through the brain to induce a generalised seizure. Although the treatment has been shown to be effective, it also comes with side effects and patients need to be under general anaesthesia during the treatment. The comparative studies are still ongoing, but early results show that those undergoing ketamine treatment experience fewer side effects and the antidepressant effects are visible quicker..

Asia

Asia, as a region, is proving to be a 'late adopter' in terms of clinical research into the potential health benefits of psychedelics. Only a single clinical trial, out of a total of over 16,000 registered in China, involves the use of any psychedelic substances as interventions, with one exception: ketamine. Nine clinical trials have originated in China, two of these studies investigate PPD; 'baby blues' after childbirth. Administering one dose of ketamine after childbirth may be able to prevent PPD.

Product development

Most recently the benefits of ketamine for treating severe TRD have been recognised. Having become the first company to patent one half of the ketamine molecule, esketamine, Janssen Pharmaceutica, a subsidiary of Johnson & Johnson, has developed a nasal spray to treat TRD under the brand name Spravato, which received FDA approval in March 2019 and authorisation from the EMA in December of the same year. It is the first new drug introduced (as part of a broader treatment regimen) for the treatment of depression in over 35 years and the only psychedelic substance with marketing approval to treat a mental health condition.

There are two phases within the treatment regimen:

- The induction phase (weeks one to four): a patient receives treatment twice a week at either a 56 milligrams (mg) or 84 milligrams (mg) dose.
- The maintenance phase (weeks five to eight): the frequency of administration is reduced to once a week. Clinicians may extend the maintenance phase if required.

Spravato is administered in tandem with an oral antidepressant. In February 2020, NICE in the UK rejected the use of Spravato, based on efficacy and cost-effectiveness grounds. There has been some controversy surrounding the approval of Spravato by the FDA, given the likely expense associated with its administration, as well as questions about its abuse

potential and safety concerns (six participants died while on the trial, three of whom committed suicide). Despite this, Spravato was approved by the FDA for treatment of a second mental health condition in August 2020, namely for the treatment of suicidal ideation.

Ketamine therapy clinics

On 4 March 2020, Field Trip Health, a subsidiary of Field Trip Psychedelics, announced the opening of its first psychedelic-assisted psychotherapy clinic in Toronto, which uses ketamine-assisted therapy as part of a broader psychotherapy protocol to treat depression. Similarly, in July 2020, Novamind closed the acquisition of a chain of clinical research sites and psychiatry clinics specialised in ketamine-assisted psychotherapy operating in Utah since 2016.

Dr Reid Robison, Director and Chief Medical Officer at Novamind, explained the treatment protocol, 'dosing begins with intention setting and ends with processing of the experience. When administered, psychedelics act on the serotonin receptors that are linked to cognitive flexibility, enhanced imagination and creative thinking. It provides a window of opportunity to disrupt patterns in the brain. The integration session is where we can make lasting change. It allows individuals to explore their psychedelic experience and discover insights and meaning that can be incorporated into day-to-day life.'

Ketamine Therapy USA, an online community resource for patients seeking ketamine therapy in the US, lists approximately 140 ketamine treatment centres nationwide.

Legality of ketamine worldwide

Ketamine is something of an outlier among the other psychedelics presented in this report in that it is not classified as a Schedule I drug. It is a Schedule III drug under the Controlled Substances Act in the US and is categorised as a Class B drug in the UK. The exception to this is in Singapore, where ketamine is classified as a Schedule I narcotic.

Ketamine has been legal for medical use by medical professionals and veterinarians for decades in most parts of the world. In 1985, ketamine was placed on the WHO List of Essential Medicines and is currently one of the most widely used sedatives in the world.

A WHO expert committee has repeatedly recommended against placing ketamine on international controlled substance lists, as controlling the drug could make accessing it for medical purposes more difficult. In 2015, following the most recent review of its efficacy, the organisation stated 'the medical benefits of ketamine far outweigh the potential harm from recreational use.' The WHO has also stated that, in its view, ketamine does not pose a sufficient health risk to warrant scheduling under the 1961 and 1971 conventions.

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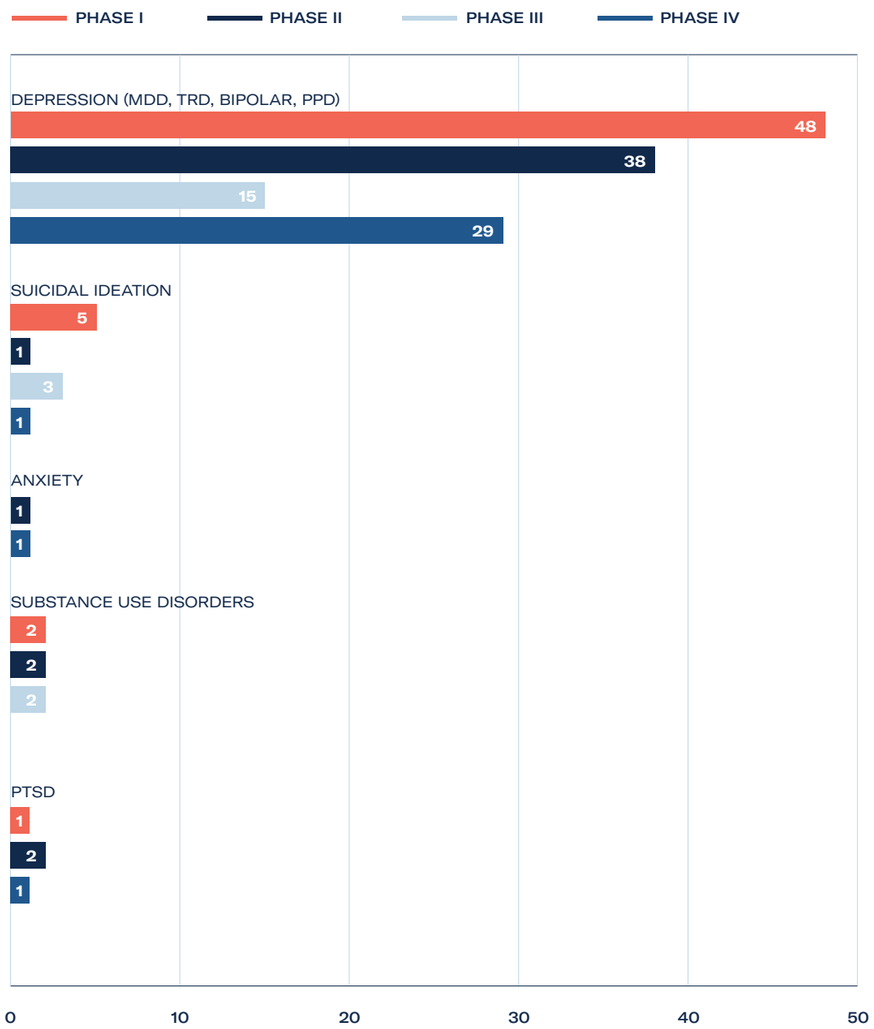
Number of clinical trials to date, using ketamine as an intervention, by condition treated



**Studies with healthy participants (usually phase I studies) or those studying ketamine as an anaesthetic are excluded from this overview.*
Source: ClinicalTrials.Gov / Blossom (correct as of 01/07/2021)

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EXPERT INTERVIEW

Dr Roger McIntyre
CEO,
Braxia Scientific

Dr Roger McIntyre, CEO of Braxia Scientific, is a Professor of Psychiatry and Pharmacology at the University of Toronto (and holds professorships at universities in New York, California, Korea and China), Head of the Mood Disorders Psychopharmacology Unit at the University Health Network, Executive Director of the Brain and Cognition Discovery Foundation, and Chair of the Scientific Advisory Board of the Depression and Bipolar Support Alliance. He has also been listed among "The World's Most Influential Scientific Minds" by Clarivate Analytics for the past seven years and counting.

What is Braxia Scientific's mission?
We have a vertically integrated business model with three units focusing on three strategic priorities. Braxia Scientific seeks to identify new, IP-capable ketamine and psychedelic derivatives, as well as novel delivery systems for those treatments. We then aim to capitalise on these innovations by implementing them within Braxia Health's multidisciplinary clinics. These clinics currently provide various ketamine treatments, including intravenous (IV). We will expand our offerings to other psychedelics as the research and regulatory environments progress. Finally, there is the Braxia Institute, which trains new clinicians to administer psychedelic-assisted therapy based on the International Guidelines published in the American Journal of Psychiatry by myself and other members of the Braxia Scientific leadership.

Considering the serious nature of depression and suicidality you are seeking to treat, are psychedelics treated with enough gravitas?
Absolutely not! Suicidality is the tenth leading cause of death overall in the United States, claiming the lives of over 47,500 people annually. In 2020 nearly 1.4 million Americans attempted suicide. More than 300 million people worldwide suffer with depression, and the currently approved treatments fail to adequately relieve symptoms for more than one-third of them. Moreover, the existing treatments for depression do not adequately address the issue of suicidality of which depression is the most common diagnosis in people who commit suicide.

Psychedelics, like ketamine, can offer rapid and significant symptom relief in adults with depression, and have also been demonstrated to rapidly reduce suicidality. However, we are doing them no favours when we play into stigma-promoting stereotypes of what they are and do, such as calling them "magic mushrooms," and talking about users going on a "psychedelic trip."

That is why at Braxia Scientific, we focus our attention on the science and medical research involved with treatments that can be implemented for depression, post-traumatic stress disorder, suicidality and other mental diseases, such as ketamine and psilocybin. We certainly welcome the excitement, hope and activity in the psychedelic space broadly but we also think the area requires thoughtful experienced leadership, which Braxia Scientific represents.

What sets Braxia Scientific apart in the psychedelics industry?
We have created an efficient organisational structure that saves time and resources by operating our own licensed clinics. These clinics provide direct access to patients and other facilities that significantly expedite our ability to develop and test drugs without compromising on the high clinical standards to which we adhere. We also aim to develop new chemical entities that could ultimately be acquired by large pharmaceutical companies, rather than market the drug ourselves. This shortens the standard R&D timeline, which usually runs seven to nine years, to only one or two years.

We believe that our outstanding personnel also gives us a considerable advantage. Personally, I have more than 25 years of experience treating depression. During this time, my program has seen more than 100,000 patients. Our team members have a long, successful track record of quality research and development, and have established themselves as world leaders in depression research, based on more than 740 published articles in peer-reviewed journals.

With these bona fides, our supremely qualified staff have been able to secure federal government funding for various clinical trials, and are positioned to capitalise on the extensive relationships they have cultivated with large international pharmaceutical companies, like Pfizer, AstraZeneca, Lundbeck and Otsuka.

What should excite investors most about Braxia Scientific?
While there is a long list, we are very excited and motivated by the discussions we are having with major drug manufacturers as to how we can move the needle for ketamine and psychedelic derivatives. Through our relationships we are refining our therapeutic research priorities in developing new products that could be ultimately acquired by large pharma.

In terms of our clinics, we are growing! As one of few IV Ketamine clinics in Canada, our referrals are increasing rapidly for patients with depression in need of rapid-acting and effective treatments. We exceeded our IV Ketamine infusion targets every month since January 2021. In our latest quarter, we reported year-over-year revenue growth from ketamine treatments of more than 80%.

Investors should also be excited about how quickly we were able to get our latest expansion clinic up and running, and the potential implications as we pursue our clinic growth strategy, which aims to add as many as 50 new clinics over time throughout North America.

Most of Braxia Scientific's current portfolio seems to be related to ketamine. Are you working with any other psychedelics at the moment?
Yes! In fact, at the end of August, we announced we would be commencing a landmark clinical trial to conduct Canada's first multiple-dose psilocybin study for treatment-resistant depression (TRD), which will take place at Braxia Health's clinics. It will be the broadest study of its kind, and what's unique about it is that we will not limit participation based on how many potential remedies patients have previously attempted, whereas most other TRD studies do impose a maximum. We will even include patients that have endured dozens of unsuccessful medical trials, including IV ketamine and/or electroconvulsive therapy.

Integrating psilocybin provides immense opportunity for benefit for those dealing with treatment-resistant depression, which is a very large market that disproportionately dominates the majority of mental health services. By including everyone with more than two failed medical trials, we are increasing the degree to which the results can be applied to a larger population, making our findings much stronger. Furthermore, we will have less exclusion criteria and are even including patients with bipolar depression – a huge first for the field – or comorbid disorders, which were excluded in psilocybin studies done by other companies.

IBOGAINE

KEY TAKEAWAYS

1. Ibogaine is not listed as a scheduled substance by the United Nations but is a controlled or illegal compound in many Western countries, with the notable exception of New Zealand.

2. Ibogaine has the potential to decrease a patient's misuse of opioids, cocaine and alcohol, and reduces symptoms of withdrawal after the administration of a single dose.

3. Ibogaine treatment is being offered in several countries around the world with costs ranging from US$5,000 to US$8,000 per treatment.

Ibogaine is a naturally occurring psychoactive compound that is found in several plants such as the roots of the iboga tree (Tabernanthe iboga); it can also be chemically synthesised. The traditional use of ibogaine stems from the Bwititribe of Gabon where it has been used for over 100 years. It has particular spiritual significance for practitioners of the Bwiti religion in West Africa and has an established history as a treatment for substance use disorders, particularly in South American countries such as Mexico and Guatemala, where ibogaine operates in a grey area, not illegal, but unregulated. The relatively unsafe profile, leading to at least 20 deaths in the past 30 years, has prompted researchers to research alternatives that offer the benefits without the cardiac dangers of ibogaine.

Clinical trials and research

Two clinical trials list ibogaine as an intervention. These trials, which are taking place in Spain and Brazil and are recruiting patients, examine ibogaine's potential to treat substance use disorder (SUD). The conditions treated were:

- methadone detoxification (1); and
- alcoholism (1).

In research conducted by pioneering advocates of the substance, such as Dr Deborah Mash, it has been shown that ibogaine has the potential to decrease a patient's misuse of stimulants, opiates and alcohol, and reduces symptoms of withdrawal (from opiates) after the administration of a single dose. Similar findings have been recorded in observational studies funded by MAPS at independent treatment centres in Mexico and New Zealand.

Other research studies have shown:

- a reduction in users' tolerance of opiates and alcohol; and
- a significant decrease in cravings for opiates and cocaine for an extended period of time after treatment.

Ibogaine therapy has been proposed for other mental health conditions, such as depression and PTSD. Its psychological effects have been reported to help people view difficult experiences in an objective way, and to help facilitate 'closure' of unresolved emotional conflicts or trauma. Ibogaine has also shown some early signs of promise in the treatment of neurodegenerative disorders such as Parkinson's disease (in rodents), and it may also help to support the growth of new neurons in the brain.

One reason why only a few researchers are actively studying ibogaine is the cardiovascular risks that are associated with its use. A Dutch study at Radboud University showed that nearly half of the patients in their study showed a delay in ventricular repolarisation, meaning the time it takes for the heart muscle to recharge between beats, of more than 450 milliseconds for over 24 hours.

Ibogaine analogues

Several companies are exploring ibogaine for its anti-addictive properties. DemeRx, in partnership with atai, is developing both ibogaine and noribogaine as oral, non-addicting treatments for opioid dependence. The latter has a greater affinity for opioid receptors than ibogaine. DemeRx has received approval from the MHRA in the UK to conduct clinical trials with ibogaine.

Given the limitation in currently available treatments, ibogaine represents an enormous leap forward for OUD (opioid use disorder) sufferers.

Deborah Mash, *CEO DemeRx*

Delix, which spun out of the Olson Laboratory, has developed a completely non-hallucinogenic psychedelic analogue, tabernanthalog. The compound has been shown, in rats, to have anti-addictive properties and to promote neural plasticity. An ongoing debate between psychedelic researchers discusses if the non-hallucinogenic nature of tabernanthalog will undermine its long-term effectiveness in humans or if this is not necessary to achieve positive results.

First synthesised in a laboratory in 1996, 18-Methoxycoronaridine (18-MC) is a derivative of ibogaine. It was developed to remove the undesirable side effects of ibogaine, including a slowed heartbeat and tremors. The hallucinogenic effect of ibogaine is absent from 18-MC. In 2014, Savant HWP filed an IND application with the FDA. However, this stalled in review for a number of years until the psychedelic pharmaceutical company MindMed acquired the patent in September 2019. In April 2020, MindMed began dosing the first patient in an additional phase I human safety trial of 18-MC for opioid withdrawal and opioid use disorder.

Ibogaine therapy clinics

An established model of ibogaine treatment centres exists for the treatment of SUD in countries where ibogaine is legal or unregulated, predominantly in Latin America. Ibogaine is an illegal substance in the US and throughout most of Europe (with the exception of a few countries, such as Portugal and the Netherlands) and occupies something of a 'grey' legal area in Canada, although a number of treatment centres are located there. More treatment centres have been established in South America. Patients living elsewhere and who suffer from a SUD are required to travel; if they wish to take advantage of ibogaine therapy. Some of the more successful clinics have been running for decades, such as Clear Sky Recovery in Mexico. More and more clinics are operating in Europe, for example, the Iboga Tree clinic in Portugal.

The sector is unregulated, so the quality varies considerably; reputable clinics offer patients access to trained medical professionals in a medicalised setting with accompanying psychological support such as talk therapy, both before and after treatment, to integrate the psychedelic experience and maximise effectiveness. In September 2015, the Global Ibogaine Therapy Alliance (GITA) published clinical guidelines for ibogaine-assisted detoxification, which outline clinical risk management protocols in detail. This measure may be due in part to a small number of deaths among detox patients who experienced cardiac arrest while receiving ibogaine treatment; mostly as a result of underlying but undetected heart conditions.

Cost to patients

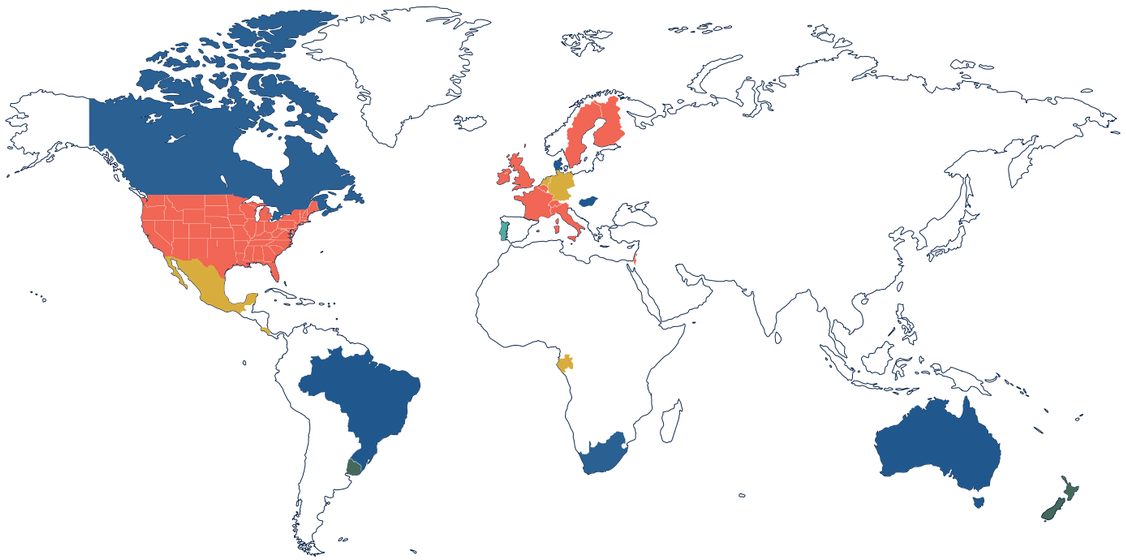
Ibogaine treatment therapy is not covered by health insurance providers in the US so its cost may be prohibitive to some; the therapy can cost between US$5,000 and US$8,000 per course of treatment when paid for privately. GITA offers 'low'-rate unsecured loans to patients from the US or Canada seeking ibogaine therapy anywhere in the world, while the majority of private ibogaine clinics offer financing options to prospective patients.

Legality of ibogaine worldwide

Although ibogaine is not listed as a scheduled substance on the United Nations List of Psychoactive Substances under International Control, its legality varies from country to country. The map below illustrates the status of ibogaine (for medical use or personal use outside a clinical setting) by country of relevance.

Legal status of ibogaine, around the world in 2021

ILLEGAL
UNREGULATED
DECRIMINALISED
PRESCRIPTION-ONLY MEDICINE
LEGAL



ILLEGAL

BELGIUM
FINLAND
FRANCE
IRELAND
ISRAEL
ITALY
SWEDEN
SWITZERLAND
UNITED KINGDOM
UNITED STATES

UNREGULATED

COSTA RICA
GABON
GERMANY
MEXICO
NETHERLANDS

DECRIMINALISED

PORTUGAL

PRESCRIPTION-ONLY MEDICINE

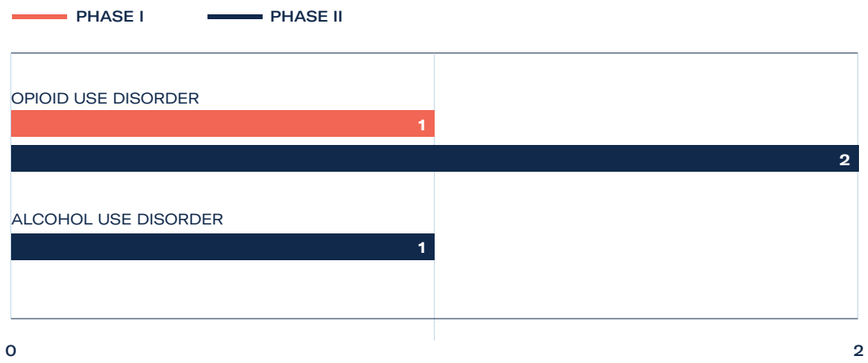
AUSTRALIA
BRAZIL
CANADA
DENMARK
HUNGARY
SOUTH AFRICA

LEGAL

NEW ZEALAND
URUGUAY

Source: Blossom / GITA

Number of clinical trials to date, using ibogaine as an intervention, by condition treated



**Studies with healthy participants (usually phase I studies) are excluded from this overview.*
Source: ClinicalTrials.Gov / Blossom (correct as of 01/07/2021)

AYAHUASCA

The Psychedelics as Medicine Report | Key Psychedelic Deep Dives

KEY TAKEAWAYS

1. Ayahuasca has been used in Latin America for over 1000 years and has been found to be helpful for treating a variety of mental health and substance use disorders. The setting often involves elaborate rituals which can add to the therapeutic effects of ayahuasca.

2. Only a few clinical trials have been done with ayahuasca, one of which showed improvements in treatment-resistant depression. The lack of clinical studies is holding back the wider adoption of this psychedelic.

3. Ayahuasca is not a scheduled drug under the United Nations conventions, but its main component DMT is. This has allowed the plants, and their use, to escape regulation based on their natural occurrence. Other exemptions have been made on religious grounds in the US, Canada and beyond.

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Ayahuasca is served as tea, made from a blend of different plants, usually the Banisteriopsis Caapi (ayahuasca or yagé) vine and Psychotria Viridis (chacruna) shrub, which contains DMT. Pharmahuasca is the name for the pharmaceutical version, which combines an MAOI (which prevents the stomach from breaking down DMT) with DMT. Because the name 'ayahuasca' denotes the brew used in traditional settings, some variations of it work via other compounds and do not contain DMT. Ayahuasca has been used for more than a thousand years and many observational studies have found positive effects on mental health and substance use disorders, though clinical studies are severely lacking.

Clinical trials and research

Ayahuasca is the topic of more than 160 papers in Blossom's research database, but at this time there have only been three clinical trials completed with the brew. The varying amounts of the different ingredients in the brew make it difficult to study in controlled settings. The setting itself is also, just like with traditional psilocybin use, a big part of ayahuasca's healing power and something not suitable for controlled clinical studies. That being said, ayahuasca has been studied for a wide range of mental health disorders. The following is a list of conditions for which ayahuasca has potential therapeutic benefits based on clinical trials and academic studies conducted to date:

- Depression, MDD and TRD;
- PTSD;
- Substance misuse, including alcohol, opioid, cocaine and nicotine dependence; and
- Eating disorders such as anorexia nervosa.

While ayahuasca has been in use for at least a thousand years and is commonly taken in modern ritual settings, there is very little clinical data on the substance. The only phase II clinical trial, with 29 patients and completed in 2019, investigated ayahuasca for the treatment of TRD. The double-blind controlled study conducted at the Onofre Lopes University Hospital in Brazil, found significant reductions in depressive symptoms one day after treatment. The response rate of patients was significantly higher in the ayahuasca group (64% versus 27% in the placebo group). Most studies of ayahuasca are taking place in Latin America.

Latin America

A 2016 study followed a group of 17 participants with recurrent depression who were given ayahuasca in a medical setting (leaving out many of the characteristics of the 'set' and 'setting'). The researchers at the University of São Paulo thus investigated the pharmacological effects of ayahuasca outside the traditional context. The study found significant improvements in depression and suicidal ideation. A follow-up, five years later, reported that participants found the experience valuable, but no long-lasting effect on mental health was reported.

Adverse events during and after the use of psychedelics is a valid concern that deserves much attention if psychedelics are to become medicines. Because of the observational nature, often without a screening of participants on pre-existing mental health disorders, research in this area is still limited. Researchers at the Universitat Rovira found this year that up to 17% of first-time ayahuasca users had experienced acute psychological adverse events. Some of these were ascribed to an unsafe environment. On average, even these participants had improved mental health scores six months after the study.

North America

An observational study conducted by the University of Victoria researchers followed 12 participants who participated in two ayahuasca ceremonies with the goal of reducing addictions. The self-reported problematic use of cocaine, alcohol and tobacco decreased significantly in the six months after treatment. These and several other studies have found positive effects of ayahuasca on a variety of addictions.

Europe

Researchers at Maastricht University have recently completed an interesting study on the effects of 'set and setting' in ayahuasca retreats throughout Europe. As in other studies, they found improvements in the mental health of the participants but found that on most measures the participants in the placebo group, who did partake in the ceremony, received similar benefits. This highlights the importance of non-pharmacological factors, not only in research on ayahuasca but also in the 'set and setting' in which other psychedelics are administered.

Several studies, one of which by a Spanish research group, has found the components of ayahuasca, specifically DMT, lead to the restoration and possibly growth of new neuronal cells. Although these studies are still in the early phases, now being conducted in mice, they may have large implications for those suffering from Alzheimer's and traumatic brain injury (TBI).

> **I am on methadone and that did not work...after that [retreat] I had no desire...I do not know what it is about that but it really is very life-changing.**
>
> **Study participant,** *University of Victoria, ayahuasca for addiction study*

The Psychedelics as Medicine Report | Key Psychedelic Deep Dives

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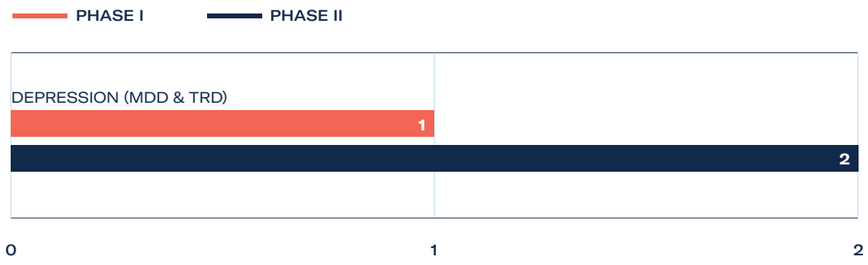
Legality of ayahuasca worldwide

The principal component of ayahuasca, DMT, is a Schedule I drug under the Convention on Psychotropic Substances, but the plants that contain DMT are not subject to international control. This exemption, which also applies to peyote and psychoactive mushrooms that contain mescaline and psilocybin respectively, means that there is less top-down regulation regarding the use and distribution of ayahuasca. Throughout Latin America, there is little to no enforcement of any restrictions on the use of ayahuasca.

Another route through which ayahuasca is available is through religious exemptions. The Religious Freedom Restoration Act has allowed groups like the União do Vegetal to import and use ayahuasca as their sacrament. The Santo Daime church has won similar cases and can use ayahuasca in both the US and Canada for religious purposes.

Number of clinical trials to date, using ayahuasca as an intervention, by condition treated



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Source: ClinicalTrials.Gov / Blossom (correct as of 01/07/2021)

The Psychedelics as Medicine Report | Key Psychedelic Deep Dives

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Other Psychedelics of Note

The Psychedelics as Medicine Report | Other Psychedelics of Note

The psychedelics we have covered above; psilocybin, LSD, MDMA, ketamine, ibogaine and ayahuasca are the clear leaders when it comes to developing psychedelics as medicines. This section of the report highlights other psychedelics of note that are ready to become medicines in their own right. Mescaline has found itself on the research menu once again and a handful of studies are already pointing towards the use of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) for the treatment of PTSD.

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SALVIA DIVINORUM

Salvia divinorum is the most psychoactive compound known to man, working in similar quantities as LSD. Salvinorin A is the principal compound of salvia, a dose of 200 micrograms is enough for psychoactive effects. Salvia divinorum is part of the salvia genus (Lamiaceae) of which mint is also a species. Little is known about the toxicology, adverse events and safety, as little clinical research has been undertaken with salvia. It has psychedelic effects when consumed by chewing, smoking, or being drunk as tea. The chemical structure of salvia is distinct from other psychedelics and it is a potent k-opioid receptor, so not a serotonin receptor agonist. Revixia Life Sciences, an entity of clinical-stage biopharmaceutical company atai Life Sciences, is developing a proprietary formulation of Salvinorin A, RLS-01, as a medication for treatment-resistant depression.

MESCALINE

Mescaline, which can be derived from cacti such as peyote and San Pedro or chemically synthesised, has been used by humans for millennia for its effects ranging from anti-inflammatory and pain-relieving properties to healing wounds and in ritual ceremonies. Although currently a Schedule I drug, peyote and San Pedro are legal for use in some regions in the Americas for religious contexts in native communities owing to a longstanding tradition of use amongst indigenous peoples. As a Schedule 1 drug, however, it is regarded as having no recognised medical benefits and is deemed to present too much of a risk of physical and/or psychological abuse for it to be legally available for purchase or prescription. There are anecdotal reports of mescaline being used for a wide range of purposes, including analgesia and headache relief, yet no evidence exists for these yet. Only three clinical trials list mescaline as an intervention, one of which will investigate mescaline for alcohol use disorder. The other trials are investigating the effects of mescaline in comparison with other psychedelics, not against any particular condition, but as they affect a broad range of psychometric measures.

DMT

DMT is a powerful yet short-lived hallucinogenic drug, which is a natural component of many living plants and animals and is found in high concentrations in some plants used for psychedelic purposes, such as Mimosa tenuiflora and Banisteriopsis caapi (one half of the ayahuasca brew). Similar to psilocybin and LSD, DMT produces a visual and hallucinogenic experience, yet at a much more intense and shorter duration. DMT is also listed as a Schedule I controlled substance under the UN Convention on Controlled Substances 1971. The chemical structure of DMT is similar to the anti-migraine drug sumatriptan, and it acts as a non-selective partial agonist at most or all of the serotonin receptors, particularly at the serotonin 2a receptor. There exists anecdotal evidence that DMT can be used to treat conditions such as chronic migraines. While research is now beginning to probe into the mechanisms of DMT, notably at Imperial College London, there is virtually no modern clinical data on the use of pure DMT for any medical purposes. A low dosage of DMT is considered to be between 0.05 and 0.1 milligram/kilograms body weight. The 'psychedelic' threshold for DMT is believed to be 0.2 milligram/kilograms body weight.

5-MEO-DMT

5-MeO-DMT is a tryptamine alkaloid found in both plant and animal sources, including high concentrations in the parotid gland secretions of the Colorado River toad and the Sonoran Desert toad. The psychedelic effects are fast-acting and short-lived, similar to DMT yet still very distinct in character. The legality of 5-MEO-DMT is similar to DMT apart from a period between 1971 and the late 1980s where the Church of the Tree of Life used 5-MeO-DMT as a sacrament. A UK-based company, Beckley Psytech, is exploring the use of 5-MeO-DMT for the treatment of a variety of neuropsychiatric disorders, including depression and substance misuse.

KRATOM

Kratom is a species of tree (Mitragynia speciosa) that grows in Southeast Asia and Africa. In low doses, kratom leaves act as a stimulant. In high doses, it has analgesic effects. It is not a classic psychedelic and it is unclear how much, if any, the serotonin 5-Ht2a receptor is involved in the effects of kratom compounds. It is likely that the combination of effects from several different types of receptors is responsible for benefits from the compound, which include relief from symptoms of opium withdrawal, anxiety and depression. More than a dozen countries have made kratom a controlled substance, limiting the sale, use, importation, and production of kratom. Neither the UN nor the US has currently scheduled kratom, the latter is considering scheduling it as of July 2021. The FDA did ban the importation of kratom in 2014; until then it was promoted as a dietary supplement.

2C-X

2C or 2C-x is the general name for a group of psychedelic compounds first synthesised by Alexander Shulgin in the 1970s and 80s. Not all of the 2C compounds are psychedelic, some of the most popular psychedelic compounds are 2C-B, 2C-E, and 2C-I. Several therapists explored 2C-x as therapeutic agents as they offered a middle road between the warm embrace of MDMA and the psychedelic effects of LSD; 2C-x are controlled substances in most countries, 2C-B is a schedule I drug in the US since 1995.

NITROUS OXIDE

Nitrous oxide, also known as laughing gas, is a chemical with significant medical uses. Similarly to ketamine, it is used for its anaesthetic and pain-reducing effects. Both compounds are on the World Health Organisation's List of Essential Medicines. When nitrous oxide gas is inhaled, it can lead to dissociative effects through its effect on gamma-aminobutyric acid type A and N-methyl-D-aspartate receptors in the brain. A small number of clinical trials have found favourable effects of nitrous oxide on scores of depression. A recent phase II study found that a 25% nitrous oxide mixture, versus a 50% mixture, had comparable therapeutic effects with fewer side effects.

NOVEL COMPOUNDS

During his lengthy career as a professional tinkerer, Alexander Shulgin created almost 200 psychedelics. Now some years after his death, a new group of researchers is taking over the discovery of novel compounds. Many novel compounds will be made by making small changes to existing psychedelics, to improve their effectiveness, shorten the duration of a trip, or make a compound that is patentable. Known examples of novel compounds are 18-MC and tabernanthalog; both from ibogaine. A manifold other second-generation psychedelics are in progress that will modify the effects of psilocybin, MDMA and LSD. Many of the compounds that are being developed will need to go through all the safety steps and can take a long time to get to market. Novel developments, including the recent open-sourcing of Google's DeepMind database on the building blocks of life (how proteins fold), mean that there is ample room for novel compounds to be developed.

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EXPERT INTERVIEW

Cosmo Feilding Mellen

CEO,
Beckley Psytech

Unlocking the therapeutic potential of psychedelic medicine is not just a business for us, it is an intergenerational family mission stretching back over 50 years. My mother and co-founder, Amanda Feilding, is one of the world's most renowned pioneers in psychedelic science and, in 1998, she set up the Beckley Foundation, a non-profit focused on scientific research into psychedelics and their medical potential. Back then, this subject was not nearly as fashionable as it is today, in fact it was shrouded in stigma, and the Beckley Foundation has been a major driver in the renaissance of psychedelic research and been involved in many ground-breaking studies over the last couple of decades.

Given our longstanding involvement in this field of science and the global network of researchers that has been established, Amanda and I decided we could increase the impact of what we were doing by setting up focussed drug development companies to bring new, effective treatments to the patients. The aim is to translate the promising academic evidence surrounding psychedelics into large-scale pharmaceutical research and development programmes, to create licensed medicines.

Beckley Psytech is now the second biotech company we have started, having successfully sold the first in 2019, and it is focussed exclusively on investigating and, hopefully, commercialising psychedelic medicines for patients in need. As we have scaled our research and operations, what we have done really well and continue to do, is combine our deep knowledge and expertise of psychedelic science with a best-in-class drug development team.

Best-in-class drug development team

Our Chief Scientific Officer, Dr Steve Wooding, is a trained physician but subsequently spent a life in research and development. His last role was Head of Global Commercial and Market Access Strategy in Johnson & Johnson's pharmaceutical division, Janssen. Our Chief Medical Advisor, Dr Fiona Dunbar, was Head of Global Medical Affairs at Janssen too, so is also very experienced in drug development and pharmaceutical commercialisation. Similarly, our Chief Operating Officer was the CEO and President of Otsuka Europe.

There are very few institutes in the world that have had the Beckley Foundation's influence in shaping this field of science or shown commitment at a time when psychedelic medicine was neither fashionable, nor profitable. This adds credibility to the integrity of our approach and has helped attract a committed mission driven team with incredible drug development expertise. The team knows not just how to develop a drug so that it receives regulatory approvals, but also how to position it so that it is commercially viable and reaches the patients it is intended to help.

We have taken a multi-platform approach to drug development, with multiple programmes running in parallel. Currently, we have three core programmes which balance and complement each other. The aim was to identify development programmes that not only made sense from a psychedelic science perspective, as well as from a feasibility and a commercial viability perspective but also differentiated our pipeline versus what competitors were doing.

We are looking at utilising low doses and high doses of psychedelics in different ways, for different categories of disease. This involves two treatment models, the first combines high doses of psychedelics with psychotherapy to create psychedelic-assisted therapy and is primarily focused on psychiatric conditions. The second is looking at low sub-hallucinogenic doses of psilocybin administered several times over a period of days or weeks. This has no psychotherapy component and is intended to be brought to market as an outpatient treatment model for neurological conditions.

Near-term opportunity

The first drug development programme, and Beckley Psytech's near-term opportunity, is exploring how low doses of psilocybin can treat an exceptionally rare headache condition known as short-lasting unilateral neuralgiform headache attacks or SUNHA. SUNHA is an extremely debilitating condition whereby patients may experience up to 200 headaches a day. At the moment there is no approved treatment for the disease, so patients suffer enormously with insufficient medical intervention available to them.

This programme is an example of our intention to use psychedelics as a pharmacological intervention, and therefore as an outpatient treatment without concomitant psychotherapy. The advantage of demonstrating that the compound can be self-administered safely, without the need for a psychotherapist, is that the treatment can be taken at home which makes it more affordable and less resource intensive for health systems.

We have already begun a clinical trial in a small group of patients to examine how different doses of psilocybin impact SUNHA, with the data expected in the coming months. Understandably, given the nature of this disease, we are targeting an orphan drug designation which could not only offer an accelerated route to market, but also provide us with extended market protections through additional data and marketing exclusivity.

The mid-term opportunity

The second programme, and what we term our mid-term opportunity, involves 5-MeO-DMT, which is naturally occurring in a variety of plant species and the Sonoran Desert toad. Despite extensive use in informal and ritualistic settings, 5-MeO-DMT has been under researched from a scientific perspective. So, while there is currently little clinical data on 5-MeO-DMT, there is an extensive body of anecdotal and real-world evidence that indicates the drug's potential as a medicine and our aim now is to prove this therapeutic potential in a controlled clinical setting.

The Psychedelics as Medicine Report | Expert Interview

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We landed on 5-MeO-DMT as an ideal candidate for psychedelic-assisted psychotherapy for two main reasons, the first is that it is very potent and known to produce profound subjective psychedelic experiences. In psychedelic-assisted therapy subjective experiences correlate with positive outcomes, and 5-MeO-DMT is reported to induce these kinds of experiences more reliably than any other psychedelic.

In addition, the drug experience is very short, normally lasting under an hour. This is important because a major challenge facing psychedelic-assisted therapy with drugs like MDMA, psilocybin and LSD is that those drugs are long acting, so essentially a therapist has to sit with a patient for six to ten hours. This is resource and cost intensive and potentially limits the number of patients you can reach with these treatments. We already have a shortage of psychotherapists, so requiring them to spend a whole day with a single patient may become a bottleneck for patient access.

With 5-MeO-DMT assisted psychotherapy, the goal is to produce similar levels of efficacy to those seen with MDMA and psilocybin, but with a treatment session that takes an hour instead of a day. By improving resource utilisation and therefore the cost and accessibility of the treatment, it would in theory allow us to help many more patients. A Phase I clinical trial of our intranasal 5-MeO-DMT formulation is currently underway in healthy volunteers and we plan to move quickly into studies with patients.

The long-term opportunity

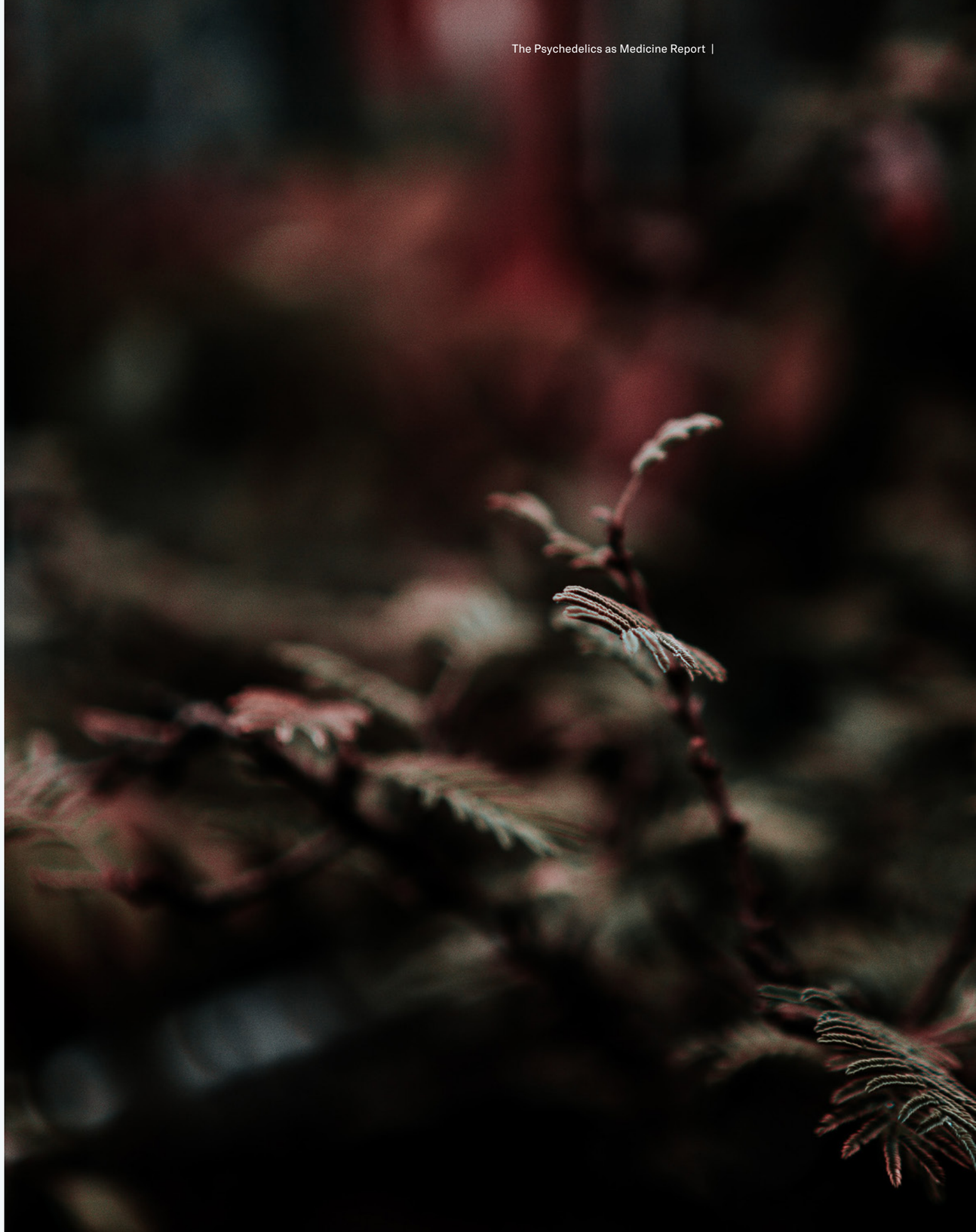
Our third programme, and our longer-term opportunity, is looking at developing brand new psychedelic compounds. This is the classic drug development approach with the strongest IP protection whereby you take known compounds and change their molecular structure to refine their effects by dialling up or down certain receptor binding profiles. This is the furthest away from market, as we are effectively creating and researching a brand-new drug, but in the long term it affords us the ability to learn from existing psychedelics and refine them to bring about the treatment outcomes we are looking for.

Future opportunities

With the near, mid and long-term opportunities, we are following a rigorous pharmaceutical drug research and development approach, going through phased clinical trials to hopefully achieve regulatory approval from regulatory bodies such as the FDA and EMA. It is a well-established pathway and it takes time, but the closer you get, the more confidence you can have that these medicines will reach their potential.

We recently sought to raise US$50m to support these development programmes and the response was incredibly positive. Due to enormous demand we decided to upsize the funding round to US$80 million and have now raised over $100m since the company was founded in 2019. It has helped that we previously founded and grew a very successful company that made investors significant returns, but we have also attracted new and very well-respected institutional investors from healthcare and breakthrough science, alongside several psychedelic-focussed funds.

In the next couple of years we believe there is going to be substantial progress made in this field of science and the industry more broadly. What is particularly exciting about this opportunity is that it is emerging rapidly, and that it has the potential to make a meaningful difference for a large number of patients worldwide. It is not only an incredible growth opportunity, but it also marries up with having a positive impact for a lot of people.



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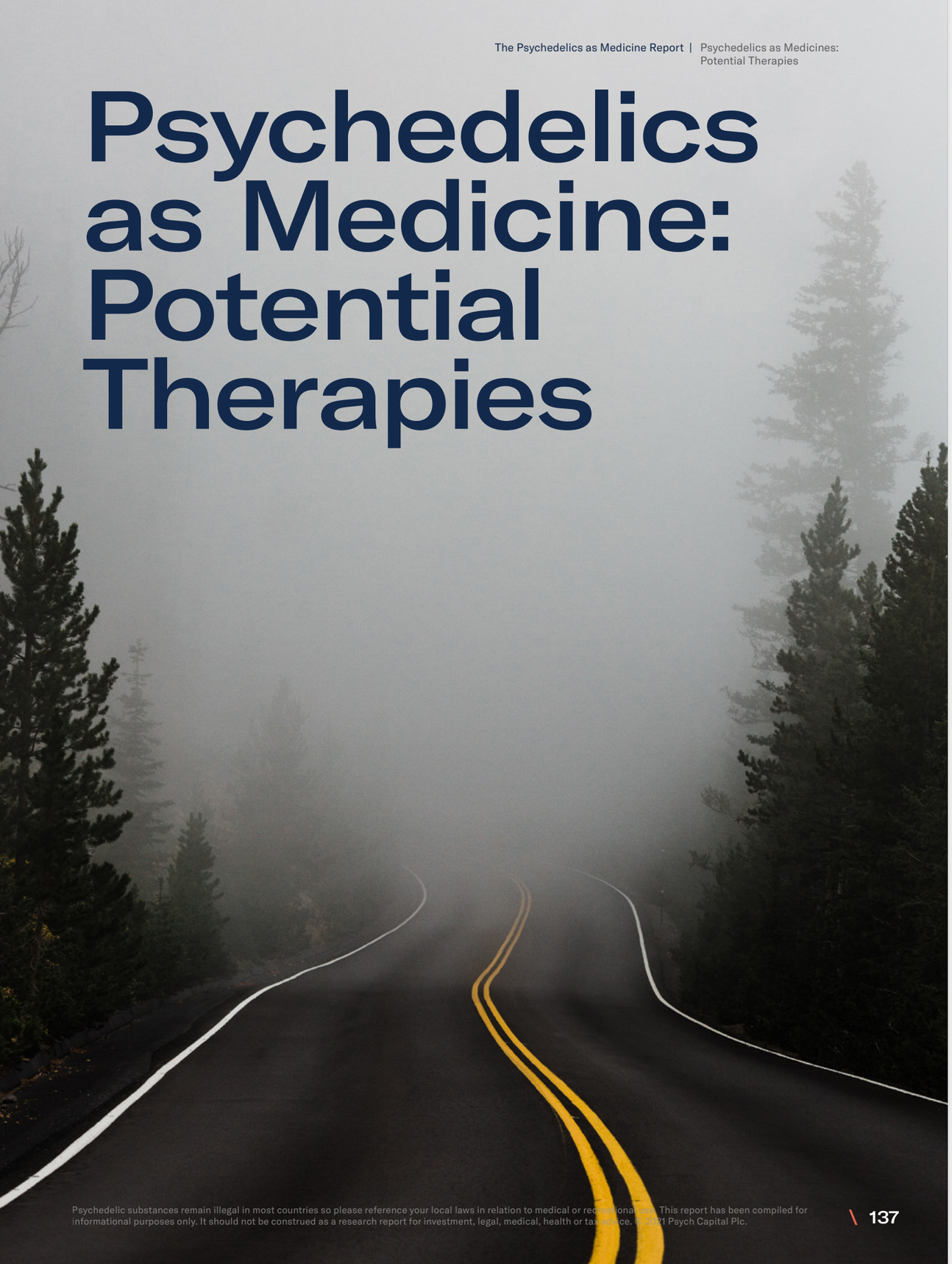
Psychedelics as Medicine: Potential Therapies



KEY TAKEAWAYS

1. Conventional medications, such as antidepressants, can have numerous negative side effects and evidence is emerging on their longer term effects. Conversely, psychedelic-study participants have consistently reported fewer negative side effects from psychedelic treatments, and psychedelics are acknowledged to have a low potential for abuse or dependence.

2. The challenges involved in developing psychedelic therapies involves converting an unstable plant-based medicine into a consistent and replicable pharmaceutical drug that can secure FDA approval so as to be covered by insurance. Otherwise, the costs associated with the treatment and the accompanying psychological support from trained therapists could be prohibitive.

3. During a psychedelic-assisted therapy session, ‘set’ and ‘setting’ are of central importance to the patient’s experience. ‘Set’ refers to the patient’s mind-set, while ‘setting’ refers to the context or environment in which the therapy session takes place. Following the supervised psychedelic ‘trip’, integration of the experience via further talk therapies is vital to the success of the treatment.

Pharmaceutical drugs may have several adverse side effects. Selective serotonin re-uptake inhibitors (SSRIs), a class of antidepressants, can be particularly detrimental to a patient in the short term with little being known about the consequences of long-term consumption. Opioids, although a godsend for pain relief, have proven to be addictive and more deadly than heroin in the US. Psychiatrists need novel treatments with higher safety profiles, and studies have shown psychedelic medicines to have a low risk of dependence.

The challenges associated with developing psychedelic medicines are similar to those for medicinal cannabis: the obstacle of converting a psychoactive plant into a consistent and replicable pharmaceutical product. This is essential for treatments to be covered by insurance providers, with the resources required for psychedelic-assisted therapy beyond the reach of many patients.

In psychedelic-assisted therapy, 'set' and 'setting' are central to the patient's experience and outcomes. 'Set' refers to the patient's mind-set, while 'setting' refers to the context or environment in which the therapy session takes place. Although critical components to the experience itself, subsequent integration through talk therapies is vital to the success of the treatment.

Psychedelic Semantics

As regulatory landscapes emerge and evolve, the psychedelics industry is subjected to a series of semantics. This report frequently references both psychedelic-assisted therapy and psychedelic treatments, with the latter encompassing medications that can be self-administered and used in combination with talk therapy.

We have categorised these treatments into three subsections:

1. Psychedelic-assisted psychotherapy;
2. Infusion therapy;
3. Available on prescription.

Psychedelic-assisted psychotherapy

The term psychedelic-assisted psychotherapy, or psychedelic-assisted therapy, refers to the consumption of a psychedelic substance in combination with several sessions with a therapist. The number of sessions with a psychedelic, usually lasting a full day, varies between one and three, with two sessions being the most commonly used regimen. The total number of supporting therapy sessions, both before and after, usually number between six and ten.

Examples of this treatment include COMPASS Pathways' protocol for major depressive disorder, which the FDA designated a breakthrough therapy. Clinical trials are also being conducted to develop MDMA-assisted psychotherapy for PTSD, with the FDA expected to approve the treatment in 2023.

Infusion therapy

Infusion therapy involves the intravenous administration of psychedelic substances, either in combination with talk therapy or as a stand-alone treatment. Ketamine infusions were recently approved in the US and EU, but must occur in controlled medical settings. In 2021, several companies started clinical trials to investigate the potential of intravenous DMT, to investigate the drug's pharmacokinetic parameters and also whether continuous intravenous infusion extends the compound's efficacy.

Available on prescription

Although psychedelic medicines are not currently widely available through pharmacies or dispensaries, several companies are developing products patients can self-administer at home. During the COVID-19 pandemic, several ketamine providers shipped patients their ketamine at home and they provided a video link in order to still provide guidance for their patients.

Making psychedelics available on prescription would substantially reduce the cost of treatments and subsequently increase their adoption. MindMed is conducting clinical trials for its LSD microdosing treatment, which it hopes will be available over-the-counter for ADHD.

THE IMPORTANCE OF SET, SETTING AND INTEGRATION

As previously stated, 'set', 'setting' and 'dose' are key to a patient's experience of a therapy session involving psychedelics.

'Set' refers to mind-set, a complex mix of expectation and mood, personality and past experience. If someone comes into a psychedelic session with a lot of grief, the session will unfold quite differently from when someone comes well-rested, regardless of the setting and dose.

'Setting' refers to the context in which the session takes place, including basic factors like the comfort and aesthetic of the room, and more complex factors like the quality of the relationship with the clinicians and the atmosphere they help to create. Even though most clinical trials take place in hospitals or research institutes, the session rooms are made as comfortable and homely as possible. There are typically two therapists in attendance. The patient can sit or lie on a couch and is often encouraged to wear an eye mask, and/or listen to a relaxing playlist of music. Oral ingestion of a capsule of synthesised psychedelic compound (e.g. psilocybin) is the most common route of administration, and the session will typically last for up to eight hours.

'Dose' refers to the amount of psychedelic that is taken. In many trials, a high-dose psychedelic session or two to three high-dose sessions (usually 20–30 milligram psilocybin or 35 milligram ketamine per 70 kilogram body weight) are conducted. Several studies are showing no difference between men and women in their reaction to psychedelics, besides the difference in average weight, and some genetic factors have been found that influence the reaction to a dose.

Immediately after the psychedelic session and in the following days, a process of 'integration' is facilitated by the therapist. During these conversations, the patient has the opportunity to process, make sense of, and give meaningful expression to their psychedelic experience. This is a vital part of the therapy and is employed in nearly all studies with the notable exception of many ketamine studies.

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PSYCHEDELICS X TECHNOLOGY
EXPERT INTERVIEW

Zach Haigney
The Trip Report

Why is the intersection of technological innovation and psychedelic medicine so important?
There are two parts to this answer, one practical, the other technical. Practically, there is a massive unmet need in mental healthcare, and psychedelics seem to offer a transdiagnostic treatment option. This means that in combination with therapy, the same molecules show promise in treating symptoms across health indicators, from PTSD to substance use disorders. The technical challenge is the massive constraint on the scalability of psychedelic-assisted therapies (PAT). At this time, two costly therapists have to be with a patient for at least eight hours, usually two to three of these sessions. Next to the therapy session with psychedelics, most protocols also include four to twelve preparation and integration meetings. The hurdle before us is making PAT safe, accessible, and deployable at scale.

If we take a broader view, we already see technological innovation and mental health care intersect. Digital Health Tech (DHT), or digital therapeutics (DTx), is at an inflexion point where the technology is good enough to become a viable option. A silver lining of the COVID-19 pandemic is that it has shown telemedicine to be a tool in the physician's toolbox. Beyond telemedicine, we're seeing the quality and adoption of trackers in smartphones and wearables such as the Apple Watch and Fitbit increase exponentially over the last few years. The rise in real-world data and real-world evidence in drug development and discovery enables better research and development. Patient care and monitoring will also benefit from real-time tracking and data analytics.

Outside PAT, companies are already using passive data from smartphones and wearables, such as steps and heart-rate variability, to relay health information. Digital phenotyping, coined only in 2016, is another name for this type of data collection, and the goal is to make behavioural and mental health more objective. We are already seeing the first psychedelic applications that support and help people with their psychedelic journeys.

In your reporting for The Trip Report, you've described drug-software combination products. Can you tell us how this applies to psychedelics as medicines?
Drug-software combination products (DSCP) combine the strengths of a specific drug and a technology like a mobile application, to create better treatment outcomes. For instance, to reduce A1C levels in diabetic patients through monitoring software and the release of drugs. Another example of DSCP is the combination of an Apple Watch and biometrics-based insights, which can help lower blood pressure.

This combination will offer possibilities for psychedelic companies to create combination products that they can patent. A whole slew of biometrics may go into formulating the optimal dose, or the optimal moment, when someone takes a dose of psilocybin. Or conversely, when not to engage in PAT if biomarkers are showing raised blood pressure.

There are, rightly, concerns about tracking all this information. The privacy of a patient needs to be protected from leaks and hacks. Privacy concerns are already heightened when it concerns data on mental health and will be even more so when psychedelics, legal or not, are involved. The current conversation about who owns medical data is a big ball of confusion that needs untangling before successfully implementing PAT with DSCP.

What exciting developments do you see happening with psychedelics and technology in the next 5 to 10 years?
Technology could allow for more objective measures of mental health and well being than is currently captured by surveys or the perception of clinicians. If this technology delivers on the promise we would see an overhaul of psychiatric disease classifications with greater emphasis on objective biometric markers. This is the premise of the US National Institute of Mental Health's (NIMH) Research Domain Criteria (RDoC). The latter provides a multivariable, biologically-based, rather than symptom-based, framework for understanding mental disorders, and the vision is that the research framework will be able to offer personalised mental health care at scale.

There are four areas where psychedelics and technology are intersecting: diagnosis and symptom management; care delivery, with increased precision in the administration and observation of patients; preparation and integration, by offering anything from health checklists to personalised questions and feedback and through technology before, during, and after PAT.

DHT is up for a challenge in all of these areas to prove that it works better than what is out there already. There is a narrow band in which PAT and DSCP can exist. They will need to offer advantages over traditional treatments without compromising the privacy of patients.

Psychedelics as medicines are very novel when viewed through the lens of the FDA - so are digital therapeutics, such as the video game for the treatment of ADHD approved only last year. How do you think PAT, in combination with DSCP, can go to market?
There are multiple different routes to market. The critical difference between the different routes turns on the question of who pays. The difficult and potentially most lucrative route is through FDA approval. MAPS, Compass, Usona and others are currently pursuing this route for PAT. If approved as medicines they could then be reimbursed by insurance, and psychedelics could become part of mainstream healthcare.

EndeavorRx is the game you mentioned that the FDA approved in June 2020. It is marketed to improve attention function in children with ADHD, and I find it fascinating. The game adjusts the difficulty level based on input from the participant and thereby improves attentive function significantly. Sensory stimuli and simultaneous motor challenges are designed to target areas of the brain that play a crucial role in attention function. About half of the

children in the studies on EndeavorRx see clinically significant improvement in ADHD-related impairments within two months.

The FDA recognises DSCP and is being proactive with the Digital Health Innovation Action Plan. According to the FDA, this is the first step to 'assuring that all Americans, including patients, consumers and other health care customers have timely access to high-quality, safe and effective digital health products.' One part of this plan most interesting to PAT is the pre-certification that could allow for faster review and approval of DSCP.

Another route to market is providing assisting technology to companies that work with PAT. Applications that support preparation, music, monitoring (mental) health metrics and integration of psychedelic experience are poised to help clinicians offer better treatments.

Finally, there is the route directly to consumers. Although the price you can charge is probably much lower, a much vaster pool of customers is available. Several psychedelic applications are currently testing these waters.

An example of DSCP is in development by Psyber, an atai Life Sciences portfolio company. They are working on electroencephalography, or EEG, brain-computer interface technology for use in combination with psychotherapy. How do you see this implemented in the next few years?
This brain-computer interface technology will allow mental healthcare professionals and patients to access real-time interpretation of emotional, behavioural and mental states. This technology will create a much shorter feedback loop from weeks to mere minutes.

The use-case here for atai will be to integrate this technology into their other portfolio companies for marketing and improved efficacy of treatments. Positioning this as a DSCP will also allow them to patent their specific protocols.

Eventually, technologies like this will be combined with PAT so that patients' health can be tracked throughout treatment. From the perspective of the caregiver, there will be massively more information. The patient will have a place to continuously connect and have an application that supports them during PAT.

Some people may find going into a psychedelic experience a bit much. You've written before about VR and psychedelics. Do you think that VR could play a role to let people experience psychedelics from a more comfortable position?
People much more familiar with virtual reality than me are saying that the current generation of VR headsets is at an inflexion point. The Oculus Quest 2 is for VR, where the iPhone 1 was for smartphones. The technology behind VR is maturing to a point where the experience becomes seamless.

There are shared characteristics between VR and psychedelics. Both can alter the consciousness of the person who's using these tools. They can change the perception of what is 'real' and augment our perception of space and time. Both are leveraging experiential medicine.

VR can help with PAT in three distinct ways. Firstly by using VR to prepare someone for what they can experience during a psychedelic trip. Showing people how perceptions can change which will do a lot to ease worries and gently introduce people to a psychedelic experience.

Secondly by offering VR experiences instead of chemically induced ones. An exciting possibility here is that neuroplasticity could be achieved through a VR experience with lower physiological risks.

Thirdly by combining VR and psychedelics. I think this is one of the most interesting applications of psychedelics and technology.

This combination could allow for closed-loop human-computer interfaces. The VR headset and other tools can collect where someone is looking, their heart-rate variability and then feed that back into the system. This information then augments the experience, for instance, to make it easier for someone to surrender to the experience, a crucial part of PAT. To hammer this point home, the combination of VR and psychedelics could allow people to learn skills the same way as athletes who are getting feedback on their movements, in real-time. The feedback loop allows for a much more robust training ground than was previously possible.

One group that is incredibly forward-looking in this space is Neuroscape. The laboratory could be the foremost space using this branch of translational neuroscience, modulating the experience based on biomarkers. Now that Robin Carhart-Harris, one of the leading psychedelic researchers, is continuing his research there, we can expect more integration of DTx and PAT.

At this time, we're flying relatively blind. PAT consists of talk therapy and during the psychedelic experience most participants listen to music and there is very little interaction with the therapists. Only, after a session, is there space to reflect and provide feedback. This would be akin to a weightlifter only getting feedback a week after training. We want to have immediate feedback, a recording that we can look back and study, and technology that assists in shaping the path. What if we can upgrade the psychedelic experience to be like weightlifting is now? That way we can use the pliable state one is in during, and after, a psychedelic experience optimally.

How can investors identify emerging trends and opportunities in the space?
That's the million-dollar question. From a chemicals and drug development perspective, many apparent opportunities are already being pursued. Maybe 'set' and 'setting' is where the next phase of development and investment will happen. Enhancing the effectiveness of PAT through DSCP may become the next place where investors can make outsized returns.

The public markets have been introduced to the recent development with the major psychedelics since the second half of 2019. And for most of the major psychedelics, companies are already developing second-generation alternatives. I wonder how many more molecules there are to create and if those can get FDA approval.

Another area that I think is interesting is the development of legal frameworks outside of FDA approval. From California and Oregon all the way down to Australia, initiatives are fighting for greater access outside the established medical route. Although here, we should keep in mind that psychedelic legalisation will create a very different market from cannabis.

Tools that help either psychedelic research and ancillary technology to support PAT are another area of interest that we've already touched upon. Companies like Wavepaths, which provides music to accompany the therapeutic benefit of psychedelics, can offer tools to make PAT more effective, safe and scalable.

This report talks a lot about psychedelics as medicines, so let's switch gears a little bit and talk about psychedelics for neurological enhancement. Can you tell us a bit about what you see happening there?
Just like psychedelics can help those with mental health disorders, they can also lead to the betterment of well people. Of course, these categories are not set in stone, and it would be amiss of me to say that people fall in either one of these categories. Still, I think there is a huge opportunity beyond treating mental health disorders and substance use disorders for psychedelics.

The way PAT can be improved, with the help of DSCP, also applies to other domains of life. For instance, a professional athlete may use psychedelics to overcome a fear that is holding them back. Becoming better attuned to their body, or seeing a mental blockage from a different angle, could mean the difference between first and second place.

It may be a long time before we see robust evidence for cognitive enhancement through psychedelics. At the same time, microdosing has taken over Silicon Valley and coaches who work with psychedelics can be found from Austin to Amsterdam. There will be a lot of developments in this space too.

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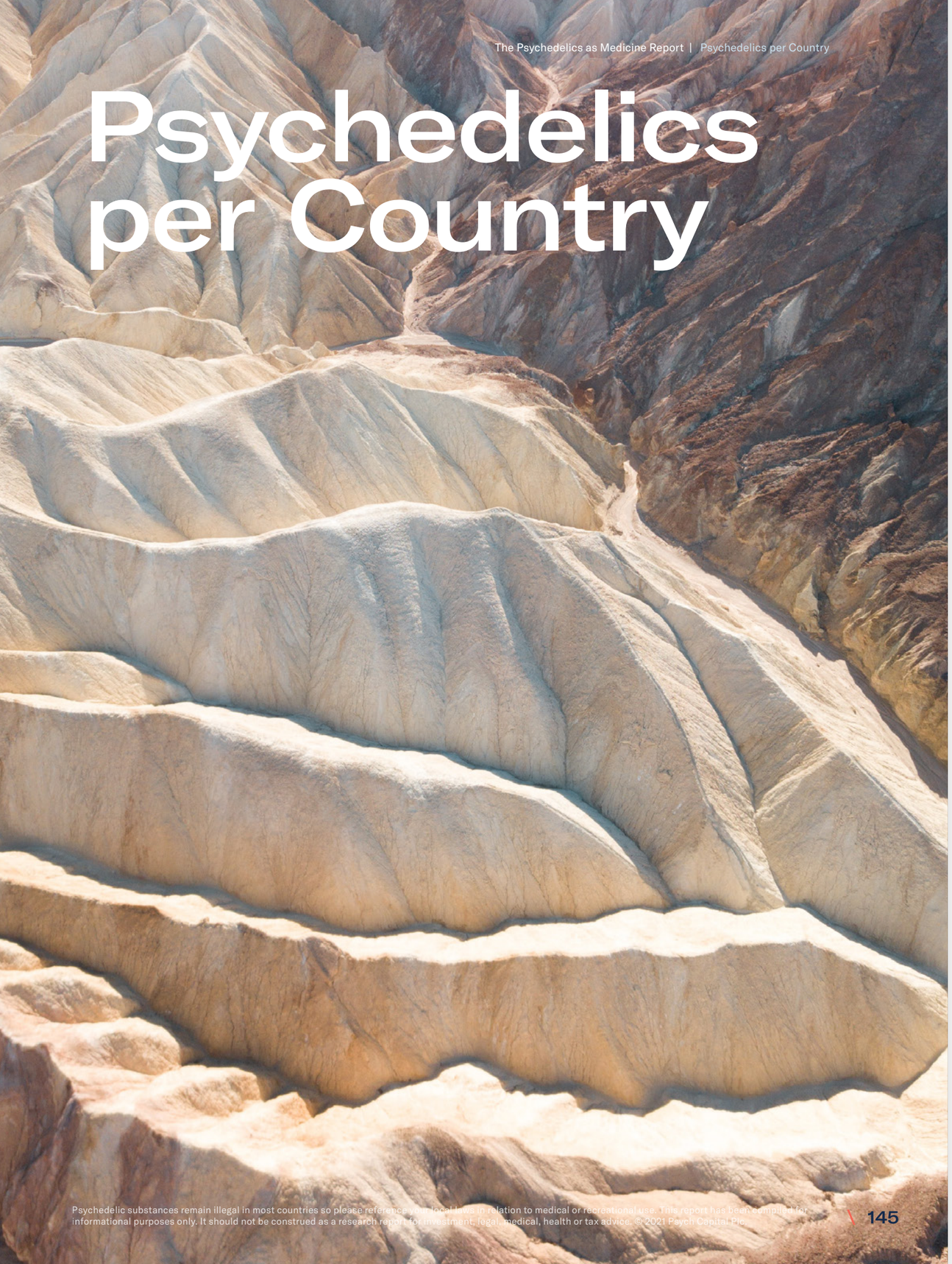
Psychedelics per Country



	Pyschedelic medicines studied	Clinical trials	Standout Companies	Valuation of companies in country
AUSTRALIA	DMT, ketamine, N2O, MDMA psilocybin	2	Creso Pharma entered the psychedelics industry in July 2021, through the acquisition of Canadian psychedelics company Halucenex Life Sciences. Mind Medicine Australia (not affiliated with MindMed) is the registered charity supports clinical research into psychedelic-assisted therapies. The Psychae Institute is headquarted in Melbourne, the global collobo-ration between universities received AU$40m in initial funding.	$171m
BRAZIL	ayahuasca, DMT, ketamine, ibogaine, MDMA, psilocybin	3	Brain Institute in the Federal University of Rio Grande do Norte, are the researchers from the institute who studied neural plasticity, inflammation and neurodegeneration triggered by 5-MeO-DMT. Núcleo de Estudos Interdisciplinares sobre Psicoativos is an organisation predominantly focused on ayahuasca, its application and anthropolical importance. University of São Paulo, the university hosted a clinical trial to investigate ayahuasca's potential as an antidepressent, in 2015.	

	Pyschedelic medicines studied	Clinical trials	Standout Companies	Valuation of companies in country
CANADA	ayahuasca, ibogaine, ketamine, psilocybin	18	Braxia Scientific owns and operates multidisciplinary clinics, with an initial focus on ketamine treatments. In July 2021, the CEO and CMO received C$918,000 in funding from the Canadian government. Cybin Corp. focuses on developing drugs and drug delivery systems. The company is currently conducting clinical trials on propreitary psilocybin-derivitive CYB001 to treat major depressive disorder. Havn Life Sciences supported by institutional investors, in March 2021 the company raised US$95m in a single funding round. Three months later Havn became the first psychedelic company to list on Nasdaq's Global Select Market. Numinus Wellness announced Health Canada had approved its study into MDMA's efficacy to treat PTSD, in July 2021. Between 2020 and 2021, Numinus' share price rose 266%. TheraPsil, the non-profit which advocates for the legalisation of psilocybin therapy, submitted its proposal for the psilocybin regulation to Health Canada in August 2021.	$2.1bn
CHINA	ketamine, psilocybin	12	The Zhejiang University School of Medicine identified the the anatomical and molecular targets of ketamine's fast-acting antidepressant properties, to enable manufacturers to develop ketamine-based antidepressants with greater safety and efficacy. M2BIO is a subsidary of Wuhan General Group researching the potential of psilocybin therapies to disrupt neuroaxtibity to treat mental health disorders. The company also develops CBD products, leveraging the cannabinoid's thereputic properties.	

	Pyschedelic medicines studied	Clinical trials	Standout Companies	Valuation of companies in country
DENMARK	psilocybin	3	Octarine Bio is backed by private investors including Oskare Capital and former Canopy Growth CEO Bruce Linton, Octarine Bio developed in-cell enzymatic platforms expanding the chemical diversity of tryptamine derivatives	$6m
GERMANY	psilocybin, ketamine	1	atai Life Sciences is a the biopharmaceutical company increased its IPO target to US$225m, to become the largest publicly traded psychedelics company, with underwriters including CitiGroup, Berenberg and RBC Capital Markets. MIND Foundation is a non-profit science and education organization that promotes psychedelic research and therapy. Every second year they organise their widely attended INSIGHT industry conference.	$2.3bn
IRELAND	5-MeO-DMT	3	GH Research - The company's 5-MeO-DMT deritive has compeleted its phase I clinical trial. In April 2021 the company announced it had raised US$125m to progress these trials to phase II and has since listed on the Nasdaq. Alvarius - In 2021, psychedelic start up Alvarius announced it had recieved €2.7m from a fund associated with Christian Angermayer, founder of atai Life Sciences. The company hopes to leverage the funds to run clincial trials into 5-MeO-DMT.	$1b
NETHERLANDS	5-MeO-DMT, MDMA, psilocybin	4	Blossom is a web platform which provides insigts on research, companies, public and governmental atittudes towards psychedelics as medicines. Synthesis Institute provides for medically-supervised psychedelic experiences, psychedelic research facilities, and education provider. Synthesis has raised over $4m.	$8m

	Pyschedelic medicines studied	Clinical trials	Standout Companies	Valuation of companies in country
			OPEN Foundation is a non-profit NGO promoting academic research and education of Psychedelics in Europe.	
SPAIN	ibogaine, MDMA	3	International Center for Ethnobotanical Education, Research, and Service (ICEERS) is a non-profit organization dedicated to transforming society's relationship with psychoactive plants.	
SWITZERLAND	ayahuasca, DMT, ketamine, LSD, MDMA, mescaline, psilocybin	36	Heffter Research Institute is large funder of psychedelic research, the institute focuses on driving scientific research on psilocybin, for mental health conditions, including addiction. University Hospital, Basel, specifically Leichti Lab, has been active in driving research across various psychedelics, including studies around the altered state of consciousness between LSD and psilocybin. University of Zurich's department of psychedelic research and therapy is developing safe and sustainable therapies for mood conditions.	
UNITED KINGDOM	ibogaine, ketamine, MDMA, psilocybin	11	Awakn Life Sciences operates treatment clinics and is undertaking research to develop new treatments for the treatment of addictions, and is trading on the NEO Exchange. Beckley Psytech is a biotech company researching first and second generation psychedelic compounds, including the advancement of 5-MeO-DMT into a licenced pharmaceutical medicine for the treatment of conditions such as depression and addiction. Beckley has received over $102m in investment. COMPASS Pathways is the second largest publicly-traded medical psychedelics company (market cap $1.35bn as at Aug 21), conducting clinical trials and developing practitioners to administer PAT.	$1.8bn

	Pyschedelic medicines studied	Clinical trials	Standout Companies	Valuation of companies in country
			April 19 is an AI-powered platform researching novel psychedelic drug compounds with minimal side effects.	
UNITED STATES	DMT, ibogaine, ketamine, kratom, LSD, MDMA, psilocybin, salvinorin A	171	Maya Health is a developing software for psychedelic practitioners and clinics to manage their practice, measure progress, and illustrate health outcomes. They have raised $2m to date. Journey Colab, a startup which raised $3m, are researching and developing new treatment compounds for the treatment of mental health conditions, including synthetic mescaline. Tactogen is a public benefit corporation developing the next generation of mental wellness medicines - starting from entactogens (like MDMA), and raised $1.5m earlier this year. TRIPP uses interactive VR and mobile experiences to companies, wellness clinics and directly to consumers, to manage mental health conditions, and is also participating in clinical trials for anxiety reduction, depression and substan ce use disorder. Wesana Health is publicly-traded life sciences company (market cap of $33m) working on the development and delivery of personalised therapies, including psychedelic compounds, to treat traumatic brain injury and related conditions. Wesana have raised approximately $17m.	$1.8bn

Source: Blossom

EXPERT INTERVIEW

Florian Brand
Co-founder & CEO,
atai Life Sciences

In 2018, we embarked on this adventure at atai Life Sciences—to pioneer the development of highly effective mental health treatments that address the unmet needs of patients. Recognizing that the existing toolbox of psychiatric medicines has proven inadequate, we set out on this journey, which has always been a personal one. Many on our team have spoken openly about direct and indirect experiences with mental health issues. Many have been failed by existing therapies, and some have personal experience with, or have observed the healing potential of, psychedelics.

These experiences are central to our founding. Our shared experience is a tie that binds our mission. As we've grown our team significantly in the past year, we continue to bring on board individuals who are committed to our mission — almost everyone has a story to tell.

We strive to be bold in our ambition, but we must not downplay the challenges ahead of us. Though regulatory bodies and the general public are starting to recognize the potential medical benefits of psychedelics, we're still working against decades of negative public opinion. Fueled by political parochialism, old narratives interfered with scientific rigor and subsequent innovation. And legislation controlling or banning the use of many of these psychedelic substances largely remains in place as a hurdle declaring in no uncertain terms that they have no potential benefit.

On the opposite side, there's a community of psychedelic advocates who see them through the lens of the spiritual or the mystical; for many in this community, pharma, Wall Street, and the medical establishment are unwelcome intruders.

We walk clear eyed into this maelstrom of strong and heartfelt opinions with a single goal: to use scientific methods to establish how these compounds can be of best service to patients living with mental health challenges. But this mission presents challenges beyond changing minds or correcting outdated notions: Pharmaceutical development is extremely challenging across all disease areas. Every year thousands of compounds must pass through rigorous preclinical testing, clinical trials, and regulatory approvals, resulting in just a few dozen reaching market in any given year. Oncology, for example, has massive investment approaching $100 billion spent on R&D a year, spanning thousands of candidate drugs. Despite this huge influx of capital and effort, since 2015, fewer than 100 new products have been approved.

Within this same time frame, mental health has seen just 7 new drugs gain FDA approval. Not surprisingly, the challenges in mental health are complex because we're dealing with the human brain. Oncology is tough, but ultimately, candidates in clinical trials are measured against endpoints that are relatively definable, such as "did the tumor grow or shrink?". In contrast, in mental health we must render what is inherently subjective into objective endpoints, finding measurable changes such as a decrease in depressive symptoms, anxiety, suicidality, etc.

In summary, developing drugs is tough work, and mental health, especially using psychedelic compounds, presents a multitude of challenges and uncertainties. These challenges are evidenced by the lack of new approvals, the small number of compounds with novel mechanisms that enter the space, and a negative feedback loop where investment in mental health has been relatively sparse for years. But we are encouraged by recent news and trends. We see a brighter future, and know we have the support of our investors, who have continued to invest in our future success, most recently through our June IPO. We are encouraged by the accumulating scientific evidence for these drugs, by the fact that psychedelics as a class have earned approvals and received breakthrough status from regulatory bodies, and by increased acceptance and interest from patients and physicians.

What makes us different? What are we doing at atai to select compounds, de-risk development, and ultimately bring them to the market?

Our process is designed for effective program selection, drug development, and value capturing. For compound selection, we have a disciplined approach to evaluating and selecting new programs, which requires prior evidence in humans to increase probability of success. We must also be able to demonstrate the potential for a differentiated treatment effect for each candidate in an area of unmet patient need, and they must have significant commercial potential, which we see as complementary to those already in our pipeline.

A wholistic view of our pipeline illustrates this careful, disciplined approach. Since 2018, we have grown our platform to five psychedelic and five nonpsychedelic drug development programs and six enabling technologies, focusing on differentiated and potentially disease-modifying mental health treatments. Treatment-resistant depression (TRD) is a key indication for us, as is opioid use disorder (OUD), and we also have programs pursuing cognitive impairment associated with schizophrenia (CIAS), generalized anxiety disorder (GAD), mild traumatic brain injury (mTBI), and post-traumatic stress disorder (PTSD).

To further illustrate our methodology selecting and developing compounds with our enabling technology platforms, we'll highlight one of our more recently added drug candidates, RLS-01, a buccal formulation of Salvinorin A (SalA), which is a naturally occurring psychedelic compound derived from the *Salvia divinorum* plant. This compound doesn't have the same level of notoriety as other psychedelic compounds, but it's been essential in ceremony and traditional healing for the Mazatec people of southern Mexico for centuries. We believe initial research on SalA suggests potential benefits as a therapeutic, which is why we launched Revixia Life Sciences, to pursue TRD as an initial indication for SalA.

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Certain aspects of SalA remain mysterious, namely its unusual mechanism of action (MoA). It's classified as an atypical kappa opioid receptor (KOR) agonist and has a complex pharmacological profile. The unique MoA shows no interaction at the 5-HT2A serotonin receptor, as with classical hallucinogens like psilocybin and LSD. In addition, SalA may indirectly influence the cannabinoid system, and is a negative allosteric modulator of the mu opioid receptor (MOR). Though we're still learning about its MoA, we believe that the existing evidence from human exposure de-risks it for further development.

In one prior third-party study, subjective effects from SalA were demonstrated to be similar to classical psychedelics. The study showed the ability of the S. divinorum leaf to effect hallucinogenic states of consciousness beyond serotonergic mechanisms. Notably, all six Hallucinogen Rating Scale (HRS) clusters were significantly elevated for participants given the active S. divinorum leaf. Crucially, no significant adverse events were observed or reported by the participants of the third-party study. And lastly, five patients reported positive changes in relationships with living family members. Based in part on the initial results of this study and others, we have plans to initiate a Phase 1 clinical trial of RLS-01, which we anticipate will start in mid 2022.

Our subsidiary structure and enabling technologies

Building on our program selection process, we operate our business in a decentralized model to enable scalable development at our atai companies, which we have either acquired a controlling or significant interest in or incubated de novo. We believe that this model provides our development teams the support and incentives to rapidly advance their therapeutic candidates or technologies in a cost-efficient manner. Together with this decentralized model, our process incorporates impactful capital allocation and strategic value capture, as illustrated by our ability to increase shareholder value via our strategic investment in COMPASS Pathways.

Our intent is to continue to strategically grow our business and to aid in the development and indication expansion of our various programs to maximize the potential of our pipeline, while we incubate, acquire, and invest in other promising companies that share our goal of advancing transformative treatments for people who live with mental health disorders.

Our enabling platform companies are set up with the goal of driving efficient drug discovery and improving treatment outcomes. To continue using Revixia as an example, the pharmacologic intervention of SalA will be paired with a digital technology, developed by our enabling company, Introspect Digital Therapeutics. The companies will collaborate in efforts to deliver high-quality psychological care supporting the therapeutic that potentially streamlines preparation, integration, and patient engagement in trials.

Introspect has a novel approach to digital therapeutics (DTx), which we intend to integrate across atai's architecture. Introspect is committed to the idea that high-quality DTx combinations have the potential to increase the safety and effectiveness of many mental health drugs, providing personalized and scalable treatment to those who might not otherwise be able to access high-quality psychological care.

The development of SalA for mental health treatments will also benefit from our recently launched enabling technology company, InnarisBio. InnarisBio is focused on one of the biggest challenges of developing medicines for mental health disorders—getting drugs to the brain. The blood–brain barrier, which serves to protect the brain, also restricts drug entry. We believe that this biological impediment is partially to blame for the stunted innovation in mental health.

Taking on this challenge, InnarisBio is developing a sol-gel, intranasal, drug delivery platform. Sprayed into the nose like a standard nasal spray, the sol-gel formulation solidifies at body temperature and adheres as a thin layer of gel at the roof of the nasal cavity, where it stays for an extended period, releasing active ingredient via the nose-to-brain route. We think that the technology has the potential to offer a painless and non-invasive administration route and may offer additional advantages such as increased patient compliance, lower dose requirements than oral administration, rapid onset of action, and minimized systemic exposure, which may reduce the risk of peripheral toxicity.

We believe that this novel approach to the delivery of medicines to the brain has revolutionary potential. atai announced the launch of InnarisBio in July 2021, and SalA represents the first compound in the pipeline to be formulated using the technology.

These pairings, complementing SalA with digital therapeutics and a novel formulation, are just two examples across our pipeline where compound and enabling technology are intended to cross-pollinate. We are also developing an EEG-based brain-computer interface technology with an initial application to help patients prepare for their experiences (i.e., their "set and setting") leading up to and during psychedelic treatments. And again meshing digital and molecular, we intend to bolster the atai pipeline with novel drug discovery through an AI-enabled computational biophysics platform.

To summarize, the atai platform approach is built to support a broad range of compounds and multiple technologies, aimed at supporting them from early discovery, through formulation, trial design, and clinical trials. Through each step, atai, through our platform approach is "loosely coupled but tightly aligned", and in step on our objectives and values, giving freedom for decentralized decision making. Our approach is designed to maintain a common theme optimizing our development in arenas of medicine that have been extremely challenging. We are strident in our approach and committed to our mission to redefine how the world treats, prevents, and heals mental health disorders.

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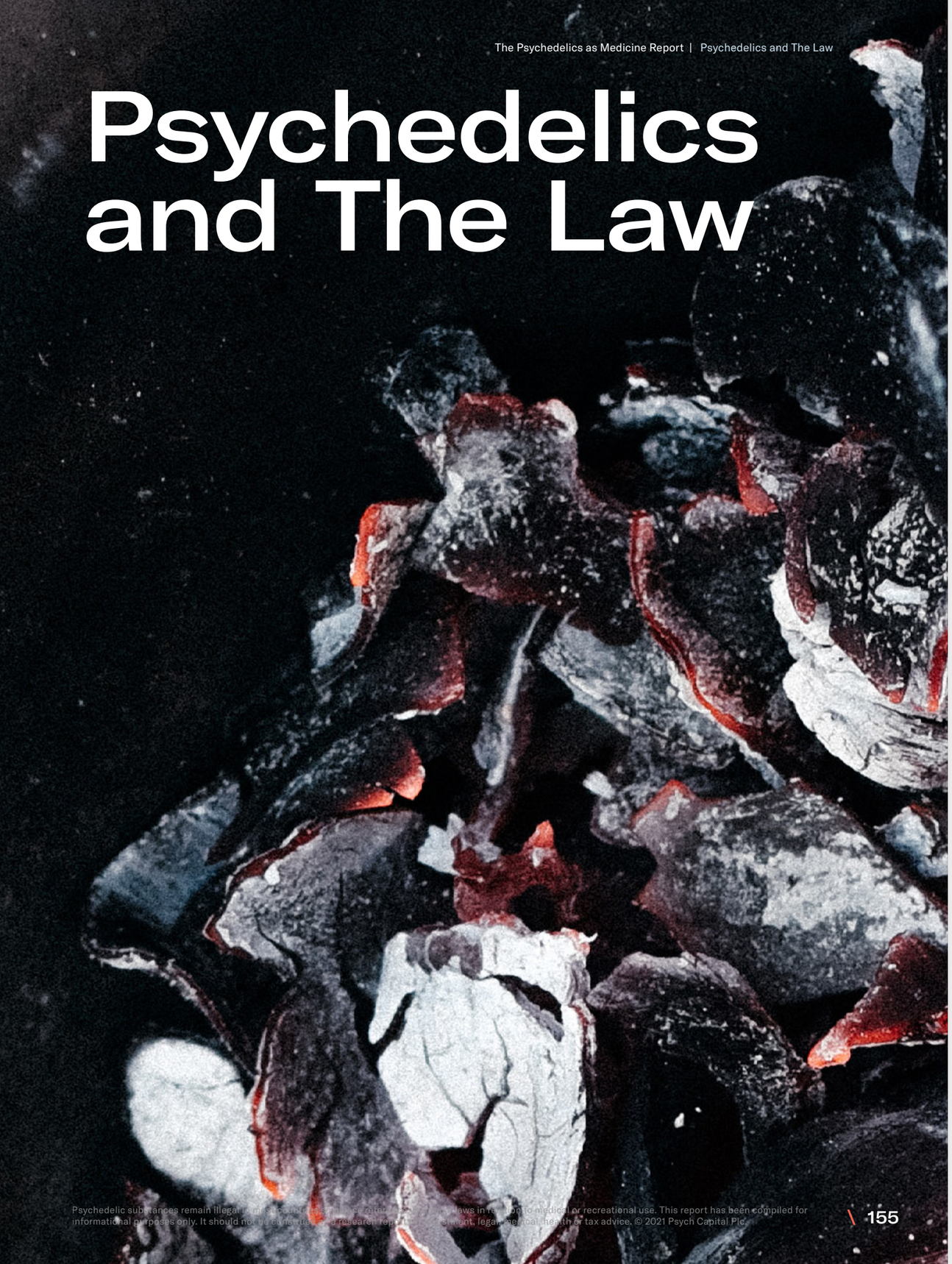
Psychedelics and The Law



KEY TAKEAWAYS

1. Psychedelics have been classified under the most stringent rules for 50 years and counting. Through research showing the effectiveness of psychedelics as medicines, the first real changes in legislation have started happening over the last two years.

2. Psychedelics have been decriminalised in six US cities and just as many states have active legislation that either decriminalises, making it the lowest priority of law enforcement, or provides a legal framework around psychedelics with Oregon leading here with a framework for offering legal psilocybin-assisted therapy.

This year, 2021, marked the fiftieth anniversary of President Nixon's infamous 'war on drugs' speech, following a surge in recreational consumption throughout the countercultures of the sixties. The impassioned speech on public safety prompted the UN to schedule a wide number of substances, implementing controls on common tryptamines and abandoning research into the therapeutic potential of psychedelic medicines.

1971 - 1985 | Becoming controlled substances

MDMA was originally excluded from this wide-reaching list of regulated compounds, although close analogue MDA was designated as a scheduled drug. As a result of anecdotal reports of MDMA's effects and potential efficacy in psychiatry, American chemist Alexander Shulgin, who first synthesised the compound in 1965, began testing the drug in 1976 and in 1978 reported 'an easily controlled altered state of consciousness', indicating its capacity for clinical application.

Despite this promise, in 1985, MDMA was subjected to an emergency ban by the DEA, and added to the controlled substances act alongside MDA, psilocybin and LSD. This ended studies into the compound with patient populations, but the results of the initial research gave rise to the re-emergence of psychedelic medicines.

2000 - 2011 | Resurgence of research

At the dawn of the twenty-first century, researchers began to re-examine MDMA's reported ability to control states of consciousness in the treatment of mental health. The world's first clinical trial of MDMA-assisted psychotherapy began in Spain in 2000 but was closed in 2002 before completion. Four patients had completed the groundbreaking trial, but the study was not extensive enough to supply data to inform regulation.

The study was sponsored by MAPS, with the non-profit psychedelic research organisation championing the compound's efficacy to combat treatment-resistant PTSD. Following continuous advocacy campaigns by the groups, and increasing medical and mainstream support, in 2004 the FDA approved two MAPS-sponsored MDMA-assisted psychotherapy studies, one of which was to treat PTSD.

The results of the study were published in 2011, with encouraging results. The research, which involved 19 subjects, who each received MDMA in conjunction with psychotherapy, demonstrated the sustained benefits of MDMA-assisted therapy with no reports of subsequent drug abuse or neurocognitive decline. This not only validated the therapy's efficacy but also its safety, achieving a milestone for the psychedelic and instigating further research into other psychedelic medicines.

2017 - now | Making psychedelics into medicines

One of the psychedelics to benefit from the reassessment of MDMA was psilocybin. An open-label study into psilocybin-assisted therapy for smoking cessation confirmed the treatment's success over other therapies, igniting renewed interest in the compound from drug developers and regulators.

In 2017, the FDA designated MDMA-assisted psychotherapy a breakthrough therapy, recognising its benefits over treatments currently available. A year later COMPASS Pathways received the designation for its psilocybin-derivative COMP360, signalling a seismic shift in policy towards psychedelic medicine. With public support backed by a shift in federal policy, US states began to decriminalise psychedelic medicines, mirroring the legalisation of medicinal cannabis, with Denver and Oakland passing legislation in 2019, and Santa Cruz, Washington D.C and Ann Arbour following suit in 2020.

Following a successful ballot initiative in November 2020, Oregon became the first state to legalise psychedelic-assisted therapy (PAT), specifically with psilocybin. Measure 109, also known as the 'Oregon Psilocybin Services Act' will allow the Oregon Health Authority (OHA) to license and regulate PAT with psilocybin starting as early as January 2023. At this time Oregon is the only state offering this unique framework, which showcases another way to state-level legalisation.

North of the border, Canada is also investigating PAT on a national level, with the country's regulator granting a number of exemptions, under Section 56, to access psilocybin in palliative care. As the body of research on psychedelic medicines in North America begins to swell, interest in psychedelics is also ramping up globally. With the UK approving its first clinical trial into DMT and the Australian government committing AU$15 million for psychedelic research.

Fifty years on from Nixon's 'war on drugs' speech, in 2021, MAPS published the results from its FDA approved phase IIIa clinical trial, demonstrating MDMA-assisted therapy's capacity to combat PTSD; 67% of patients in the randomised placebo-controlled trial no longer met the criteria for PTSD at the end of the treatment, with little to no side effects. As a result of these impressive safety and efficacy results, MAPS is expected to receive regulatory approval for MDMA-assisted therapy in 2023.

Psychedelics are still far removed from complete legalisation or from becoming widely accepted medicines. The first proposals have found their way to the US Congress where an amendment by representative Alexandria Ocasio-Cortez to remove barriers for federal research on the therapeutic potential of psychedelics has been rejected. Still, groups like the Plant Medicine Coalition are hoping for federal reform with them specifically aiming at US$100 million in federal funding for psychedelic research.

The long road ahead for psychedelics mirrors that travelled by cannabis. Although still illegal at the federal level in the United States, they have become widely accepted both for their medical benefit and for recreational use. It was in 1996 that California approved cannabis for medical use, now 25 years later it has become one of the biggest industries in several US states.

Patents and Intellectual Property

The Psychedelics as Medicine Report | Patents and Intellectual Property

KEY TAKEAWAYS

1. Patents are not possible on the first generation of psychedelics which have all expired. Therefore novel formulations of these compounds or second generation psychedelics will need to be made to create an intellectual property (IP) moat. The former being easier to create but considerably less innovative.

2. Data exclusivity is an overlooked opportunity where one would be able to protect a specific compound for a specific mental health or substance use disorder combination. MAPS will use this data exclusivity period of five to ten years to build a network that serves 500,000 patients and positions them as the provider of choice for PAT with MDMA for PTSD.

3. Producing psychedelics at scale, with good manufacturing practice (GMP) levels of purity, is another frontier where more than a dozen companies are competing to offer both natural psilocybin, extracted from mushrooms, and synthetic versions to be produced at large scale.

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Many of the traditional psychedelics were synthesised many decades ago and the patents governing their use have long since expired. MDMA was first patented in 1914, LSD in 1957 and psilocybin in 1963. As a result, companies are creating novel psychedelic compounds based on classic tryptamines that can be patented.

In the UK, US and Canada, new drugs are patented upon discovery, rather than regulation, with a patent term of 20 years. Patenting medications provides drug manufacturers with a period of market exclusivity in order to incentivise the development of new treatments by enabling the company to monopolise sales.

Patenting ketamine

Johnson & Johnson successfully secured a patent, and regulatory approval, for its esketamine nasal spray to treat treatment-resistant depression. Although Spravato was approved by the FDA, it fell short of regulation in the UK due to its prohibitive cost and a failure to significantly improve patient outcomes, above and beyond existing medications. Health Canada did approve Spravato as a treatment, but has recently rejected its patent claim. This signalled muted success for Johnson & Johnson, as it restricted Spravato's use to a specific jurisdiction and a limited patient population, despite the company heavily investing in the drug's development.

While the FDA's approval of Spravato was an important milestone for the psychedelic industry, the failure to gain accreditation in other countries is a warning lesson for other manufacturers. It is not enough to develop new treatments with better patient outcomes, the treatments need to provide far greater efficacy than medications currently available and also be cost-effective for healthcare providers.

Novel psychedelics under patent

This is one of the main challenges facing the psychedelic industry, as the majority need to be applied in controlled settings and followed up with sessions with a trained therapist. This significantly adds to the cost of treatments, with companies exploring how compounds can be modulated for shorter durations and to mitigate the reliance on healthcare professionals.

One way this could possibly be achieved is reducing the hallucinatory experience, with non-hallucinogenic analog tabernanthalog engineered as a non-toxic ibogaine derivative. In an attempt to dominate the emerging industry, drug developers are filing dozens of patents on psychedelic-compounds, long before they are thoroughly researched or subjected to clinical trials. Some stakeholders see the application of over broad patents as strangling industry innovation, whereas others believe it is crucial to protect and futureproof a business model.

To prevent patents being applied that will stifle research and using information that has been known to the public, which is called 'prior art'; two different organisations are challenging overreaching patents and collating earlier work. Freedom to Operate, a non-profit led by Carey Turnbull, the founder of the Heffter Research Institute, and Porta Sophia, supported in part by Usona Institute, are fulfilling these respective roles. This work should help patent reviewers to better judge if the work detailed on a patent is not already in the public domain.

Data exclusivity for MAPS

In addition to a patent to secure market exclusivity, organisations can also apply for data exclusivity to secure ownership and confidentiality of data provided to regulators. This typically includes the data generated through clinical trials, so it cannot be used to obtain regulatory approval for a similar medication. In the US data exclusivity lasts five years, eight in Canada, and ten in Europe and the UK.

MAPS will get data exclusivity for its clinical trials to treat PTSD with MDMA, as MDMA was originally patented in 1914 and its patent has long expired. Consequently, MAPS required data exclusivity to achieve returns on its investment, when the treatment is expected to be regulated by the FDA in 2023. This will give them five to ten years, depending on the continent, to scale up treatments and

build a moat before others will also be able to offer MDMA-assisted psychotherapy for PTSD. In that time MAPS will scale up to over 1 million sessions in 2029, which means that they will be able to serve at least 500,000 patients between 2023 and 2029.

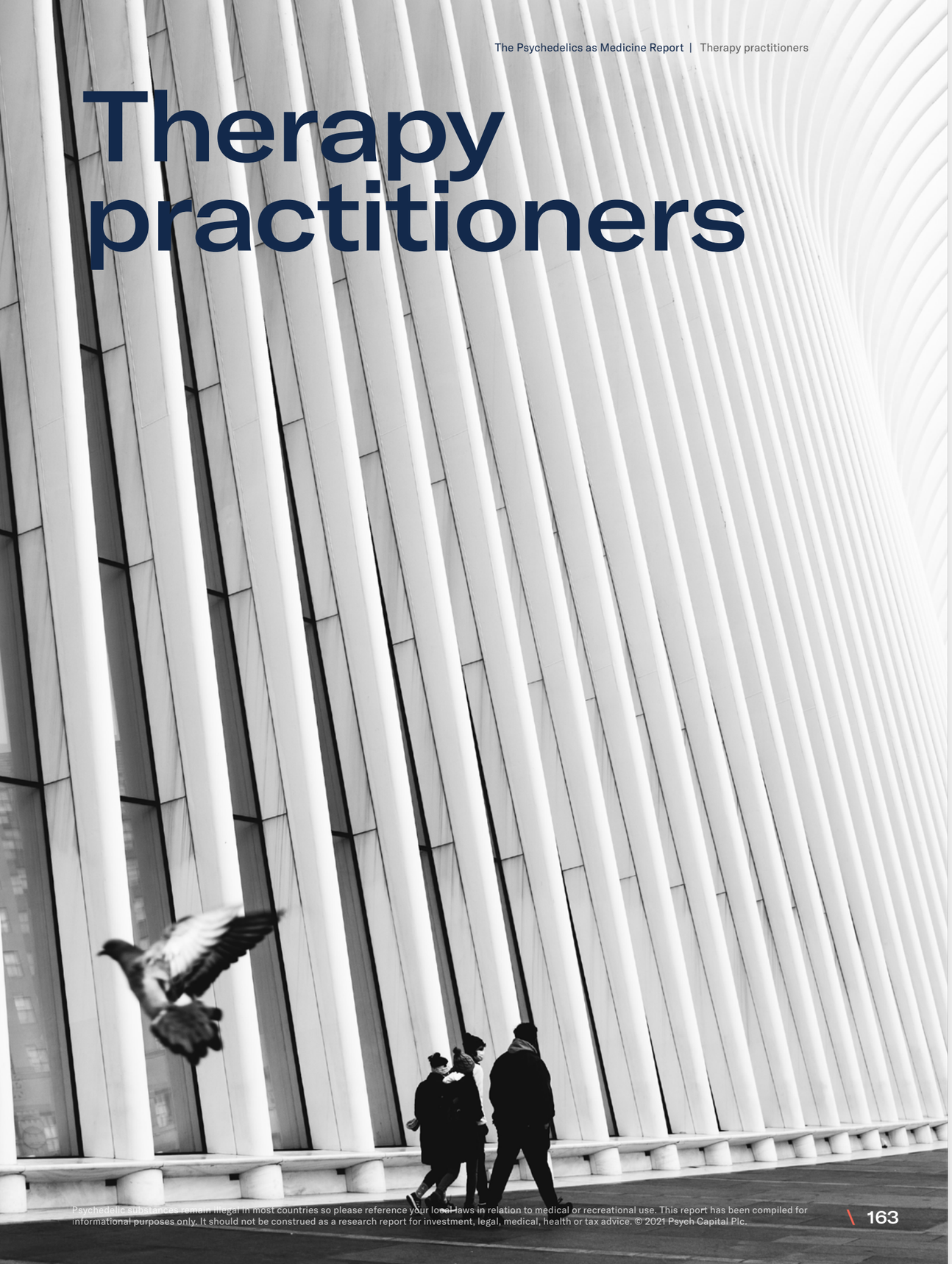
In the meantime, other organisations will still be able to generate their own data to get a treatment with MDMA approved. This can even be for MDMA-assisted psychotherapy for PTSD, but that would entail them generating the same level of data and efficacy as MAPS has done so far.

Making psychedelics at scale

Another area where patents are playing a role is in the production or extraction of psychedelics. Whereas natural production costs US$10-US$15 per effective dose, a novel yeast-based production method may, if scaled up, provide psilocybin at a much lower cost. Already in the year 2000, without wanting to be involved in psychedelics as medicines, the Royal Dutch DSM, applied for a patent, that was granted in 2007, for the improvement of the yield of psilocybin. To prevent others from patenting known ways of producing psilocybin, and to advance Open Science, Usona Institute has published all their psilocybin production methods without patenting them. In August 2021, Filament Health became the first company to be issued a patent for the extraction of natural psilocybin.

Still, in the last few years, many companies have filed patents on different proprietary manufacturing processes for making psilocybin, DMT, MDMA, and many novel psychedelics. The same can be said about the different delivery methods which range from soft gels to small films that sometimes extend the period over which a psychedelic is released. It will be up to the patent reviewers to judge the innovative nature of each of these applications.

Therapy practitioners



The Psychedelics as Medicine Report | Therapy practitioners

KEY TAKEAWAYS

1. More than 50,000 therapists will be trained to administer psychedelic-assisted therapy within the next ten years. MAPS, COMPASS Pathways, CIIS and many other organisations have already started scaling up training programmes.

2. Therapists in the ongoing clinical trials work in dyads and a full treatment can take upwards of 42 hours. New ways of administrating therapy through groups or with novel shorter-lasting compounds could drastically lower the time requirements and related costs.

Therapists and clinicians are the backbone of psychedelic therapy delivery, and the capacity to fund and provide training, plus ensuring that a steady supply of therapists are consistently being trained, upskilled, and retained, is of utmost importance in the wider distribution of psychedelic therapies. It will be a key piece of the puzzle when scaling up psychedelic-assisted therapy (PAT), both for non-profit and for-profit organisations who are delivering these training courses.

PAT is generally available for mental health professionals who are seeking to work with clients who are receiving therapy, in conjunction with a psychedelic supplement. This could range from training specifically in integration services, through to becoming a practitioner of PAT. Training equips health professionals with the tools they need for supporting the experiences of their clients and integrating these into their lives, as well as harm reduction techniques. Many therapists also choose to train in other complementary modalities, such as breathwork.

Therapy training providers

Several non-profit and for-profit companies are currently training psychedelic therapists. We expect more than 50,000 therapists to be trained to administer PAT within the next ten years. Here we highlight the work being done by MAPS who have been transparent about their training goals.

MAPS wants to train 24,000 therapists in the six years that they expect to have data exclusivity following successful New Drug Application (NDA) approval in the USA for MDMA-assisted therapy (2023-2029), for the treatment of PTSD; data exclusivity is much longer in Europe. Their training is formed from online modules (100 hours), plus therapists can expect to be supervised and receive feedback on their first PTSD patients. The 100-hour training costs US$5,000 but does not include the voluntary option to partake in MDMA-assisted therapy themselves.

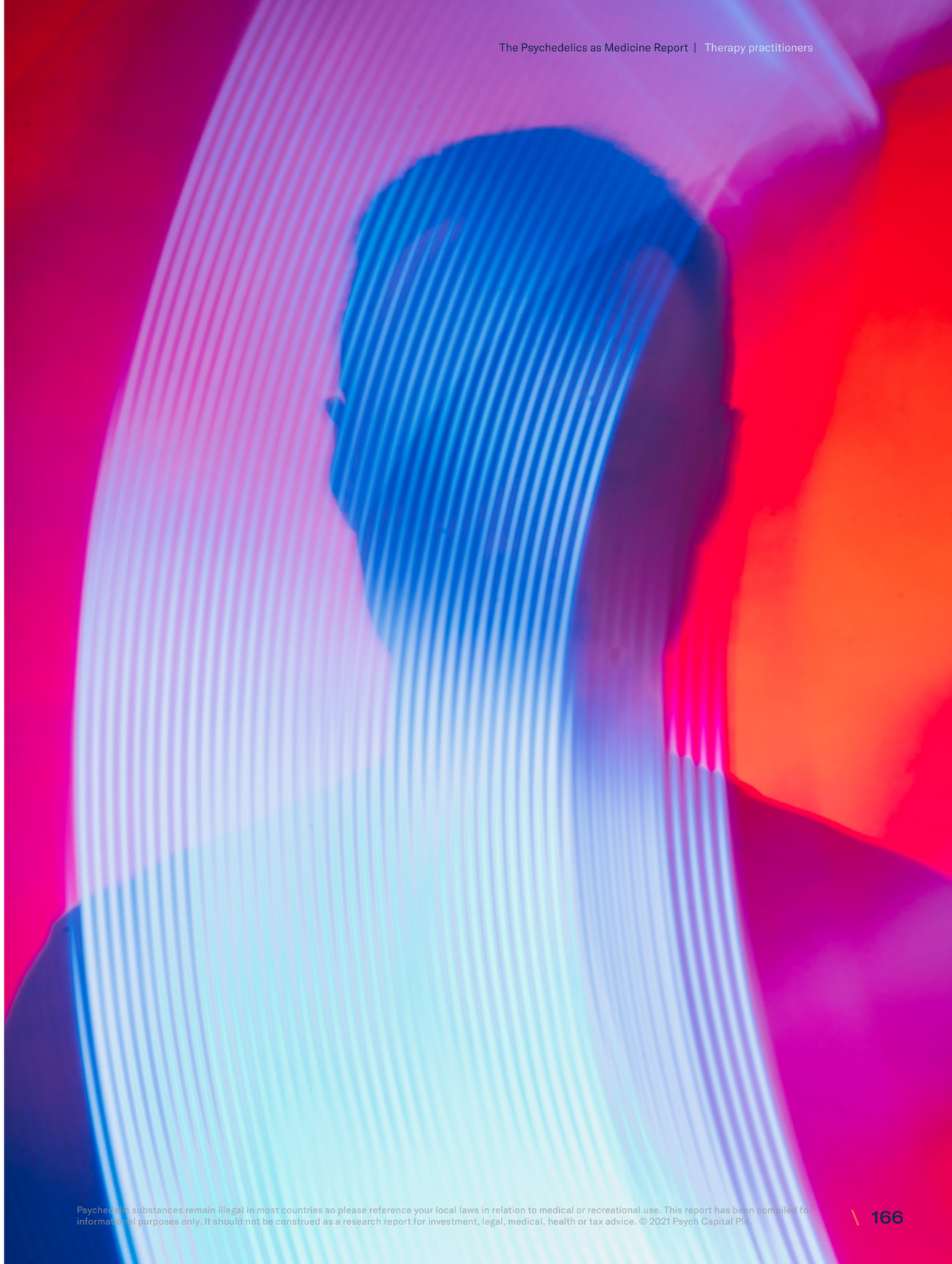
Considering that each patient currently, in the PAT clinical trials, undergoes 42 hours of therapy with a male/female co-therapy team, increased therapy delivery will be intrinsically linked to mobilising more trained therapists. Considerations such as shorter in-person therapy, group therapy, or use of technology, as detailed earlier in the report, could be options to enhance accessibility to more people, but the efficacy of such methods remains to be tested.

While therapists who want to work with MDMA will need to undergo the MAPS' training programme, there is a common desire to be trained as a general psychedelic therapist, in order to customise treatments (for instance, by providing a sequence of psychedelic compounds) for their clients. Currently, there are 310 therapists being trained by MAPS, with another 500 expected to begin training in September. Physicians prescribing MDMA will also require training, though their limited involvement in the therapeutic setting means their training could be completed in around 2-4 hours.

There are many training programmes emerging, seeking to build the next generation of therapy providers. Among psilocybin training providers, Canadian organisations such as ATMA Journey Centres recently completed training with 35 professionals, and the non-profit, Therapsil launched its beta training programme in March, earlier this year. US-based Fluence provides integration training, as well as ketamine-assisted psychotherapy training to aspiring practitioners. Access to a ketamine prescriber is a common bottleneck for independent practitioners who want to provide ketamine-assisted therapy. A US-based start-up, Journey Clinical, is providing in-house trained ketamine prescribers to independent therapy practitioners, and has partnered with Fluence for their therapist training programmes. Aspiring psychedelic clinical researchers can also take a post-graduate training course at the California Institute of Integral Studies.

In a bid to increase therapy providers, collaborations between experienced training practitioners and education systems will be key in providing more aspiring therapists to gain psychedelic therapy training, and encourage a diverse set of therapists to consider psychedelic therapy as a specialisation - to help the expanding groups of beneficiaries.

The Psychedelics as Medicine Report | Therapy practitioners



Psychedelic substances remain illegal in most countries so please reference your local laws in relation to medical or recreational use. This report has been compiled for informational purposes only. It should not be construed as a research report for investment, legal, medical, health or tax advice. © 2021 Psych Capital Plc.

EXPERT INTERVIEW

Dr sc. hum. Henrik Jungaberle
MIND Foundation &
OVID Health Systems

Since the turn of the century, there has been a resurgence of research into psychedelics as medicines. In 2021, MAPS published the first results from its phase IIIa clinical trial to treat PTSD with MDMA-assisted psychotherapy, and COMPASS Pathways' completed its phase IIb study into psilocybin's efficacy against treatment-resistant depression. As companies position themselves to treat patients with psychedelic-assisted psychotherapy, what do you see are the biggest roadblocks to the widespread accessibility of psychedelics?

I think that the last part of the journey can be the hardest. From phase II to phase III and everything that happens after phase III, when companies are negotiating with regulators. That is when the authorities will talk about risk mitigation strategies, setting up the criteria on how the medicines will be applied. This is the challenge that will soon be faced by MAPS, COMPASS Pathways' and all those that try to gain approval for psychedelics as medicines.

The second bottleneck or challenge that I see is the training of psychedelic therapists. Rick Doblin of MAPS recently said that he wants to train 24.000 therapists. I think the strategy or the goal to train a lot of therapists in a very short timeframe could be very challenging to not only MAPS but the whole field. I hope that we will be able to keep the quality of training high because there could be a real big backlash when we finally get to real life implementation and phase IV studies, which serve the purpose of further risk-benefit assessment in a larger patient collectives and/or special patient groups to determine the therapeutic significance with more practical relevance in "naturalistic environments". This is to identify if a drug really holds the promise in the field that it was approved for.

If we train a lot of unreliable therapists who misleadingly think psychedelic therapy consists of giving a drug to a person or "tripping" it could derail the whole process. To avoid this, we need to ensure that training is done at high quality and that we assess therapist's capabilities properly before they enter the trainings, especially before they embark on short online training programmes. I am personally sceptical that these courses will provide the skills people need in the first generation of modern psychedelic therapists.

To bring psychedelics to market, therapists will need to be trained to offer new forms of therapy. How do you think we can train these therapists, and what kind of training do they need? The MIND Foundation is training therapists through its Augmented Psychotherapy Training (APT). Can you elaborate on this two-year programme and what skills therapists will obtain?

The MIND Foundation has worked hard in the last few months to build a curriculum that is different from what we currently see in the field. The APT curriculum is a two-year 400-hour training in-depth programme. Our concept was to build the long version of the curriculum first and then develop medium and five-day intensive versions of the training.

We consider psychedelic-assisted therapy to be psychotherapy - not an exceptional and mysterious thing. The embedding into the mental health care context, the screening and treatment planning, the preparation sessions, the dosing session, the after care/integration and follow-up activities. All of the therapy sessions are important, it is not some kind of magic pill therapy or psychedelic pharmacotherapy with a little bit of preparation and integration.

Components of a mental health system integration of psychedelics, including factors to be considered in Health Technology Assessment (HTA) and future formulation of REMS criteria.

1.	REFERRAL SYSTEMS	• Check consent and education of co-treatment (liaison) system for interaction pre-, during, and post-treatment • Availability of emergency care facilities
2.	SCREENING & INDIVIDUALIZED TREATMENT PLAN	• Ensure application only after the psychiatric screening procedure • Check patients' social support systems • Check substance co-treatment regime: interactions with classic psychotropic drugs, concomitant medication • Ensure process diagnostics: decide whether a self-directed salutogenic process is underway or whether intervention by the help system is necessary and who will carry this out • Screen for an understanding of and willingness for integration (defined as engaging in adaptive learning processes) • Define treatment plan • Ensure drug is administered only in the context of a minimum of psychotherapeutic embedding • Define qualifications of multi-professional teams (medical responsibility in relation to treatment responsibility) • Test quality of screening
3.	PREPARATION	• Check accuracy and understanding of patient consent information • Include information about sociocultural risk factors in patient consent

4.	DOSING SESSION	• Ensure application under the supervision of a physician • The drug is administered only in certified health care facilities that can observe patients for at least 3 hours after drug effects wear off and provide the medical care necessary in case of an adverse event • Define rules for individual treatments, parallel individual treatment, and group treatment dosing sessions • Epistemic narratives and regime: Creating a shared system of ideas about psychedelic treatments and assessing their effect (limiting irrationality and esotericism)
5	AFTER-CARE/ INTEGRATION	• Check existence of a system for co-treatment with non-psychedelic practitioners • Check epistemic narratives • Check existence of rational community building systems
6.	FOLLOW-UP	• Monitoring of symptom reduction, suicidality, well-being, and substance use patterns • Consider digital technologies in follow-up strategies • Investigate post-treatment patient group therapy (online and on-site) and patient community systems in their role for sustaining positive treatment effects • Evaluate and discuss possible post-treatment self-administration of psychedelic drugs by subjects

Source: Gründer, G., & Jungaberle, H. (2021). The Potential Role of Psychedelic Drugs in Mental Health Care of the Future. Pharmacopsychiatry, 54(04), 191–199.

Instead, the APT training is looking at how the psychotherapy process is intensified, expanded or sometimes accelerated. We are training people either to become certified psychedelic therapists or co-therapists that can work alongside other therapists in a coherent team. These therapists could come from a broad spectrum of alternatively trained disciplines, too.

Other things stand out in our training program. The first is that we believe in training therapists to become group players - with medical doctors and psychotherapists working closely together. The second is that we are also training people in non-pharmacological methods and for atypical psychedelics like ketamine - as well as for serotonergic psychedelics like psilocybin. We want therapists to be familiar with a broad pharmacopoeia and a diversified toolset to alter consciousness. Then, in the outcome-based training (OBE) that we created we involve techniques like patient actors, mentoring and mindfulness meditation - next to a sound introduction into

The last characteristic of APT is its deep focus on integration. We are basing the curriculum, and the whole therapeutic process, not only

on the latest therapy models such as Acceptance and Commitment Therapy (ACT). We are applying an integrative psychotherapy theory and teach the so-called general change mechanisms, as they have been shown to be effective by psychotherapy research in the last 50 years. This is the work of Jerome Frank in the US, but much more the work of the groups around Klaus Grawe, a German-Swiss psychotherapy researcher who worked at the University of Basel. They have shown that independent of certain schools of therapy, there are five common underlying factors present in effective psychotherapies, and this is the theoretical basis that we are building the APTtraining upon.

In your latest research article, co-authored with Prof. Dr med. Gerhard Gründer, titled 'The Potential Role of Psychedelic Drugs in Mental Health Care of the Future' you recognise the different aspects needed to integrate psychedelics in mental healthcare. Can you elaborate on the role of screening in this process? Will psychedelics be available to most patients or only a small group?

In our paper, we describe a six-step model (see above), not only the three most known - preparation, dosing and integration. When you look at how things are already done in real-life therapy within an existing mental health system it gets a little bit more complex. For example, before a patient arrives at our OVID Clinic in Berlin, the first two steps have already taken place as a lot of our patients are referred by other doctors, psychotherapists, or even other patients.

Future psychiatric therapists will have to build referral systems and train non-psychedelic therapists so that they know who to send and who not to send. And following the end of psychedelic therapy, some patients will still be vulnerable and some will have setbacks, so a non-psychedelic psychotherapist will have to continue with the therapy or provide a stabilising role because it is simply not the reality that people all get magically better forever.

Keeping that in mind, we do want to reach a large group of patients. But reaching a large group without the correct approach could have dire repercussions and nobody wants that. Having qualitative screening procedures in place will ensure that we reach a large group, but also that treatments are successful.

Our experience at OVID, MIND Foundation's clinical sister organisation that today is providing ketamine- and breathwork-assisted psychotherapy, is that turning down unsuitable patients builds trust within our referral system. By having a good screening procedure, referring doctors know that we are not here just to "drop acid" into somebody's organism and hope that it magically works. It does help, but you really have to build the context and care for the long-term perspective of the patients.

We do not know yet if psychedelic therapies make healing processes faster though. This is not what the studies show yet and will be the terrain of comparative and phase IV studies. Current studies show that for a large proportion of study participants, psilocybin has been very effective and that the effects endure for some months, but not for all patients. Building on our psychiatric and psychotherapeutic experience, we believe that psychedelic therapists and psychotherapists largely play the same role in the treatment. Outside of the therapists' office, both connect the patients to a social ecosystem that helps her or him to get better.

Psychedelic-assisted therapy (PAT) has shown some incredible results in clinical studies. Some follow-up studies have found lasting positive effects up to five years later. At the same time, other studies, mainly with ketamine, find acute positive effects which seem to dissipate within the first month. Do you think that psychedelics will be something a person with a mental health disorder should go back to periodically, or is it a one-treatment and done deal?

This is one of the extremely thrilling components of PAT that need to be worked out much more. It is very likely that a number of patients will have to return to psychedelic therapy from time to time. The phase IV studies will

show who will have to come back and at what intervals. People will also come for different reasons, with psychopathology and self-development being disparate scenarios.

A patient who has struggled with depression for 30 years may find great relief after one or two psychedelic sessions like our colleagues are already beginning to see in the German EPIsoDE study (Efficacy and Safety of Psilocybin in Treatment-Resistant Depression in Mannheim and Berlin with 144 patients). But the psychosocial system around them that stabilises their pathologies will not just go away for everybody. For many patients, we may need another session, two or more each year.

For self-development, we are at an even earlier stage. The MIND Foundation is beginning to have conversations with legal authorities and politicians. Which systems of law, legal regulation or architecture need to be created around psychedelic use for healthy people? In medicine, we have the term 'prophylaxis', meaning treatment given or action taken to prevent disease. Part of these processes could be seen as prophylaxis, with psychedelic therapy for personal growth preventing the deterioration of mental health. The study of psychedelic use for personal growth and insights should also become part of the fields in the years to come.

OVID, MIND's sister organisation, is offering augmented psychotherapy, meaning you augment psychotherapy either with non-pharmaceutical methods or with ketamine, and in the future with other psychedelics. Is this treatment currently supported by insurance? From your perspective, what evidence is needed for insurance to pay for these treatments?

Public health insurance companies do not pay for PAT in Germany at the moment, but we have some private health insurance companies that have begun to pay for it, which is great progress already. The effectiveness of PAT has never been demonstrated in Germany, nor in many other countries, so we do need to generate this data for insurers to justify paying for PAT. That way the treatments become available to more than only those who can afford to pay for it themselves or can be enrolled in our diversity programs.

We do not only have to show that PAT has a slight advantage compared to talk therapy, but also that it is better than electroconvulsive therapy (ECT) for example - as that is what it is being compared to. This is the reality of the medical system and we need to do head-to-head comparison studies with the current gold standards, such as ECT, behavioural therapy and antidepressants.

In the long-term though, in order for people to have access to these therapies, we need to bring them into public health care systems. This is different in the EU from the United States. Here in Germany, the Netherlands, Switzerland, and the Mediterranean countries, we need to get it covered by public health care systems. We need to talk to insurers, public health officials, and learn from other experts to set up these studies so they are done well.

Your colleague Prof. Dr med. Gerhard Gründer is leading the phase IIb Efficacy and Safety of Psilocybin in Treatment-Resistant Depression (EPIsoDE) study, which has received more than €2 million from the German government. Why is it necessary to undertake this study as others such as COMPASS Pathways' and the Usona Institute are doing similar studies?

The EPIsoDE study serves several societal and scientific goals. Our study is unique in that it provides two 25 mg doses of psilocybin and it is being tested against two different placebos. This will give us much more information about which placebo we can best use going forward in future studies.

We will also train our MIND and OVID staff with this study, prepare them to work on studies with other psychedelics or mental health disorders and involve them in the APT training for future psychedelic therapists. We have not talked about it publicly yet, but we are currently negotiating cooperations between OVID and public universities to conduct future studies together.

We also want to make the German medical and psychotherapy system aware that this kind of therapy can be performed safely within the system. There is a lot of resistance and if you want to overcome resistance, you have to do it on a country by country level in the EU. We are aware of the impressive results from US-American and multi-national studies, but their outcomes are largely confined to the psychedelic bubble still, and is not knowledge shared by mainstream psychiatrists and psychotherapists. They either do not know about it or they are not taking it seriously. If you want to get novel treatments to patients, you have to convince those who work in the traditional system.ÖL

This takes us back to the six-step process around psychedelic therapies that we talked about earlier. The referral system needs to be informed. At OVID, we have monthly referral system meetings, online and onsite, for colleagues from Berlin and globally. Colleagues in the US and Canada, where ketamine clinics are already more prolific, still seem to face a lot of resistance and medical professionals are not referring patients for these types of therapies at a large scale yet.

In Blossom's survey, featured earlier on in the report, 65% of participants were aware of the use of psychedelics for the treatment of mental health conditions. This is already an amazing number, at the same time much more education is needed. Can you highlight how the MIND Foundation and OVID are filling this role?

We are currently in the fifth year of the MIND Foundation's existence and year two of OVID. In these first five years, MIND has focussed a lot on the academic system. Now, we have ten programmes in place that help educate and connect everyone, from established researchers to therapists, students and junior academics. The emphasis for the next five years will be translating academic knowledge into public awareness, so people have the information to build a critical assessment of the results that psychedelic treatments can produce.

Our educational programmes, such as Footsteps and BEYOND EXPERIENCE help a wider audience gain an understanding of altered states of consciousness, and how they can use these altered states of consciousness to create a better life. We want to expand that these programs for everyone by training more facilitators so that switching in and out of altered states of consciousness is normalised and integrated into a framework of integration.

Additionally, this year we will hand out several awards at the INSIGHT conference, our bi-yearly psychedelic research conference and on November 26th, the fifth anniversary of MIND. The goal is to raise awareness and create recognition for the junior and senior pioneers in the field. And to help them being taken seriously in the wider scientific community. This is also why we are providing endowed awards. The MIND Foundation Award will come with a €4.000 grant, and the Willy Schweitzer Young Researchers Award comes with € 1.000 due to generous donors.

Finally, our aim is to change the perspective from a drug-centred model, which is also very present in the psychedelic field, and includes the magic pill narrative, to an integration-centred model. Integration is about transforming experience into health and happiness related behaviours. Integration is all about creating a better life beyond altered states of consciousness. , We are not there yet as a field, but putting a little bit more focus on integration in the next ten years will serve everyone well - those looking for healing and those looking for growth.

We cannot do it alone, a lot of organisations will need to work together and steer the field into the next generation. Not only by replicating scientific results but also by translating science into real-life practices and using all our creativity to build up-to-date, secular spiritualities that invite people to steer out of esoteric self-referral. Thereby, we have a chance to build a place for psychedelics in modern societies.

Psychedelic Research

KEY TAKEAWAYS

1. Ketamine is currently the only psychedelic in widespread clinical use. MDMA for the treatment of PTSD is currently in phase IIIb and is expected to be approved by 2023. Psilocybin for depression has just finished the data collection on a large phase IIb trial, of which a total of 26 have been conducted or are currently ongoing.

2. Universities and hospitals commonly sponsor trials; companies have sponsored an average of 10 trials annually over the last three years, which will rise to 40 annually in 2024. More than 30 companies have indicated an intent to run clinical trials.

3. We can expect MDMA-assisted psychotherapy for PTSD to be approved by the FDA in 2023. Psilocybin for depression, both major depressive disorder (MDD) and treatment-resistant depression (TRD), will probably be approved by 2025. Other approvals for ibogaine, LSD, DMT and ketamine could follow soon afterwards.

Psychedelic research is pushing ahead at a pace never seen before. Where in the early 2000s, you were lucky to find a handful of researchers doing animal studies with mind-altering substances; nowadays, more than 100 exciting papers on psychedelics are published every month.

These papers detail the results of clinical trials, of which a new one is started every week, observational studies often in traditional settings, new hypotheses, and reviews that bring together what we currently understand about psychedelics as medicines.

Psychedelic Research Groups

The astronomical rise of research into psychedelics is a result of the work from several research groups that have found the balance between the multidimensional world of psychedelics and the rigorous demands of scientific inquiry. This work has also been made possible by foundations that have paid for much of the early research, specifically the Heffter Research Institute, the Beckley Foundation and MAPS.

The new wave of research arguably started with the study of DMT experiences by Rick Strassman in the 1990s. At that time, as far as we know, his group at the University of New Mexico was the only place doing research with psychedelics on humans. Although the study didn't investigate psychedelics as medicines 'per se', it showed others that, with enough persistence against wider discourse, research could be done.

The Johns Hopkins research group got permission in 2000 to reinitiate research with psychedelics, this time in patients who were psychedelic-naive, not having taken psychedelics before. The Centre for Psychedelic and Consciousness Research at Johns Hopkins, founded in September 2020, marks the next phase of research intensification as the group expands and investigates psilocybin for many different mental health disorders.

On the other side of the pond, the Imperial College London (ICL) team has been the first to study psychedelics with brain imaging techniques. After more than a decade of research, the Centre for Psychedelic Research at ICL was launched with the explicit goal to develop psilocybin-assisted therapy into a licensed treatment for depression.

These pioneering centres are not the only places where research is taking place. Everywhere from Maastricht University in The Netherlands to the University of São Paulo in Brazil, individual researchers and research groups have studied psychedelics, each through their own unique lense. We can expect more research centres to join those already established.

In the last two years, many new research centres have joined the two original groups. Researchers, including the author Michael Pollan, have launched the UC Berkeley Centre for the Science of Psychedelics in September 2020 with the aim of educating the public, training therapists and conducting more research. Mount Sinai, which launched the Centre for Psychedelic Psychotherapy and Trauma Research at the start of 2021, will also research MDMA, psilocybin, and other psychedelics for the treatment of those with complex mental health issues.

In February this year, Mass General launched the Center for the Neuroscience of Psychedelics, where neuroimaging will be leveraged to better understand how psychedelics work. The University of California San Francisco (UCSF) has launched The Translational Psychedelic Research, which will investigate psilocybin for hard-to-treat mental health disorders such as bipolar depression. Finally, UCSF has also set up a psychedelic section within its Neuroscape laboratory, where Robin Carhart-Harris serves as a director.

Founding of dedicated psychedelic research centres

Year	University Research Centres	Seed Funding
2019 APRIL	Centre for Psychedelic Research at Imperial College London	$4 million
2020 SEPTEMBER	Center for Psychedelic and Consciousness Research at Johns Hopkins University	$17 million
2020 SEPTEMBER	UC Berkeley Center for the Science of Psychedelics	$1,25 million
2021 JANUARY	Center for Psychedelic Psychotherapy and Trauma Research at Mount Sinai	$2,1 million
2021 FEBRUARY	Center for the Neuroscience of Psychedelics at Mass General	
2021 MARCH	UCSF Neuroscape Psychedelics Division	$6,4 million
2021 APRIL	Translational Psychedelic Research Program at UCSF	$3,4 million
2021 JULY	Project on Psychedelics Law and Regulation at Harvard Law School*	

**Undisclosed amount of funding received from the Saisei Foundation, led by Tim Ferriss (podcast host, author, philanthropist) with funds also provided by Matt Mullenweg (WordPress)*
Source: Blossom

CLINICAL TRIALS WITH PSYCHEDELICS

Of all the research that has been done with psychedelics, psilocybin and MDMA get to share the limelight. But it's actually ketamine that has generated the most amount of research. As of July 2021, 140 clinical trials have been conducted with ketamine for the treatment of mental health and substance use disorders. As detailed earlier in the report, this had led to the approval of Spravato for TRD and for the widespread use of ketamine for the treatment of MDD and suicidal ideation.

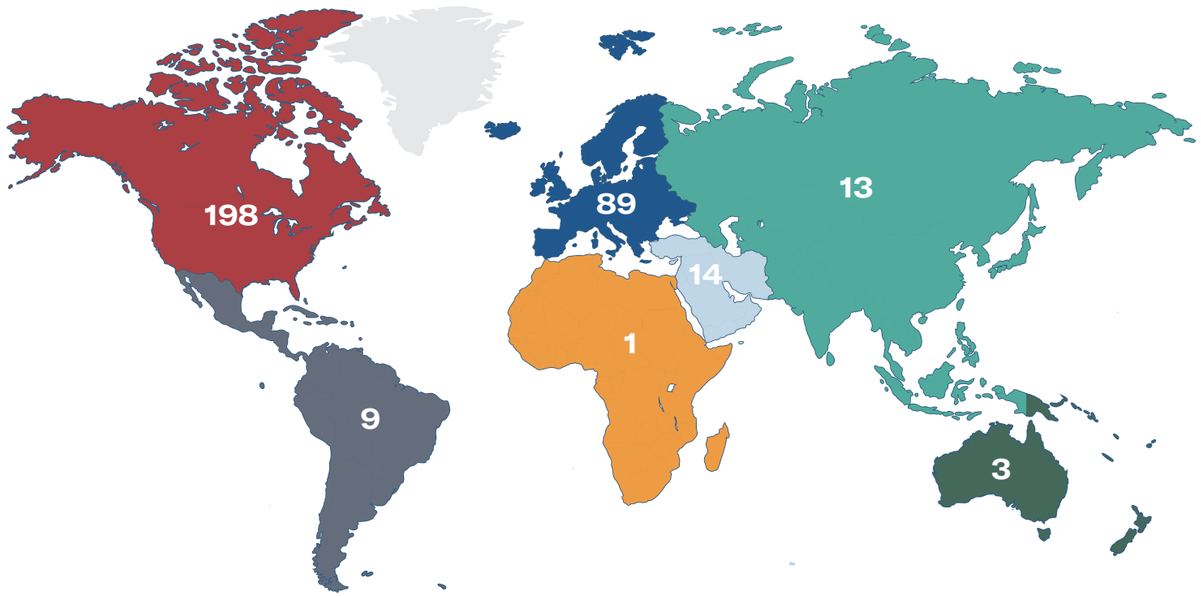
Over the years, we can clearly see a strong upwards trend in the number of patients that have participated in clinical trials. Where an average of 1,100 patients per year were studied between 2016 and 2018, this more than doubled to 2,450 patients in clinical trials between 2019 and 2021. The average number of participants in each trial is 52, which is higher than one might expect. The numbers increase from 36 on average in phase I trials, up to 96 per phase III trial. Looking at the data, without ketamine trials, lowers the average in phase I trials to 30 patients per trial.

Clinical Trial locations

Looking at geographic trial activity, America is the most active when it comes to running clinical trials, with Switzerland, mostly the Liechti Laboratory, coming in second place. The UK takes the fourth spot after Canada and has recently been ramping up the number of trials in the country. Surprising to note is a dozen trials in China, one of our profiled countries, where ketamine has been researched since 2012. China has also conducted a study on psilocybin for the treatment of migraines.

Not only are most of the studies in Western Educated Industrialised Rich Democratic countries but the patient populations are currently not that diverse. A review in 2018 found that 82% of patients are white and only 2% are of Asian origin – a startling discovery, given that this is where 60% of the world lives. Other ethnic groups are similarly underrepresented. Studies on dosing, efficacy, genetics and differing attitudes towards health services should be aimed at a more diverse and representative group for society to better generalise the results of the current body of research.

Location of clinical trials conducted from 2000 to 2021



Source: ClinicalTrails.Gov / Blossom

Number of Clinical Trials

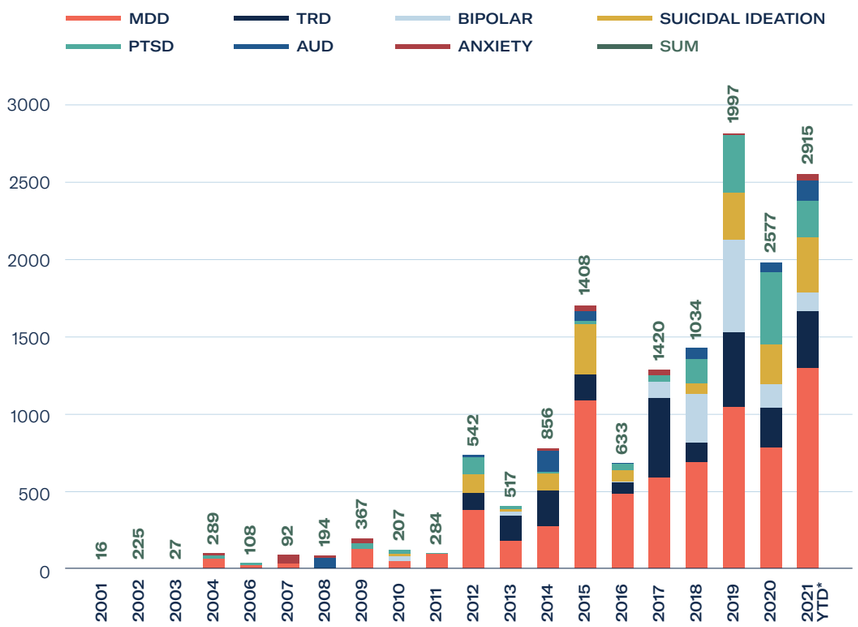
The number of trials that have been sponsored has shot up in the last three years, with an average of ten trials being sponsored each year. Most of the current studies are being conducted by universities, which have recently also significantly increased their output.

The data for 2021 does include some trials that haven't started yet, but we can expect some more to be registered before the year is over. At this time the biggest sponsors of research are COMPASS Pathways, MindMed, Johnson & Johnson, atai and its various subsidiaries.

Somewhat surprising is the number of trials already sponsored by governments. This is mostly done by the Veterans Affairs services in America. In the coming years, we expect this number to rise as psychedelic research becomes more mainstream, and more data is readily available. News from Germany and Australia indicate that more government funding is on the way.

Projecting the current numbers into the future, we can expect the number of trials to continue to rise quite quickly. Not only should many companies actually deliver on their plans to run trials, but we can also expect more studies to be sponsored by governments – such as the German government who is sponsoring the MIND Foundation's psilocybin trial.

Number of patients in clinical trials



**2021 includes all trials registered; more trials are expected to be registered, continuing the upward trend observed.*
Source: ClinicalTrails.Gov / Blossom

Psychedelic trials sponsored by industry

The commercial interest in research with psychedelics has only recently been ignited. There are more than 30 companies that are either running a clinical trial, have run a trial or have indicated that they plan to pursue a trial with a psychedelic. Although some of these press releases may not materialise as completed studies, many well-funded companies are on track to start clinical trials in the next few years.

There are currently tens of companies pursuing trials, of which the most certain are listed here. The duration to develop a psychedelic as medicine can vary widely. At this time, we only have Spravato for TRD and SI, and MDMA for PTSD as examples.

With the very short development cycle and because it was a known chemical entity, the cost of development for Johnson & Johnson most probably is way below their average of the US$5.8 billion that they've spent per newly developed drug. Presumably, it is also below the average of US$800 million that is the estimated cost to bring a single drug to market.

We do know that MAPS, although with a longer timeline, is following a far leaner approach, with their total costs still under US$100 million; they expect to spend an additional $100 million in further research expenses plus around $70 million in commercialisation expenses prior to launch. Although the expected approval has crept up over the years, 2023 seems to be a reasonable estimate.

The trials listed on the next two pages are sorted by either their start date or probable start date if the trial isn't ongoing right now. As previously mentioned, much research is picking up in the UK, with Beckley Psytech, Awakn and Small Pharma being three of the companies running trials.

Many more companies are running or planning to run clinical trials.

In alphabetical order:

Algernon, Alvarius, Awakn, BMORE, Beckley Psytech, BetterLife Pharma, Bexson, Bright Minds, CaaMTech, Ceruvia, COMPASS, Cybin, Delix, DemeRx, Diamond Therapeutics, Eleusis, EmpathBio, EntheogeniX, Entheon Biomedical, Field Trip Health, Filament Health, GH Research, Gilgamesh, Journey Colab, Lobe Sciences, Lophora, MAPS, MindMed, Mindset, Mydecine, Neonmind, Perception Neuroscience, PharmaTher, Psilera, Psybio, Revixia, Sacred Medicines, Seelos Therapeutics, Small Pharma, Tactogen, Tryp Therapeutics, Usona, Viridia and Wesana.

Notable ongoing and planned clinical trials

	Sponsor	Compound	Condition	Start
PHASE III	MAPS	MDMA	PTSD	2020
PHASE II	Compass	Psilocybin	TRD+	2019
	Usona	Psilocybin	MDD	2019
	MindMed	LSD	Cluster Headaches	2019
	Seelos Therapeutics	Ketamine	Suicidal Ideation	2020
	Small Pharma	DMT	MDD	2020
	GH Research	5-MeO-DMT	TRD (and others)	2021
	MAPS	MDMA	Eating Disorders	2021
	MindMed	LSD	Anxiety	2021
	Mydecine	Psilocybin	PTSD	2021
	Awakn	MDMA	Alcoholism	2022
	Cybin	Psilocybin	MDD	2022
	DemeRx	Ibogaine	Opioids	2022
PHASE I	MindMed	Ibogaine (18-MC)	Opioids	2020
	Perception Neuroscience	Ketamine	TRD	2020
	Beckley Psytech	5-MeO-DMT	MDD	2021
	Eleusis	LSD	Alzheimers	2021
	Algernon	DMT	Stroke	2021
	Beckley Psytech	Psilocybin	Headaches/pain	2021
	Entheon Biomedical	DMT	SUD	2021
	Eleusis	Psilocybin	MDD	2022
	Lophora	Psilocybin	MDD	2022
	Journey Colab	Mescaline	AUD	2022

Source: ClinicalTrails.Gov / Blossom

Notable Scientific Papers

Research is a cumulative process where later research papers build on the work that has come before. A new process is better understood, or a more controlled study is done to confirm the findings from an open-label trial. Some studies, however, are revolutionary and bring about a change in perspective that moves a field ahead to a new milestone, from which small new steps can be taken again.

Based on the database of more than 1,200 psychedelic research papers, we've highlighted some of the most influential, revolutionary papers on psychedelics below. These mark some of the moments that marked the age of psychedelics as medicines.

1. **Antidepressant effects of ketamine in depressed patients**

   This paper, published in 2000, is the most cited paper in our database and one of the first to investigate ketamine for depression in a double-blind randomised controlled trial (RCT). The study found improvements in depressive symptoms for patients three days later.

2. **Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer**

   Ten years later, in 2010, this RCT investigated the effect of psilocybin on anxiety in those battling life-threatening cancer. It found reductions in anxiety and depression which later studies found helped up to five years later. The study was conducted only with 12 patients; a 2016 study with 51 patients found similar results.

3. **Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction**

   It is hard to believe that it is already seven years ago that, in 2014, an open-label trial showed that 80% of patients were smoking-free six months after undergoing two sessions of psilocybin-assisted therapy. Five years later, 60% were still free from smoking. Unfortunately, no other research papers on smoking, which kills eight million people per year, have been published.

4. **The safety and efficacy of ±3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant post-traumatic stress disorder: the first randomised controlled pilot study**

   The first RCT that studied MDMA for PTSD was published in 2010. The study was incredibly successful and showed that 83% of participants who received MDMA did not qualify for PTSD anymore; this was only 25% in the control group. Many studies, after this one, have been finding similarly spectacular results. A follow-up four years later found that, of those treated with MDMA, only two, out of the 16 contacted, had relapsed.

5. **Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin**

   Many hypotheses existed around what happens when psychedelics are administered; in 2012, we get a first glimpse at what lies below the hood. The ICL team finds that blood flow decreased in several hub regions of the brain, something that was quite surprising at that time. Although more fMRI studies have been done since that time, there are still many open questions about how psychedelics influence brain processes.

6. The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs

A bridge between the neuroscience and the psychology of psychedelics was built with the publication of 'the entropic brain'. The paper proposes two different forms or states of cognition where one is more 'critical' and unconstrained; the psychedelic state. Several revisions since the publication in 2014, such as the Relaxed Beliefs Under Psychedelics model, have continued refining this framework.

7. Psychedelics and Mental Health: A Population Study

Psychedelics were studied in patients with life-threatening diseases not only because of their need for help but also because regulators were more likely to approve the study if patients had a shorter life to live during which they could be negatively impacted by the use of psychedelics. Studies like this survey of nearly 22,000 people show that these concerns may not be valid, as it found a slightly lower rate of mental health problems for those who used psychedelics than the general public.

8. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance

Through which mechanisms psychedelics have long-term positive effects, when the molecules have long since left the body, is hotly debated. One line of thought finds that the more intense the mystical experience, the better the effects on mental health. Since the publication of this paper in 2006, many others have found similar correlations. Other processes such as long-lasting neurological changes have also been identified that may (together) underlie the therapeutic effects of psychedelics.

9. Human hallucinogen research: guidelines for safety

Less exciting than other studies, the guidelines for safety that were published in 2008 have served a critical role in the development of psychedelic research. The 'set' and 'setting', knowledge of dosing, and developing trust with the participants, are key elements to facilitating a good research protocol.

10. Trial of Psilocybin versus Escitalopram for Depression

Contrary to the other papers indexed here, this RCT was only published in April 2021. The study pitted psychedelics directly against an antidepressant (escitalopram). The study found that the psilocybin group had better results, but unfortunately, the main measure was not statistically different. Still, this marks a seminal moment where a direct comparison against one of the most widely used antidepressants was made.

Psychedelics as medicines approval

	2019	2023	2025	2026	2027
MDD			Psilocybin	DMT	
TRD	Esketamine		Psilocybin	DMT	Ketamine
PTSD		MDMA		Psilocybin	
HEADACHES/ MIGRAINES				LSD	Psilocybin
SUICIDAL IDEATION	Esketamine		Ketamine		
EATING DISORDERS				MDMA	
ANXIETY				LSD	
SUBSTANCE USE DISORDERS				Ibogaine, MDMA	DMT, Mescaline
ALZHEIMERS					LSD
STROKE					DMT

Source: Blossom

Psychedelics making it to market

The timeline presented here is our best, arguably optimistic estimate, for when the different psychedelics or their second-generation equivalents could be approved for medical use.

This is based on the current drugs under development, such as MDMA for PTSD, and drugs that are just now going into clinical trials. There is good anecdotal evidence for many compounds and health indicators, and we expect many to pass through the trials successfully.

Based on research from Biotechnology Innovation Organisation, QLS Advisors andInforma UK from this year, the chances of developing a novel compound as a medicine are below 10%. Repurposing a drug, for a new health indicator, faces somewhat better odds and has about a 25% chance of getting approved.

Will this be different for psychedelics? Possibly. For many, we know the safety profile from earlier research and a lot of evidence is pointing towards effectiveness. But enthusiasm and personal transformation stories may not always translate to success in phase III trials. Novel psychedelics will also have to prove their efficacy against those already approved; something that will turn out to be difficult if real-world data supports the effectiveness found in trials conducted with classical psychedelics. Off-label use of psychedelics could also be expected in the future, much as it has been with ketamine.

Thank you to everyone who believes in us and in our mission. Our successful IPO is just one measure of this ongoing support and has set us up to continue to do incredible work.

Our deepest gratitude to those who recognized the therapeutic potential of these compounds long before we did, often risking their careers and livelihoods in the pursuit of public health and good. We also recognize that much of our work builds on hundreds, if not thousands of years, of indigenous knowledge. Without the wisdom, ingenuity of indigenous cultures our current frameworks—and knowledge of these medicines—would not be as sophisticated as they currently are. But we believe that there is still far more to be revealed.

We also thank those who have become believers in the potential therapeutic value of these compounds. Together we can see a bright future, and we hope we can be part of the solution, addressing the crises occurring in the field of mental health.

And lastly, a big thank you to the most important person in the room – the patient. While struggling with mental health disorders for so long, we thank you for bravely participating in clinical trials, for your open-mindedness, and for your persistence in gaining acceptance of these unfairly maligned compounds.

Glossary

The Psychedelics as Medicine Report | Glossary

ACT	acceptance and commitment therapy
ADHD	attention deficit hyperactivity disorder
AUD	alcohol use disorder
BTD	Breakthrough Therapy designation
CBCT	Cognitive behavioural conjoint therapy
CBT	Cognitive behavioural therapy
CIIS	California Institute of Integral Studies
CSE	Canadian Stock Exchange
CNS	central nervous system
DALYs	disability adjusted life years
DEA	Drug Enforcement Administration
DMT	Dimethyltryptamine
DSCP	Drug software combination products
ECT	electroconvulsive therapy
EDs	eating disorders
EEG	electroencephalogram
EMA	European Medicines Agency
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GITA	Global ibogaine therapy alliance

Psychedelic substances remain illegal in most countries so please reference your local laws in relation to medical or recreational use. This report has been compiled for informational purposes only. It should not be construed as a research report for investment, legal, medical, health or tax advice. © 2021 Psych Capital Plc.

GMP	Good Manufacturing Practice
ICL	Imperial College London
IND	investigational new drug
IM	intramuscular
IP	intellectual property
IPO	initial public offering
IV	intravenous
LSD	lysergic acid diethylamide
MAOIs	monoamine oxidase inhibitors
MAPS	Multidisciplinary Association for Psychedelic Studies
MAPS PBC	Multidisciplinary Association for Pyschedelic Studies Public Benefit Corporation
MDD	major depressive disorder
MDMA	methylenedioxymethamphetamine
MMA	Mind Medicine Australia
NGO	non-government organisation
NHS	National Health Service
OCD	obsessive-compulsive disorder
OUD	opioid use disorder
PAT	psychedelic assisted therapy
PPD	postpartum depression
PTSD	post-traumatic stress disorder
RCT	randomised controlled trial
SI	suicidal ideation

SNRIs	serotonin and norepinephrine reuptake inhibitors
SSRIs	selective serotonin reuptake inhibitors
SUD	substance use disorder
TBI	traumatic brain injury
TGA	Therapeutic Goods Administration
TRD	treatment-resistant depression
UCLA	University of California, Los Angeles
VR	virtual reality
WHO	World Health Organisation

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CONTACT DETAILS:

London
A: 17 Hanover Square
London W1S 1BN
United Kingdom
T: +44 20 38387621

info@psych.global
@psychglobal_
psych.global

info@blossomact.com
@blossomact
blossomanalysis.com

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