THE PSYCHEDELICS AS MEDICINE REPORT

Fourth Edition

PSYCH™

About

Unlocking the commercial potential of psychedelic medicine.

A data and insights platform for the psychedelic 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 to, 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 cohesive 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, who are ready to support industry growth and help them achieve their goals.

PSYCH unlocks the commercial potential of psychedelics.

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Empowering our partners to make better business decisions.

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If you would like to partner with PSYCH and access the largest B2B audience in global psychedelics, please contact our Commercial Director, Grace Cook, grace@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.

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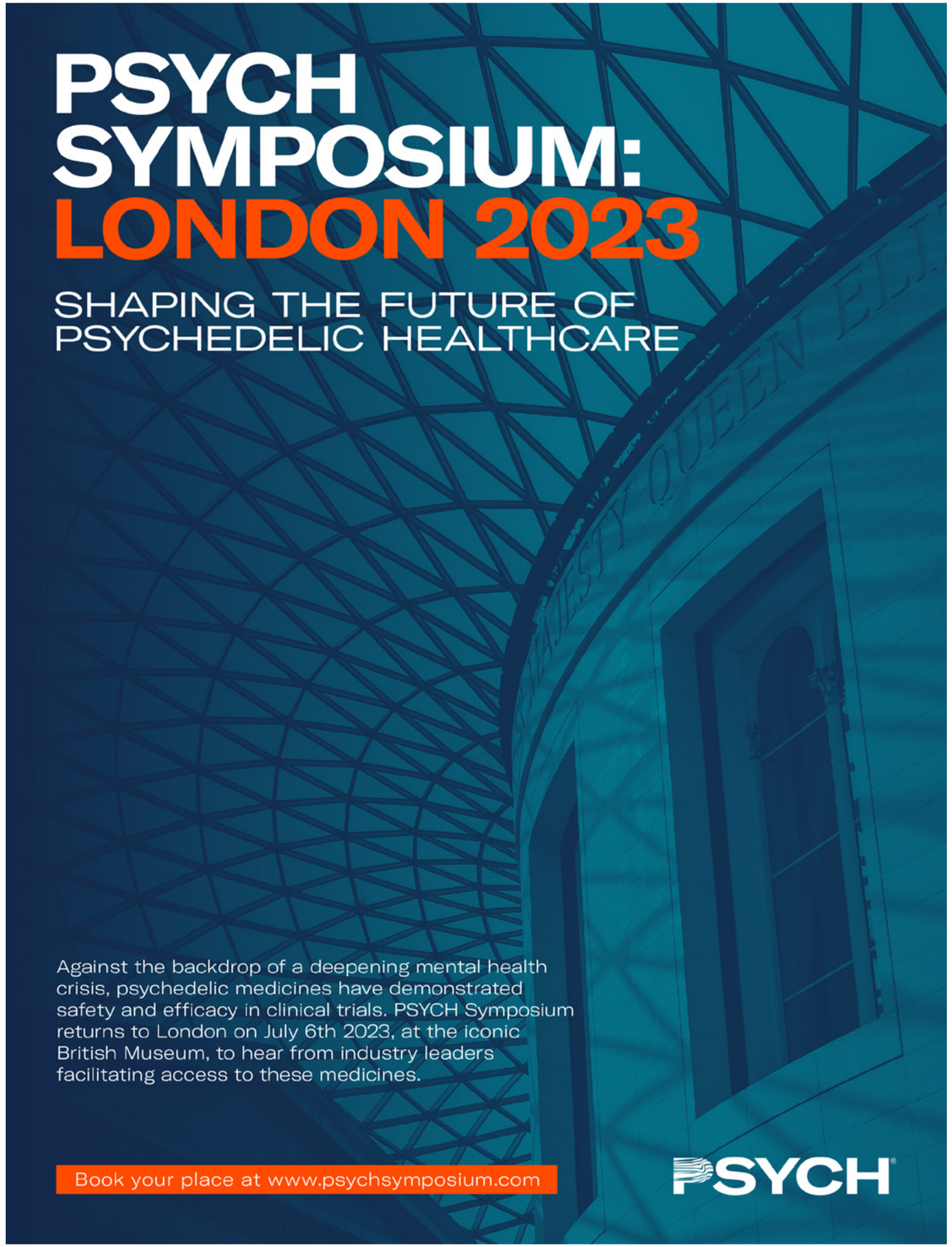

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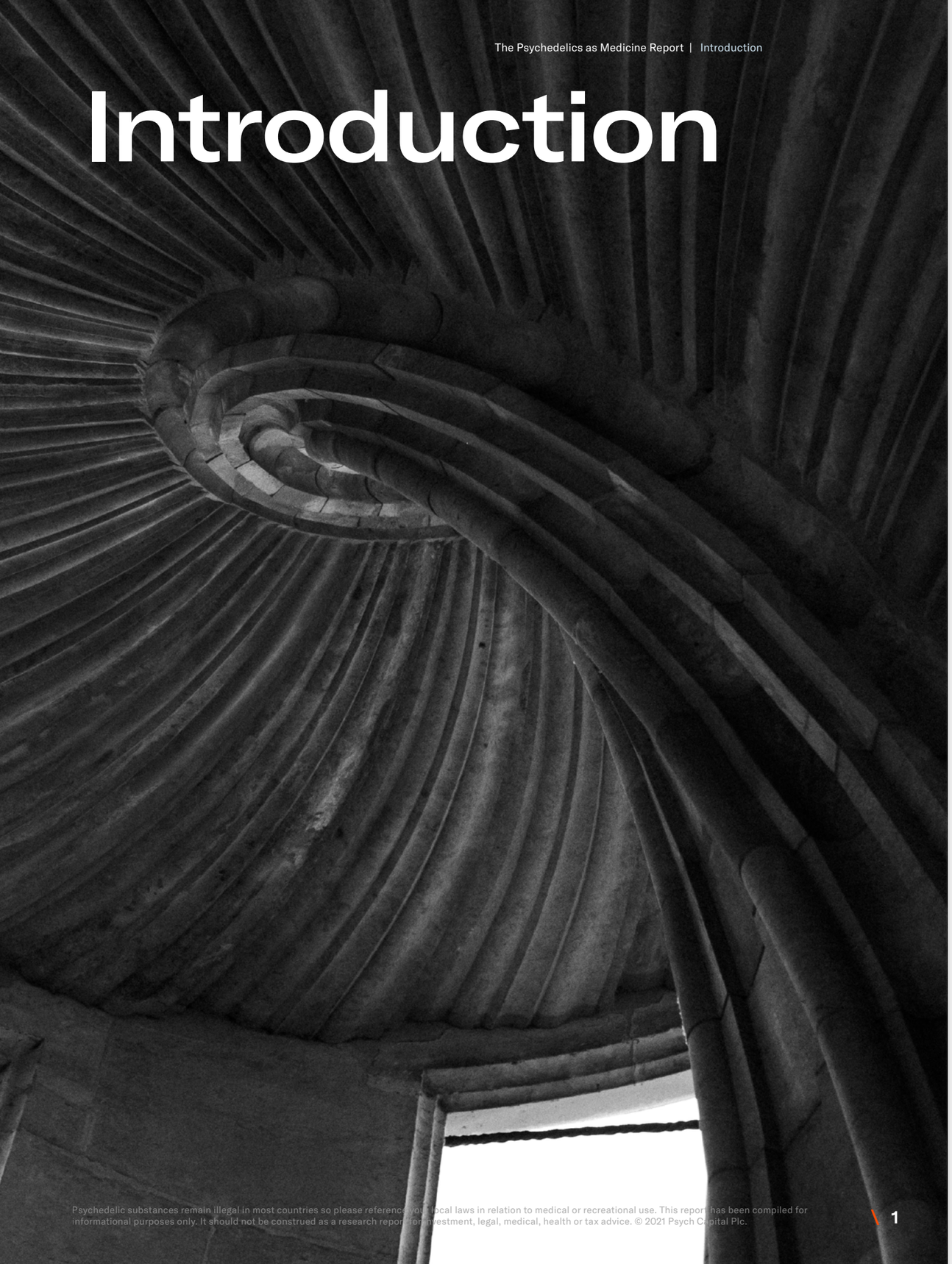
Introduction



The Psychedelics as Medicine Report | Introduction

The Psychedelics as Medicine Report: Fourth Edition serves as a comprehensive account of the psychedelic healthcare industry.

Following the success of the third edition and the sold out PSYCH Symposium, this report provides market data and insights from thought leaders across the sector - empowering regulators, researchers and investors to make informed decisions.

The next 24 months will be pivotal for the psychedelic healthcare industry, with MDMA and psilocybin-assisted therapy expected to be regulated by the Food and Drug Administration (FDA). This follows clinical trials that demonstrated the efficacy of psychedelic medicines to treat a number of mental health conditions.

The regulation of psychedelic healthcare in Europe will not be far behind the FDA regulation, with world-leading publicly listed companies, research organisations and academic institutions creating a distinct ecosystem across the Atlantic - with social health systems.

There has never been a greater need for innovation in psychiatry, with the World Health Organisation (WHO) declaring mental health disorders as the leading cause of disability worldwide - impacting nearly a billion people. During the first year of the pandemic, cases of depression and anxiety increased by over 25%, with political and economic uncertainty exacerbating the mental health crisis. To face this crisis head on, we need to continue to invest in the sector, not only through capital and human resources, but through pursuing regulatory reform which is based on evidence-based science.

With research at a tipping point, the industry needs the infrastructure to deliver these groundbreaking treatments at scale, focusing on patient accessibility and adoption.

However, challenges remain in moving these medicines from clinical trials to clinics and then to emulating success with patient outcomes.

In 2024, MDMA could become the first classic psychedelic approved for medical use in the twenty-first century. Psilocybin is expected to be regulated in 2025, with the introduction of both medicines forecast to create a psychedelic healthcare market worth over £3 billion.

However, for the market to realise its potential, collaboration amongst psychedelic researchers, medical regulators and local legislators will be key. If legislators pass reforms to allow greater psychedelic research, researchers can conduct further studies that then enable regulators to approve novel medicines for underserved patients.

With this updated version of The Psychedelics as Medicine Report, PSYCH presents an extensive overview of the psychedelic medicines which are in the latter stages of clinical trials and the associated market opportunities.

Expanded to reflect this burgeoning sector, analysis of regulatory frameworks enables stakeholders to competently navigate this burgeoning landscape and identify emerging opportunities.

Market data and insights have been compiled from across the industry for a holistic and impartial perspective on the commercial potential of psychedelic healthcare. This is substantiated by modelling created in collaboration with drug developers, healthcare providers and financial analysts.

Psychedelic Medicines

Psychedelic medicines are compounds with hallucinogenic properties which alter states of consciousness, with the majority tryptamines, phenethylamines and lysergamides.

Acting on serotonin 5-HT2A and 5-HT2C receptors, psychoactive compounds modulate brain activity to impact sensory perception.

Notable exceptions include; ketamine, ibogaine and salvinorin A, which are not directly serotonergic.

Psychedelic medicines increase connectivity between different regions of the brain, or neural plasticity, which can lead to changes in the nervous system's functionality.

Psilocybin

Psilocybin is a prodrug derived from psilocybe fungi such as Psilocybe cubensis. When metabolised into psilocin, the indole alkaloid activates 5-HT2A receptors to produce psychoactive effects, and it is expected to be regulated for medical use in 2024.

Ibogaine

Ibogaine is a psychoactive phenethylamine extracted from the root of the shrub, Tabernanthe iboga. First isolated in 1901, in low doses it acts as a stimulant and in high doses it causes hallucinations. The psychedelic medicine has been used to attenuate opioid withdrawal and is being studied for application in substance-use disorders.

Mescaline

Mescaline is a naturally occurring psychoactive phenethylamine derived from the cactus plant. First isolated from the peyote cactus in 1896, the molecular structure of mescaline is adrenaline and noradrenaline.

Ayahuasca

Ayahuasca is a brew made from a blend of different plants, primarily the Psychotria viridis chacruna shrub; chacruna, which contains DMT and the Banisteriopsis caapi vine, or yagé. Banisteriopsis caapi contains monoamine oxidase inhibitors (MAOIs) which prevent the stomach from breaking down DMT and thereby prolongs its effects.

DMT

Dimethyltryptamine (DMT) is a naturally occurring chemical found at low concentrations in both plants and animals. When taken in high doses, it produces powerful psychedelic effects as a serotonin agonist.

5-MeO-DMT

O-methyl-bufotenin (5-MeO-DMT) is a tryptamine alkaloid, first synthesised in 1936. Similar to DMT, the compound is found in both plants and animals, with high concentrations in the parotid gland secretions of Bufo alvarius - the Colorado River toad.

LSD

Lysergic acid diethylamide (LSD) is a synthetic psychedelic compound which binds to both

serotonin and dopamine receptors. First synthesised in November 1938, LSD belongs to a chemical group named lysergamides, which have both phenethylamine and tryptamine formulations embedded within their structure.

MDMA

Expected to be regulated for medical use in 2024, MDMA was first synthesised in 1912. Similar in molecular structure to mescale and methamphetamine, MDMA is a central nervous system stimulant and empathogen which increases serotonin, dopamine and noradrenaline activity.

Ketamine

Ketamine was first synthesised in 1962 and is commonly used as an anaesthetic, but it is increasingly used off-label in therapeutic settings for its antidepressant and dissociative properties. It is available in liquid-soluble form as ketamine hydrochloride and is marketed by Endo Pharmaceuticals and Pfizer, under the brand names Ketalar and Ketanest respectively.

Esketamine

Esketamine is the S(+) enantiomer of ketamine, which is one half of the two mirror images that make up racemic ketamine. Janssen & Janssen, a subsidiary of Johnson & Johnson received Food and Drug Administration (FDA) approval to manufacture an esketamine nasal spray for treatment-resistant depression (TRD) under the brand name Spravato.

Salvinorin A

Salvinorin A is a psychoactive compound found in salvia divinorum, a plant native to Central America. Distinct from other entheogens, it is a terpenoid, rather than an alkaloid; it causes dissociative effects and hallucinations as a potent opioid receptor agonist.

Milestones in Psychedelic Medicine

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
1985	June	DMA joins other psychedelics and is added to Schedule 1 under an emergency ban by the Drug Enforcement Agency (DEA)	US

Year	Month	Event	Location
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	Spain
2001	July	Personal possession of all drugs decriminalised in Portugal	Portugal
2017	August	MDMA-assisted psychotherapy granted Breakthrough Therapy designation (BTD) from US FDA	US
2018	October	COMPASS Pathways receives BTD from 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
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
2020	July	Oregon Psilocybin Service Initiative (IP34) succeeds in placing psilocybin legalisation on the state ballot	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

Year	Month	Event	Location
2020	November	Oregon decriminalises psychedelic medicines and creates framework for psilocybin services	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
2021	May	MAPS publishes results from Phase IIIa clinical trial, showing potential for MDMA to combat PTSD	US
2021	November	COMPASS Pathways publishes positive data from Phase IIb clinical trial with psilocybin	UK
2022	January	Health Canada expands Special Access Programme to include psychedelic medicines	Canada
2022	May	Psychedelic research centre opens in London with National Health Service (NHS) involvement	UK
2022	May	Oregon adopts rules for psilocybin framework	US
2022	November	Colorado decriminalises psychedelic medicines and creates framework for psilocybin services	US

Ketamine

In 2021, the psychedelic healthcare market was worth US$190 million, dominated by ketamine-assisted therapy. Distinct from other psychedelic medicines, ketamine is a dissociative anaesthetic, with psychedelic properties and it features on the World Health Organisation's List of Essential Medicines as an anaesthetic.

Traditional psychedelic medicines work by binding to receptors that detect serotonin, antagonising the 5-HT2a receptor, specifically. Ketamine, however, works by activating AMPA receptors, which are responsible for the majority of excitatory synaptic transmissions throughout the central nervous system, thereby strengthening the connections.

It was first synthesised in 1962 and approved by the FDA in 1970, with extensive research conducted on its efficacy in mental illness. It is widely used off-label to treat a variety of mental health conditions in conjunction with therapy, utilising its psychoactive and sedative attributes.

However, while ketamine has been administered off-label for depression for many years, it wasn't until 2019 that esketamine, a ketamine derivative, was ratified by the FDA for treatment-resistant depression and psychiatric emergencies.

The esketamine nasal spray is manufactured by Johnson & Johnson under the brand name Spravato, with ketamine therapy available through over 150 clinics across North America and Europe. Publicly listed, Awakn Life Sciences, opened the UK's first ketamine-assisted therapy clinic in June 2020, with a course of low-dose treatments alongside talk therapy costing £6,000.

Clinical trials

Excluding studies that look at the anaesthetic effects of ketamine, nearly 150 clinical trials have taken place to investigate ketamine-assisted therapy for mental health conditions. Of these, 50 have progressed to Phase III. Research in patient populations has demonstrated ketamine's efficacy for treatment-resistant depression, PTSD, bipolar disorder, anorexia and chronic pain.

Similar to psilocybin, the duration of ketamine's efficacy has been disputed, with some patients returning to the same level of depression 28 days later. Two studies sought to reinforce ketamine's therapeutic value when administered repeatedly.

The first study found that a 96-hour infusion of intravenous ketamine lowered depression scores for those with treatment-resistant depression for up to 50 days. The second trial gave six weekly oral doses of ketamine to those suffering with suicidal ideation (SI), with significant reductions in symptoms up to four weeks after the end of the study.

Commercial opportunity

Revenue from ketamine-assisted therapy for treatment-resistant depression and major depressive disorder, at US$600 per session, could exceed US$230 million by the end of 2022. By the end of the decade, this number could swell to US$1 billion, with over 500 clinics and 1.5 million patients being treated.

MDMA

MDMA was first synthesised in 1912 by Dr Anton Köllisch at Merck, and patented by the company in 1914. However, its therapeutic utility lay undiscovered until research by the acclaimed tryptamine chemist, Alexander Shulgin, half a century later. Shulgin introduced the compound to his wife, a psychotherapist, for use in couples therapy. MDMA is an empathogen, a psychoactive chemical that elicits feelings of empathy, similar in structure to both mescaline and methamphetamine. In response to a rise in recreational use in nightclubs, the Drug Enforcement Agency (DEA) declared an emergency ban on MDMA in 1985, despite its medical potential.

Clinical trials

Over 50 clinical trials have been conducted on MDMA's efficacy to treat mental health disorders, with 40% progressing through to Phase II and III studies. In addition to MAPS' Phase III trial to treat PTSD, the company is exploring its utility in Phase II trials to treat anxiety-related disorders. To support the development of MAPS' MDMA treatment, the FDA granted Breakthrough Therapy designation to the psychedelic medicine in 2017.

In the UK, Awakn Life Sciences' Phase II trial has demonstrated significant potential to treat alcoholism. The Bristol Imperial MDMA in Alcoholism trial, an open-label safety, tolerability and proof-of-concept study, indicated that only 21% of patients who received MDMA-assisted therapy returned to pre-treatment levels of drinking after nine months, as compared to 75% with conventional treatments. As alcoholism costs the NHS £3.5 billion a year, the treatment could hold significant commercial promise for drug developers and their supporters.

In MAPS' Phase III study to treat PTSD, 90 participants received 12 therapy sessions, of which three were with either a placebo or MDMA. Of those who received MDMA, 67% no longer qualified for PTSD diagnosis and 88% saw a clinically significant reduction in symptoms.

The data represents half of the participants who will be treated in the full Phase III trial, with the results from the second half expected later this year. The clinical trials are conducted by MAPS PBS, a wholly owned subsidiary of non-profit organisation MAPS, which aims to make MDMA-assisted therapy as widely accessible as possible.

With FDA approval anticipated in 2023, health practitioners may be able to provide MDMA-assisted therapy as early as next year. Based on MAPS' therapy goals during its data exclusivity period from 2023 to 2029, revenue gains from therapy and therapist training have been forecast in the region of US$7 billion.

Commercial opportunity

A key driver behind the FDA's support of MDMA-assisted therapy is PTSD's heavy burden on the US economy. A total of 870,000 veterans are in receipt of disability payments for PTSD from the Department of Veterans' Affairs, which costs the government an estimated US$17 billion a year.

Psilocybin

The Psychedelics as Medicine Report | Psilocybin

Psilocybin-assisted therapy for major depressive disorder and treatment-resistant depression are in Phase II trials, and may be approved by the FDA as early as 2025. The US federal department granted Breakthrough Therapy designation to the treatment, with 17 million people suffering from major depressive disorders in the US alone.

Psilocybin is a naturally occurring prodrug found in over 200 species of fungi. When ingested and metabolised, psilocybin converts into the tryptamine alkaloid psilocin, which imitates the neurotransmitter serotonin to produce psychoactive effects.

Brain imaging studies suggest that high doses of psilocybin disrupt negative thought patterns through frenzied neurodynamics, which then creates different neural pathways from those that are habitually used. By disrupting default mode networks, psilocybin can lead to a loss of self-awareness, or ego dissolution, which is considered fundamental to the psychedelic experience. This triggers opportunities for creativity outside the usual realm of consciousness, which can be particularly beneficial in psychotherapy.

Clinical trials

Psilocybin, after ketamine, is the second most studied psychedelic medicine – over 70 clinical trials have taken place, with 26 progressing to Phase II. A total of 21,000 subjects have been enrolled in the studies to treat a wide range of illnesses, including addiction disorders, cluster headaches, fibromyalgia and, most extensively, treatment-resistant depression.

Last year, UK-based COMPASS Pathways reported top line data from its Phase II trial to combat treatment-resistant depression, with its proprietary psilocybin formulation, COMP360. The study was the largest ever conducted with psilocybin, with 216 patients treated and hosted at 22 sites across Europe and North America.

The data demonstrated that COMP360 was well tolerated in patients and produced a statistically significant reduction in depressive symptoms. A patient's severity of depression is charted on the Montgomery–Åsberg Depression Rating Scale (MADRS), which ranges from 0 – 60, with individuals at zero expressing no symptoms of depression.

Scores on the MADRS depression scale fell the day after a single COMP360 dose, with the steepest decline being seen in patients who received 25 milligrams, the highest dose. This was still observed at three weeks, at which point the average MADRS score in the 25-milligrams cohort was 6.6 points lower than in the 1-milligram group.

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Commercial opportunity

Revenue from COMP360 psilocybin therapy for treatment-resistant depression could generate US$1 billion by 2028. However, the company's patents, related to psilocybin, have been challenged and decriminalisation efforts are potentially opening markets to other providers.

Cities in Colorado and California approved the decriminalisation of psilocybin-producing fungi in 2019. In 2020, Oregon decriminalised psilocybin and moved to regulate psilocybin-assisted therapy, accepting applications for registered practitioners from 2023.

There are now 17 jurisdictions in the US who have, either deprioritised the prohibition enforcement of psilocybin possession, or decriminalised the psychedelic compound altogether. Many of these amendments have been enacted under wider legislation pertaining to plant medicines, with the possibility of federal medical programmes for psilocybin being enacted as early as 2024.

LSD

Lysergic acid diethylamide is a synthetic serotonergic psychedelic. It binds to both serotonin and dopamine receptors, in key contrast to psilocybin, and its effects are noticeable at dosages measured in the millionths of a gram.

In November 1938, Albert Hofmann synthesised LSD-25 for the first time. By 1947, it was introduced as a psychiatric medication under the trade name Delysid by Sandoz and was found to disrupt negative thought patterns.

Studies throughout the fifties and sixties resulted in over 1,000 scientific papers on the potential applications of LSD-25. Trials were conducted to study the effect on alcohol dependence, autism and schizophrenia, but due to the lack of control groups and ethical review boards much of the data generated failed to reach today's standards of objectivity. In response to a rise in recreational use, the states of California and Nevada banned the manufacture, sale and consumption of LSD. This was reinforced nationwide by the Staggers-Dodd Bill of 1968, which prohibited the possession of LSD, other stimulants and depressants without a prescription.

Abuse of the compound was indicted as public enemy number one by President Nixon in his infamous 'War on Drugs' speech. This influenced the UN's publication of the 1971 Convention on Psychotropic Substances, which made psychedelic medicines including LSD, DMT and MDMA, internationally controlled substances. This largely stopped research on LSD's medical potential until the end of the 20th century.

Clinical trials

Although less intensely studied since then, LSD has played a pivotal role in psychedelic research and the discovery of serotonin receptors in the brain. In the current era of research, 21 clinical trials have been conducted with LSD.

At PSYCH Symposium: London 2022, MindMed Collaborators from University Hospital Basel, Professor Doctor Matthias Liechti and Dr Friederike Holze, released topline data from the largest-ever commercial trial with LSD.

In a study of 500 patients with anxiety disorders, 65% saw anxiety levels reduced by over 30%. It was the first study to show significant lasting effects of a psychedelic medicine, with LSD producing fast and long-lasting reductions in anxiety and symptoms of depression for up to 16 weeks post-treatment.

Studies have found that people who lack copies of the Cytochrome P450 gene, which codes for an enzyme that breaks down LSD, had up to 75% more exposure to the psychedelic medicine in their blood plasma levels. These individuals had more intense and longer-lasting LSD experiences, with conclusions from genetic data leading to the development of personalised dosing.

In the UK at Imperial College London, the Centre for Psychedelic Research has been established with £3 million in capital. Researchers from the group previously studied the effects of LSD on brain activity, and they will now investigate the potential of psychedelic medicines to treat mental health disorders.

Psychedelic Research

SCIENTIFIC STUDIES

The timeline here presents an estimate of when psychedelic medicines or their second-generation equivalents (indicated by *) could be approved for medical use. This timeline has been created on the basis of treatments that are currently under development, such as MDMA-assisted therapy for PTSD. Typically the drug development process is lengthy, and the probability of success is low, with only one or two drugs from an initial 10,000 compounds reaching FDA approval. Psychedelic research for many mental health indications presented in this timeline is only just beginning. Given the early success of such trials and the vast amount of anecdotal evidence regarding the therapeutic efficacy of these compounds, we anticipate that many will pass through the development process.

Psychedelic Medicine Approval Timeline

	2019	2024	2025	2026	2027	2028
MDD				Psilocybin	DMT, 5-MeO-DMT	
TRD	Esketamine		Psilocybin*	5-MeO-DMT		
PTSD		MDMA		Ketamine		
HEADACHE DISORDERS						LSD*, Psilocybin*
SUICIDAL IDEATION	Esketamine					
EATING DISORDERS			Ketamine			MDMA, Psilocybin
ANXIETY				MDMA		LSD
ALCOHOL USE DISORDER				Ketamine, MDMA		
SUBSTANCE USE DISORDERS			Ketamine	Ibogaine*		
ALZHEIMER'S						LSD*
STROKE						DMT*
BRAIN INJURY						Psilocybin*

Over the past year, we have witnessed an exponential increase in the number of private companies developing proprietary analogues of psychedelic compounds like psilocybin, DMT and LSD. While many hope these compounds will provide improved safety profiles and higher efficacy, their success is not guaranteed. An alternative route for many of these new chemical entities may be repurposing. If a drug like psilocybin gets approved for the treatment of depression, it may get used off-label, as is currently being done with ketamine. However, real-world data supporting the efficacy of such treatments will be needed before off-label use is permitted.

Ultimately, well-designed clinical trials with larger numbers of participants are needed in relation to psychedelic healthcare. Regulatory agencies require vast troves of data before deciding if such drugs can reach the market. Nonetheless, the use of psychedelic medicines for specific indications like PTSD and Treatment- Resistant Depression (TRD) may soon become a reality.

Clinical research with psychedelics is going from strength to strength. Ketamine continues to generate the most amount of research, given its legal availability, while compounds such as psilocybin and MDMA are close behind. One of the most exciting developments that has taken place over the past year is the significant increase in research taking place with DMT and 5-MeO-DMT. TRD and PTSD continue to dominate the landscape in terms of potential indications, but with new research institutions and industry players entering the space, psychedelic compounds are being tested in the treatment of an array of mental health conditions - such as substance-use and eating disorders.

Moreover, many of these new players are carrying out research with second-generation psychedelic medicines, which come with different chemical and safety profiles as compared to the classic psychedelic compounds like psilocybin, LSD and MDMA.

As of October 2022, over 50 clinical trials involving psychedelic medicines have been announced this year. While many trials are yet to commence, this number is a testament to the renewed interest in psychedelic research.

Accompanying this increase in trials is an increase in the number of study participants. Whereas, on average, 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, with the mean rising from 30 in Phase I trials to up to 96 in Phase III trials.

Clinical trials with psychedelic medicines

The commercial interest in psychedelic research continues to grow. There are more than 30 companies who have either; run a trial, are currently running a clinical trial, or plan to pursue a trial with a psychedelic medicine. One of the most exciting developments this year was the announcement of a partnership between Mindset and Otsuka Pharmaceuticals. This partnership marks the first agreement between a category-leading pharmaceutical company and a psychedelic-focused biotech company. We anticipate more partnerships like this in the years to come, as clinical trials continue to yield positive results.

While developments like this are positive, it is likely that many clinical trials may not materialise as completed studies. Next to regulatory challenges, which are dissipating in certain jurisdictions, the drug development process is costly. Recently the psychedelic healthcare conglomerate Atai Life Sciences 'streamlined' operations by stopping the development of three programmes (Revixia Life Sciences - Salvinorin A, Neuronasal - NAC and DemeRx - noribogaine). At MindMed, the development of 18-MC, an ibogaine derivative, was also put on hold.

Despite the largely positive developments in the field; Spravato for TRD and SI, alongside MDMA-assisted therapy for PTSD, remain the only examples of psychedelic medicines

progressing to Phase III. Given that Spravato was a known chemical entity, its development cycle was relatively short. As a result, the development cost for Johnson & Johnson was way below the company's average of US$5.8 billion which was spent per developed drug. Presumably, it is also below the average of US$800 million - the estimated cost to bring a single drug to market.

MAPS is taking a far leaner approach to developing MDMA-assisted therapy for PTSD, given its significantly smaller cash flow levels when compared to a pharmaceutical giant like Johnson & Johnson. While their process is estimated to be longer, its costs remain under US$100 million. MAPS expects to spend an additional US$100 million in further research plus around US$70 million in commercialisation expenses before any launch.

Clinical trial locations

Geographically, the United States continues to house most of these clinical trials. While Johns Hopkins University and New York University have been investigating psychedelics for several years, many more research institutions have entered the space following regulatory reform at the state level permitting such research. Switzerland remains in second place regarding the number of clinical trials hosted, most notably at the Liechti Lab at the University of Basel. While Canada is in third place, other countries are now close behind as a result of this renewed interest in psychedelic research.

One country of note is the United Kingdom which now boasts an array of dedicated psychedelic research teams at academic institutions and a host of commercial entities. Many believe that the UK has become a hub for psychedelic research now that it is no longer bound to the regulations of the EU. Earlier this year, Clerkenwell Health became the country's first contract research organisation (CRO) to announce the construction of a purpose-built facility carrying out clinical trials with psychedelic medicines.

In Australia, psychedelic research is also booming. Institutions such as Monash University and Macquarie University are home to researchers carrying out some of the world's first studies for certain indications. Interestingly, research on the potential of ketamine to treat mental health disorders continues to emerge from China.

As detailed in the last edition of this report, most of the research is taking place in Western Educated Industrialised Rich Democratic countries, and patient populations remain homologous. While much of the industry has recognised this shortcoming of psychedelic research, few have made efforts to rectify the situation. If psychedelic medicines are going to be widely accessible, studies should include a genetically diverse population representative of society, in order to generalise research outcomes.

Government funded studies

Psychedelic research is increasingly re-entering the mainstream arena thanks to the work of various institutions across the globe. Accompanying this research is a vast amount of data demonstrating that these medicines are both safe and effective. Once limited to private funding, government agencies worldwide are increasingly involved in psychedelic research.

The Department of Veterans Affairs (VA) in the United States remains one of the largest government agencies in the country which is funding psychedelic research. Over the past year, clinical trials with psilocybin and MDMA have commenced in several Veterans Affairs Clinics across the US - a testament to the efficacy of these treatments amongst a population disproportionately affected by mental health disorders.

The National Institutes of Health (NIH) awarded a US$4 million grant to Dr Matthew Johnson and his team of researchers at Johns Hopkins, making it the first federal grant for psychedelic research in over 50 years. Johnson and his colleagues at the University of Alabama at Birmingham and New York University will use the grant to explore the effects of psilocybin on smoking cessation.

In Canada, researchers are proposing studies that may receive up to C$1 million from Canadian Institutes of Health Research (CIHR). Grants will be issued at the end of Q1 2023.

Across the Atlantic in Europe, the MIND Foundation is studying the effects of psilocybin in treating TRD. Led by Prof. Dr. med. Gerhard Gründer, this study is taking place largely thanks to sponsorship from the German Federal Ministry of Education and Research. It is being conducted at the Central Institute of Mental Health (CIMH) in Mannheim and Charité Universitätsmedizin, Berlin.

Government agencies in the UK have also started to recognise the potential of psychedelic medicine. No longer bound by the regulations of the European Union, several psychedelic-focused biotech companies have been awarded 'Innovation Passports' by the MHRA. Similar to the 'Breakthrough Therapy designation' awarded by the FDA, the Innovation Passport supports and expedites the drug development process. Small Pharma has been granted such a designation for its lead DMT candidate, SPL026, for treating major depressive disorder (MDD). MAPS has received a similar designation for its MDMA-assisted therapy in the treatment of PTSD.

At the beginning of 2022, the Australian Government's Medical Research Future Fund committed A$15 million to universities across the country investigating the therapeutic potential of psychedelic medicines. The largest of the grants, totalling more than A$3.8 million, will go to a research team at the University of Melbourne, for a trial of MDMA-assisted psychotherapy for treatment-resistant social anxiety in young adults with autism spectrum disorder. Other funded trials are investigating the efficacy of psilocybin in the treatment of anorexia nervosa, depression and alcohol-use disorder (AUD).

With new developments in psychedelic research emerging and an urgent need for innovation in treating psychiatric disorders, public perception surrounding psychedelic therapy is beginning to change. As such, we will possibly see more governments sponsoring psychedelic research.

REPORTING ON THE HISTORIC RE-EMERGENCE OF RESEARCH INTO PSYCHEDELIC MEDICINES IN THE UK AND EUROPE.

PsychedelicHealth

Europe has a deep-rooted history with psychedelics and is home to the world's leading scientists that have pioneered this field of research.

Psychedelic Health aims to give psychedelic medicine a platform of its own as research and policy progress.

OUR AIMS

- Report specifically on developments being made across the UK and Europe as the psychedelic industry's ecosystem evolves.
- Bring together key individuals in the field.
- Share the stories and perspectives of patients to convey the real-life impact of psychedelic medicines.
- Facilitate wider discourse around the topic.

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Scientific papers of note

Research is a cumulative process, with subsequent research building on previous work. However, some research is revolutionary and brings about a change of perspective, advancing a field to a new milestone from which new small steps can be taken.

Based on a database of over 1,600 psychedelic research papers, we've highlighted some of the most influential and revolutionary papers from the last few years. These mark some of the most pivotal studies conducted on the use of psychedelics to improve mental health.

1. Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder

The largest published double-blind study on psychedelics finds tremendous positive effects on reducing drinking after psilocybin-assisted therapy. Two administrations of psilocybin reduced the number of heavy drinking days from 52% to 10% at the 32-week follow-up. Almost half of those treated were not drinking at all during the follow-up, versus 25% of those who received only therapy.

2. MDMA-assisted therapy for severe PTSD: a randomised, double-blind, placebo-controlled Phase III study

The first half of the MAPS-sponsored Phase III trial with MDMA-assisted therapy for PTSD reports overwhelming positive results, with 67% of participants not qualifying for PTSD anymore. This is contrasted with 32% success for the therapy-only group. Other studies on this trial also report lower instances of eating disorders, alcohol use, and substance use.

3. Updated cost-effectiveness of MDMA-assisted therapy for the treatment of post-traumatic stress disorder in the United States: findings from a Phase III trial

One pivotal question for psychedelics is the cost-effectiveness of the treatments. This latest analysis finds that MDMA-assisted therapy will cost about US $12 thousand per patient, but will save US $133 million (per 1,000 patients) over the next 30 years. If scaled up to 50% of eligible patients with PTSD, in the US alone, more than 6 million extra good years (quality -adjusted life years - QALYs) will be added.

4. Trial of Psilocybin versus Escitalopram for Depression

Another pivotal trial is the first large-scale comparison of a psychedelic (psilocybin) and an antidepressant (escitalopram). The study finds that the psilocybin group had better results, but unfortunately, the primary measure was not statistically different. Still, this marks a seminal moment where a direct comparison was made against one of the most widely used antidepressants.

5. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: prospective 12-month follow-up

Classical psychedelics not only work in the short term, but they also do not need continued daily dosing. A long-term follow-up to a rigorous trial with psilocybin-assisted therapy for depression finds that 12 months later, 75% of participants still showed a treatment response (defined as a 50% or more reduction in depression scores). Similar long-term effects have also been reported for MDMA for PTSD.

6. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later

Whether subjective (psychological-level) effects are necessary for the treatment effect of psychedelics is hotly debated. Many studies have shown that those with so-called mystical experiences respond better than those who don't have these experiences. Mystical experiences are defined by ineffability, feelings of ego dissolution, and positive mood.

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

A bridge between neuroscience and the psychology of psychedelics was built with the publication of 'the entropic brain'. The paper proposed 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 (REBUS) model, have continued to refine this framework.

8. A non-hallucinogenic psychedelic analogue with therapeutic potential

The invention of novel molecules promises the therapeutic effect of psychedelics without the hallucinogenic effects. This is done by changing how molecules interact with the brain. One such example is the formulation of the ibogaine derivative tabernanthalog, which isn't showing hallucinogenic effects in mice. Studies in humans with novel molecules are, however, still scant.

9. Psilocybin-induced reduction in chronic cluster headache attack frequency correlates with changes in hypothalamic functional connectivity

Next to mental health, psychedelics show promise in alleviating long-lasting and debilitating (cluster) headaches. The first rigorous study of three modest doses of psilocybin finds a reduction in the frequency of headaches by 30%. One participant who suffered from chronic cluster headaches was free from them during the whole follow-up period of 21 weeks.

10. Efficacy and safety of flexibly-dosed esketamine nasal spray combined with a newly initiated oral antidepressant in treatment-resistant depression: a randomised, double-blind, active-controlled study

Not always considered a psychedelic, ketamine is currently the most widely available treatment option for patients with treatment-resistant depression. This study on esketamine (Spravato) provides evidence of efficacy in alleviating depression when used in combination with an antidepressant. Until more psychedelics become available, ketamine is currently the best option for a significant fraction of patients.

Accessing psilocybin in the UK

Crispin Blunt MP
Chair of Conservative Drug Policy Reform Group

EVALUATING PROGRESS IN 2022

The enhanced ability to recognise patterns is a property of the psychedelic experience consistently noted in clinical trials. One's ability to notice patterns, however, does not need enhancing in order to notice a sobering parallel between the legacy of earlier research from the Centre for Psychedelic Research at Imperial College London on psilocybin and the launch of the world's largest medical psilocybin access and data project, Project Solace.

Both involve British innovation, but in the UK, psilocybin remains subject to the strictest possible scheduling in British law, meaning its enormous potential benefits to public health are under wraps on home turf and are reaped exclusively in other jurisdictions.

It is hard to find a better example of British innovation in biosciences in recent years than the 2017 psilocybin for depression study at Imperial College. Psilocybin's scientifically unjustified placement in Schedule 1 of the Misuse of Drugs Act 1971 meant that it was conducted against the odds of increased expense and the aggravated difficulty of it being over an extended time period – hurdles which precluded clinical research on psychedelics taking place in the UK at a volume conducive to rapid advances in treatment development. On its completion, the study, which was led by Prof Robin Carhart-Harris, launched a global research effort to develop psilocybin into a licensed treatment for depression.

Leaving the UK to work somewhere which embraced evidence-based drug policies was a no-brainer for many of the UK's clinical researchers in the years that followed — including Carhart-Harris who took up a directorship at the University of California in 2020.

Oregon led the way in the United States in providing access to psilocybin with Measure 109 in November 2020. Generalised anxiety disorder (InCannex), major depressive disorder (Usona) and treatment-resistant depression (Usona), alcohol dependency (B. More, and Clairvoyant) are some key areas of focus for clinical trials now progressing in the US.

Imperial College London are recruiting participants for clinical trials with psilocybin in the treatment of anorexia, fibromyalgia and obsessive compulsive disorder. The success of trials with psilocybin for treatment-resistant depression enabled the Institute of Psychiatry, Psychology & Neuroscience and South London and Maudsley NHS Foundation Trust to hatch further plans for psilocybin-assisted therapy in the treatment of post-traumatic stress disorder. The first trials of psilocybin therapy as a treatment for adjustment disorder by Europe's first commercial psychedelic research facility, Clerkenwell Health, began in the UK in August 2022, in collaboration with the Canadian bio-technology company, Psyence.

Outside of qualifying to participate in forthcoming clinical trials, however, where can British citizens suffering from major depression, end of life distress, cluster headaches and addiction – some of the many diverse treatment applications of psilocybin – seek solace?

No patient access scheme can grant it. There is not a UK equivalent to Project Solace, which enables Canadian patients to access therapies assisted by psilocybin by collecting real-world treatment data to further widen the scope of patient access. Project Solace is ironically modelled almost exactly on Drug Science's, UK-based Project Twenty21, which enabled UK patients to access medical cannabis at a capped price and to then have their treatment tracked by Drug Science. However, medical cannabis products, crucially, were moved from Schedule 1 to Schedule 11 of the Misuse of Drugs Act 1971 precisely to enable doctors to prescribe them, when appropriate. A similar scheduling decision – while this would be appropriate for psilocybin and commensurate with its proven clinical efficacy and low toxicity and profile of harms – eludes us in the UK; even though according to national YouGov polling in 2021, the majority of the British public are supportive of it; simply due to the inaction of a Home Office as yet reluctant to engage with the evidence, despite the Prime Minister at the time signing off on rescheduling psilocybin in a meeting with me in May 2021.

Risking our stake in a global psychedelic treatment development market that is projected to reach US$10.75 by 2021, is increasingly likely, the longer we delay in rescheduling psilocybin for research and treatment development. As long as psilocybin remains in Schedule 1, investment in the UK's advances in psychedelic treatment provision is confined to the realm of clinical trials. Depression is the greatest contributing factor to suicide, a cause of disability and it costs the UK £10 billion annually, according to research from the Faculty of Public Health. Employment costs associated with mental ill-health cost the UK £94 billion per annum, as discussed in the Conservative Drug Policy Reform Group's report joint-published with the Adam Smith Institute, Medicinal Use of Psilocybin (July 2020).

Morgan Stanley Investment Management's Counterpoint Global recently identified psychedelics as the next, 'big idea that has the potential to trigger far-reaching consequences' in a dedicated July 2022 report on the burgeoning industry. Evident immediately on visiting Canada – at the 2022 Catalyst Summit in Kingston, Ontario; in the extraction labs of Filament Health, and at the inaugural launch of Optimi Health's 20,000 square foot facility for psilocybin cultivation in British Columbia – is the extent to which industry leaders in drug development, production and provision can mobilise to enable access to psilocybin-assisted treatments in a climate where policy is favourable, redressing some of the damage done to the economy by failing to improve collective mental health.

Outdated drug law, based on flawed policy making obstructing the necessary research, is all that prevents the rapid expansion of patient access to vital treatments with psilocybin like those currently under clinical trial in the UK. When the Conservative Drug Policy Reform Group polled Members of Parliament between June and July 2021, it found that more than three-quarters of MPs, even within the Conservative party, believed that the time was right to update UK drug laws based on evidence – which points overwhelmingly to the need for the Home Office to heed the anticipated recommendation from the Advisory Council on the Misuse of Drugs to reduce existing barriers to research and reschedule psilocybin.

The Psychedelics as Medicine Report | Accessing psilocybin in the UK

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Intellectual Property

The Psychedelics as Medicine Report | Intellectual Property

Patenting medications, delivering technologies and treatment paradigms provide drug manufacturers with a period of market exclusivity, which then incentivises innovation by enabling the company to monopolise sales.

In the UK, the US and Canada, new drugs are patented upon discovery, rather than on regulation, with a patent term of 20 years. The majority of psychedelic compounds, such as psilocybin, LSD and MDMA were first synthesised in the early and mid 20th century, so their patents have since expired.

These compounds have limitations which inhibit their integration within existing medical frameworks. For instance, they are typically long-lasting and subsequently treatments that utilise these drugs can be prohibitively expensive.

By creating new molecules based on these classic psychedelic compounds, companies are investigating how to reduce treatment timeframes and therefore costs. In publicly funded healthcare systems, such as the NHS, ensuring cost-efficiency is key.

Treatment cost was a principal reason for Spravato's failure to gain traction in the UK and Canada, where it was rejected by both NICE and Health Canada. This illustrates that it is not enough to develop new treatments with greater efficacy than conventional medications, they must also be cost-effective.

With psychedelic healthcare set to be regulated around the world, a race is on to secure intellectual property and stake a claim in the emerging landscape. To futureproof business models, some are preemptively filing patents on psychedelic-compounds and their delivery technologies. This remains a point of contention in the industry, with arguments that over broad patents stifle market innovation.

In addition to applying for a patent to obtain market exclusivity, drug developers may also apply for data exclusivity - whereby they secure sole rights to the data generated through clinical trials. Data exclusivity lasts ten years in Europe, but only five years in the United States.

As MDMA was originally patented in 1914, MAPS required data exclusivity for a return on its investment in developing MDMA-assisted therapy for PTSD. With the treatment expected to be regulated across Europe and North America in 2023, MAPS will have up to ten years to scale its infrastructure. By 2030, the company aims to have trained 25,000 therapists and to have served 500,000 patients.

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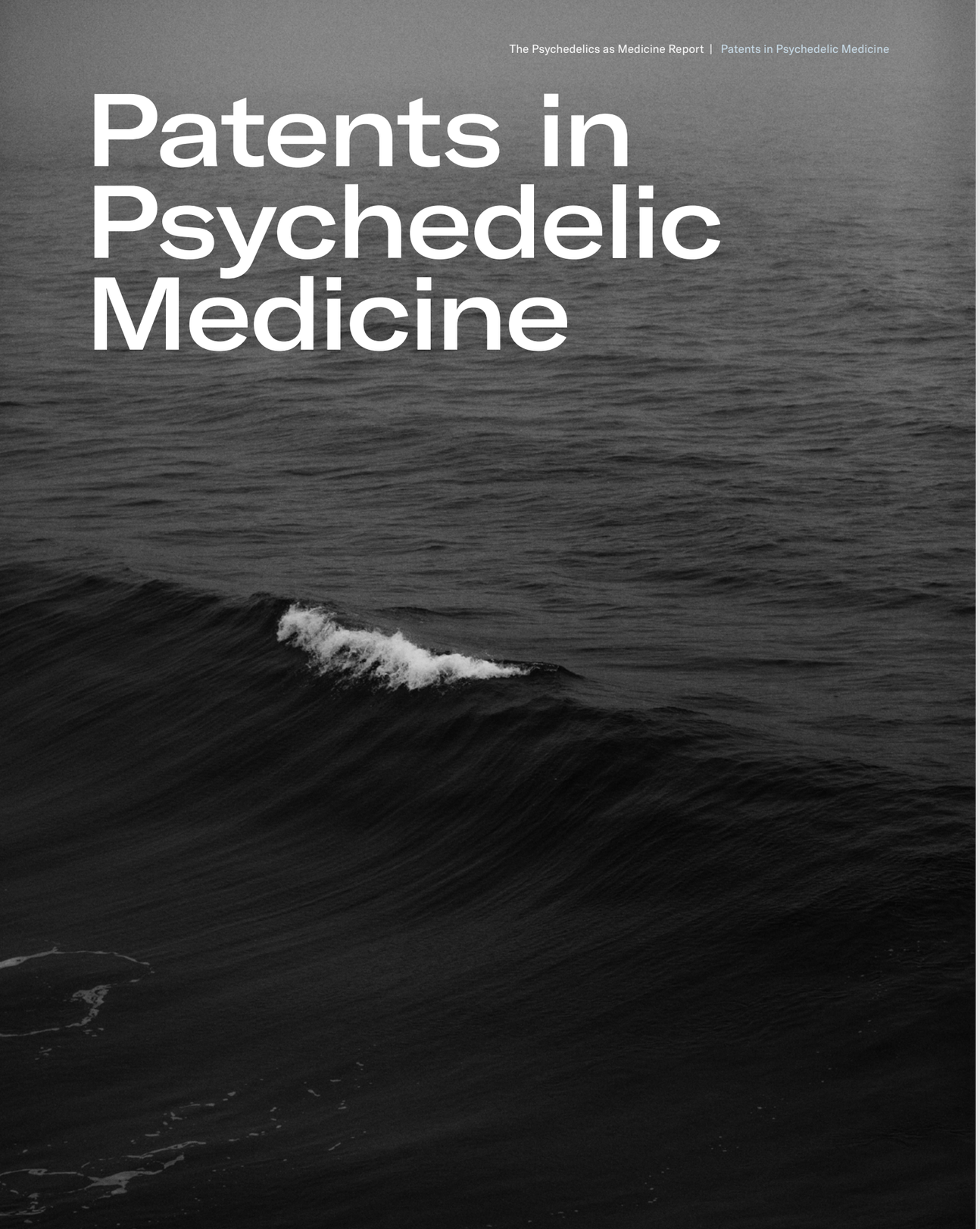
Patents in Psychedelic Medicine



IS LESS MORE?

The patent portfolio of a pre-revenue pharma company with significant R&D burn can be its lifeblood. Absent an exclusionary right, to protect the fruits of the R&D, all the resources and talent in the world may not be enough for a company to prevent a less endowed pirate from 'ripping-off' a future blockbuster—and capturing the profit for itself.

Enter patents. A patent does not guarantee a right to practice an invention. Rather, it bestows a right to exclude competitors. By excluding other players for a limited term, the theory goes, an inventor can capture the fruits of production for him or herself over that term, thereby rewarding and incentivising innovation.

Thus, a patent's value derives from what it excludes. Think of a patent like a fence surrounding a vineyard. The value of that fence comes not from the area it covers—the breadth of coverage—but from the value of the vines contained therein. A fence could cover very little property, but, if the enclosed vines yield many grapes, that fence could be quite valuable. Indeed, a small fence ensconcing a single productive vine could be far more valuable than a fence surrounding a vast, barren acreage.

In addition, for a patent to have value, it must be valid. A valid patent claim must be new and inventive or non-obvious. This means that the exclusionary fence must enclose new, non-obvious material.

As such, the name of the patent game is not always breadth. After all, the more area enclosed by a fence, the greater the danger that the fence covers old ground.

Orange Book patents

Many (but not all) patents in the emerging psychedelic space are pharma patents: patents directed to a product or process involved in the administration of an approved pharmaceutical product or therapy. In addition, for the reasons stated above, such patents that closely track new drug products—even very narrow ones—can be some of the most lucrative in the world. Weeks of exclusivity tied to a blockbuster drug product can translate to millions in revenue. Also, these pharma patents tend to fare better when challenged in court, with significantly lower invalidation rates.

In 2021, the US Patent Office granted 327,798 utility patents. Common wisdom suggests around 95% of these patents will not amount to much. Pharmaceutical patents are no exception. Many pharmaceutical products never make it out of clinical trials. If the value of pharma patents relates to the things they are guarding, the pharma patents have little value if the products they guard never make it. But when those products do make it, patents covering those products are king.

This has a lot to do with the regulatory environment. To balance innovation and access, drug approval laws contain provisions that involve exclusivities related to new drug applications. When a drug is approved, the US FDA grants new drug exclusivity rights for a period of up to seven years, depending on the submission type. This type of exclusivity—called data exclusivity—keeps firms from using submission data in obtaining approval for generics, whether a patent is tied to a product, or not. MAPS, for example, expects approval by the FDA for its MDMA formulation sometime in, or after, 2023, and intends to rely on data exclusivity rights—not patents—to exclude competitors to recoup R&D.

In addition to, or in place of, market exclusivity, a drug manufacturer may also rely on patents. Among other benefits, patents last longer than data exclusivity: 20-years from the date of filing. Patents related to approved drug products must be listed in FDA's Orange Book, which identifies drug products approved by the US FDA. Applicants for non-disclosure agreements (NDAs) must file an application for all patents 'which a claim of patent infringement could reasonably be asserted.' If an unauthorised person engaged in the manufacture, use, or sale of that drug. This requirement extends to patents covering the active ingredient, formulation of drug products, and methods-of-use.

Orange Book patents have unique characteristics that distinguish them from other pharma patents and make them even more valuable. For example, under US law, some Orange Book patents get longer terms and the power to prevent a generic drug from getting FDA approval to enter the market for up to 30 months until any patent litigation is resolved – in effect, an automatic preliminary injunction that is rarely available in normal patent litigation.

COMPASS Pathways v. Freedom To Operate (FTO)

Perhaps the most notorious group of psychedelic pharma patents destined for Orange Book status are COMPASS Pathways's patents. U.S. Patent No. 10,947,257, for example, issued on 16 March, 2021, covers silicified microcrystalline cellulose and, 'a therapeutically effective amount of crystalline psilocybin in the form Polymorth A', characterised by five specific peaks in an XRPD diffractogram with a variance of ±0.1°2θ, where the crystalline psilocybin has purity greater than 97% and no single impurity greater than 1%. The claim appears narrow, but obviously covers COMPASS Pathways's proprietary COMP360 synthetic psilocybin product. COMPASS Pathways has obtained additional patents related to COMP360, including method-of-use patents.

In December 2021, FTO filed two post-grant petitions with the Patent Trials and Appeals Board (PTAB) challenging two of the COMPASS Pathways's patents that cover the specific form of Polymorph A described above. In the petition, FTO sought a broad construction for the term, 'polymorph' to mean 'a solid crystalline phase of a given compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state.' Presumably, FTO sought a broad construction to dovetail with its arguments that the COMPASS Pathways fence enclosed prior art. Broader peaks could have invalidated the patents based on the prior art, as one of the cited references taught peaks very close to the COMPASS Pathways peaks, but outside the specific variance of ±0.10°2θ.

In denying the petition, the Patent Office agreed with COMPASS Pathways and applied a narrow construction of the patent claim terms. The PTAB concluded that even if 'polymorph' were typically understood to be as broad as FTO argued, 'Polymorph A' had a specialised meaning in the patents limited to the five specific peaks listed in the claim. It also concluded that, while those peaks would involve some degree of experimental error,

the claim language specifically accounted for that error by, 'expressly reciting a variance of ±0.1°2θ.' Under these narrow constructions, the PTAB denied institution on FTO's petition, concluding that the prior art did not teach two of the five peaks within the stated variance.

Looking Forward

Following the denial of the petition, FTO proclaimed that 'COMPASS Pathways is now on notice that its 'Polymorph A' patents cannot be asserted recklessly against any commercial-scale manufacturer or distributor of a psilocybin-based medicine,' and that psilocybin manufacturers, 'now have a clear pathway for making sure that psilocybin they manufacture or sell is not at risk of infringing COMPASS Pathways's 'Polymorph A' patents.' But, the fact remains that COMPASS Pathways's intellectual property (IP) remains wholly intact, ready to protect its product as soon as COMP360 runs the regulatory gauntlet. Whatever one thinks of the outcome, the dispute between the warring psilocybin factions could be a harbinger of things to come. It also illustrates some of the principles described above. COMPASS Pathways was successful with a narrow construction covering a specific form of 'Polymorph A.' Nonetheless, there should be little doubt that FTO challenged the patents precisely because these narrow patents; will still be quite valuable, will likely attain Orange Book status, and will help COMPASS Pathways with a strategy to build an IP/regulatory thicket around its proprietary psilocybin product.

Market Sizing

The size of the psychedelic healthcare market is dependent on the patient populations that are eligible to receive psychedelic-assisted therapies through medical regulation and the scale of the local adult-use frameworks, such as in Oregon.

Mental health conditions not only burden a patient's quality of life and their support networks, they also have an economic impact that extends beyond healthcare spending. Impaired labour participation has a major impact on national economies and consequently innovation in the sector has significant socio-economic benefits.

The number of patients with depression and anxiety surged due to the outbreak of the COVID-19 pandemic. However, the long term impact of the pandemic, and the subsequent 'cost of living' crisis' is yet to be understood.

Expectations of new and additional mental health services required for patients with depression and post traumatic stress disorder (PTSD) have been extrapolated from data modelled by the UK's National Health Service.

In Europe, the number of patients suffering with depression could double - with rates of PTSD rising by 20%. This would cost healthcare systems in Europe an additional US$41 billion annually.

The cost of mental illness extends beyond healthcare spending, with compromised labour forces undermining national economies. There has been a rise, both in public-private partnerships and in terms of investment to support innovation, which has led to socio-economic benefits and the treatment of underserved populations

In the UK, annual costs associated with mental health disorders total £94 billion a year. In the United States, where healthcare costs are far greater, the economy could save US$270 billion through innovations in psychedelic medicine.

The economic burden of mental illness across Europe and North America can be quantified through both direct and indirect healthcare costs. The extent to which these costs can be alleviated is modelled on its application in four indications; treatment resistant depression, major depressive disorder, post traumatic stress disorder and alcohol-use disorder.

MODELLING

Medical frameworks

The models used to evaluate market size were formulated on the condition that psychedelic-assisted therapies are approved by the FDA, EMA and MHRA on their current timelines. The models also incorporate scalability factors, such as; data on the availability of therapists, therapist training revenue and consumer demand.

Ketamine is the only regulated psychedelic medicine featured in this report, however MDMA-assisted therapy and psilocybin-assisted therapy are expected to be regulated in 2024 and 2025 respectively. MAPS and COMPASS Pathways both have commercialisation goals, with targets for therapist training programmes.

To infer the market sizes for ketamine, MDMA and psilocybin-assisted therapies; patient populations, therapist numbers and the attitudes of healthcare providers have all been accounted for.

Adult-use programmes

When calculating the total addressable markets for adult-use programmes, consumer demand for psilocybin services was ascertained through a survey conducted in Oregon.

The data was then extrapolated across markets with legislation pertaining to the creation of adult-use frameworks. The total addressable markets were identified by applying this data to eligible populations in respective jurisdictions.

The development of these markets will depend on the efficiency of regulators to issue licences and promote industry accessibility. As a result, information gleaned from conversations with regulators and service providers has been factored into market scalability and sizing.

The Psychedelics as Medicine Report | Market Sizing

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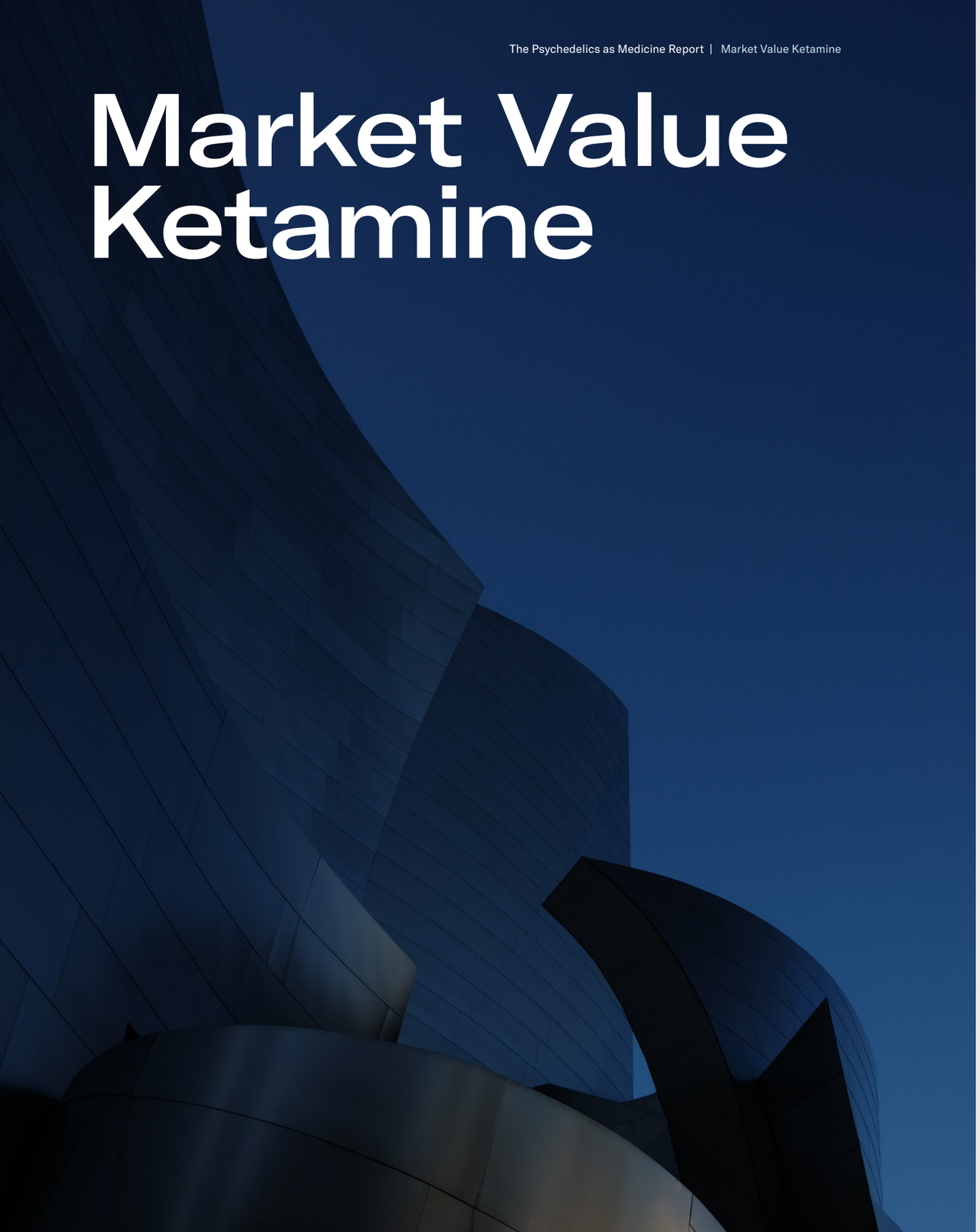
Market Value Ketamine



In 1985, ketamine was placed on the World Health Organisation's list of essential medicines - for use as a sedative. Due to its off-label use, ketamine treatments will account for the lion's share of the global psychedelic healthcare market for the next five years.

Although not a classic psychedelic medicine, ketamine activates AMPA (a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors as opposed to 5-HT2a receptors. The compound is widely used therapeutically as an antidepressant and to promote neuroplasticity.

Liquid-soluble ketamine hydrochloride is marketed by several pharmaceutical companies, including Pfizer, in Europe and North America. Over 600 clinics across North America offer ketamine services, but there is a large disparity in treatment modalities and costs.

Administration sessions are priced between US$400 and US$1,200 and the sector is largely unregulated, with ketamine infusions often taking place without a therapy component.

As recognition grows of the value of the psychedelic experience when combined with therapy and with efficacy being demonstrated through clinical trials, the demand for ketamine-assisted therapy is set to surge.

Ketamine-assisted therapy could be effective in the treatment of a wide range of psychiatric disorders. More than 150 studies have been conducted on indications including; alcohol-use disorder, anxiety, bipolar disorder, chronic pain, cluster headaches, major depressive disorder, treatment resistant depression and substance-use disorder.

Typically, ketamine-assisted therapy courses consist of between six and nine sessions, covering preparation, administration and integration. In Europe, a course of ketamine-assisted therapy, consisting of nine sessions, can cost the equivalent of US$6,800.

Ketamine is often administered off-label for psychiatric conditions, as it is more economical than the esketamine nasal spray, Spravato, which has been approved for treatment-resistant depression.

Spravato

Janssen Pharmaceuticals, a subsidiary of Johnson & Johnson, received FDA and MHRA approval for its esketamine nasal spray, Spravato, in 2019.

It was the first new medication approved for the treatment of depression in over 35 years, and signified a milestone in the provision of psychedelic healthcare.

There are two phases within the Spravato treatment regime, an induction phase followed by a maintenance phase. In the induction phase, a patient receives esketamine twice a week. In the maintenance phase, this can be reduced to once a week. Patients then typically take Spravato once a week for six months, with a dose costing up to US$555.

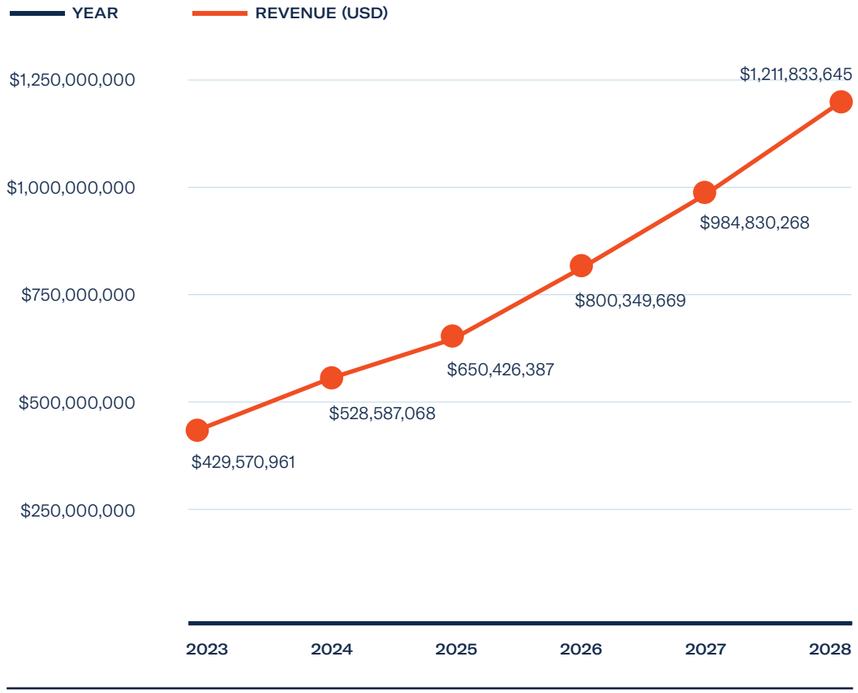
Due to the drug's high cost, in conjunction with safety and efficacy concerns, the treatment has not been approved for adoption on the National Health Service (NHS). Spravato costs roughly US$14,000 per course of treatment, with suggestions that the price would need to be reduced to US$8,400 to be cost-effective for treatment-resistant depression.

Market modelling

In modelling the size of the market for ketamine treatments, we incorporated all delivery methods, including intramuscular injections, intravenous drips, oromucosal sprays and transdermal patches.

Revenue from licensing and training has also been factored into the overall market sizing.

Market size of ketamine-assisted therapy



North America

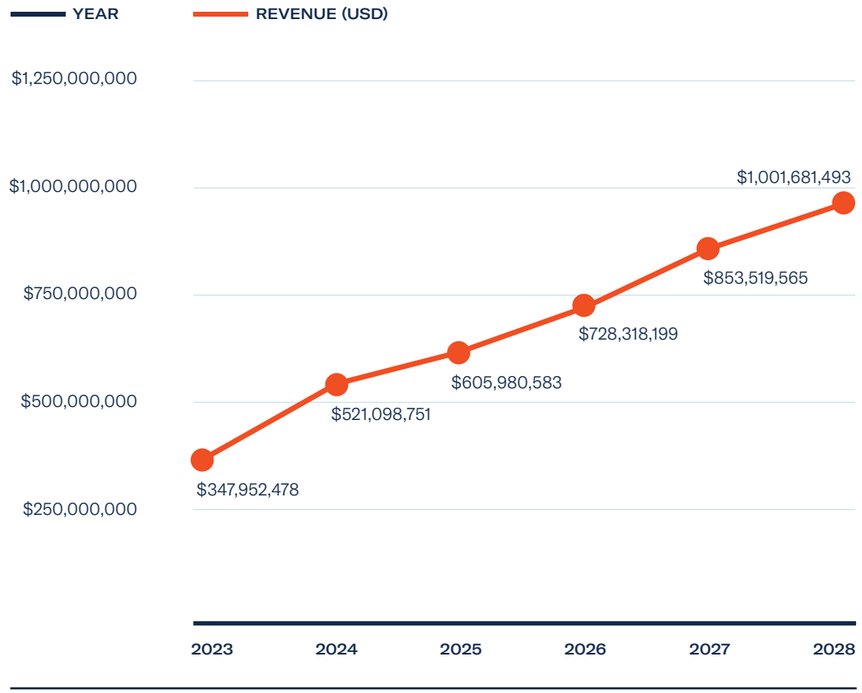
The price of ketamine services in North America will be impacted on by the creation of local psilocybin frameworks and this is considered in terms of revenue estimates.

With adult-use psilocybin frameworks not expected to be fully operational until 2025, the ketamine therapy market is expected to grow steadily. As these programmes emerge, they will further legitimise psychedelic-assisted therapy, attract investment and increase competition in the sector.

This market pressure could lead to a rapid expansion, followed by short term consolidation. However, improved treatment accessibility is expected to instigate exponential revenue gains in the latter half of the decade.

Assuming a linear growth rate of clinics, at US$600 per course of treatment, the revenue generated by ketamine clinics could surpass US$1.1 billion by 2028. Revenue from clinics in the US, Canada and Mexico has been factored into market size projections.

Market size of ketamine-assisted therapy - North America



Europe

In Europe, the adoption of ketamine services largely depends on its provision through public healthcare providers. Despite the National Institute for Health and Care Excellence's (NICE) rejection of Spravato, which has stalled its availability on the NHS, there is growing advocacy for the treatment's approval.

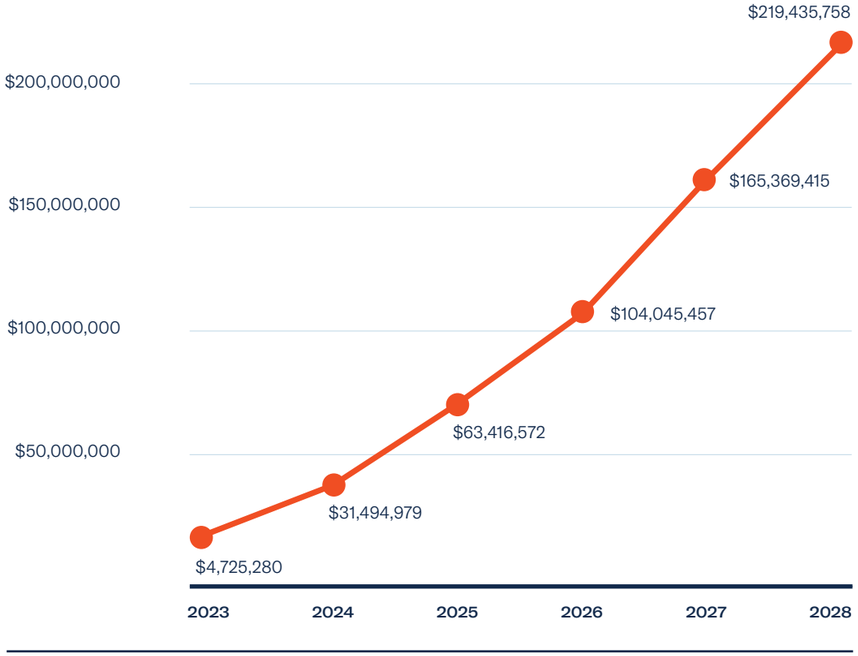
In addition to appeals from Janssen Pharmaceuticals, Spravato's manufacturer, The Royal College of Psychiatry contends that NICE's verdict prevents any treatment from securing approval for treatment-resistant depression.

In light of private and public pressure, it is anticipated that Spravato will be available on the NHS for treatment-resistant depression by 2025.

Considering a linear growth rate of trained therapists, with courses of ketamine-assisted therapy priced at US$6,400 per course of treatment, the revenue generated in Europe could be worth US$249 million by 2030.

Revenue will increase as the industry matures from 2025 onwards, with greater market accessibility.

Market size of ketamine-assisted therapy - Europe



Labelling ketamine as a psychedelic medicine is a misnomer, but due to similarities in its therapeutic application, and in the absence of approved classic psychedelic molecules, it is commonly referred to as such.

Ketamine is the most widely studied compound in this report. Excluding clinical trials that assess the medicine's efficacy as an anaesthetic, more than 150 clinical trials with ketamine have been conducted.

Of the clinical trials, 60 have progressed to Phase III studies, with ketamine's fast onset and the short duration of psychedelic experience promoting its integration into existing medical frameworks.

The antidepressant properties of ketamine are immediate and persist for seven days. After seven days, without re-administration or integration, depression scores in patients have returned to baseline after 28 days.

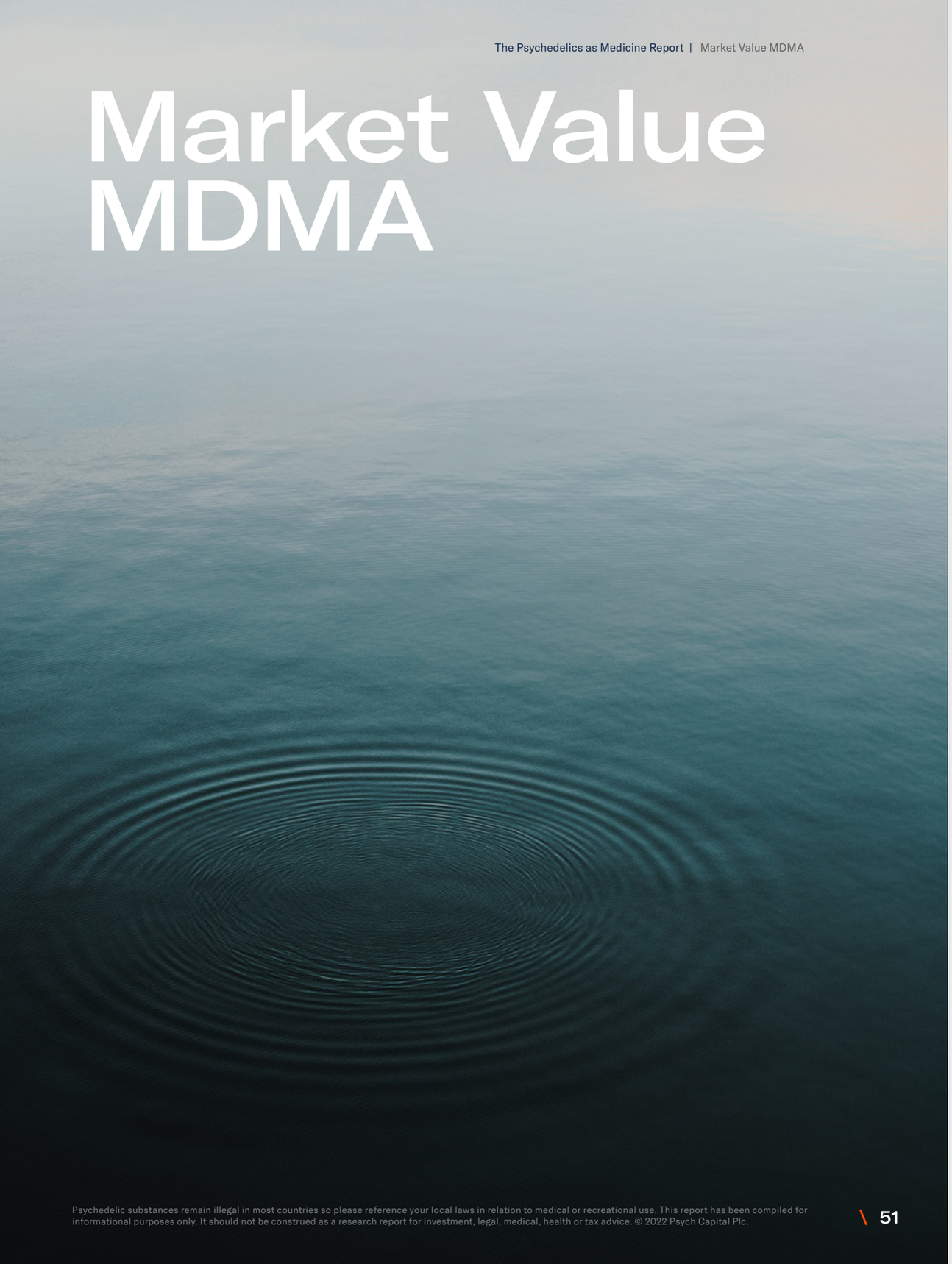
Two studies conducted last year provided evidence that the longevity of ketamine's antidepressant effects can be extended through repeated administrations of the drug.

Six weekly doses of ketamine, in conjunction with therapy, significantly reduced suicidal ideation four weeks after the last administration. The Washington University School of Medicine also lowered depression scores for up to eight weeks through extended intravenous ketamine infusions.

Studies have shown that ketamine-assisted therapy can treat substance-use disorders, and that the compound's mechanism does not exacerbate psychotic symptoms.

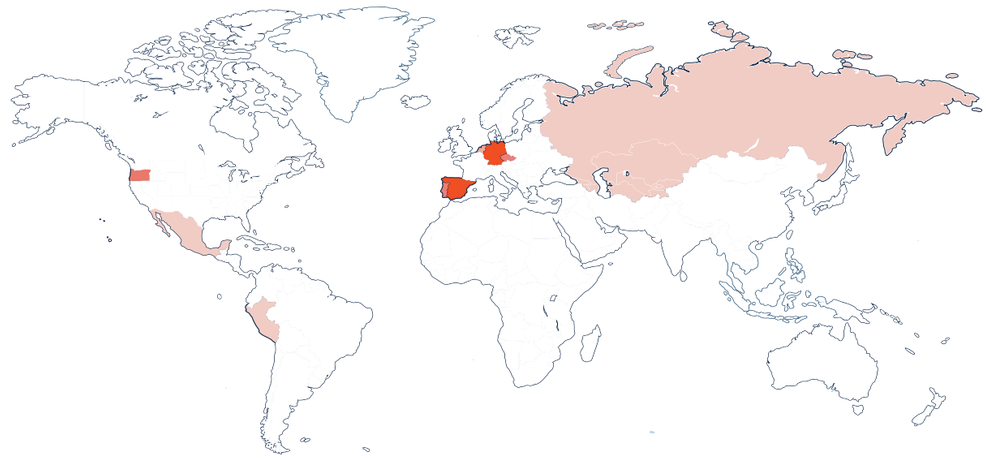
Ketamine-assisted therapy has proven particularly efficacious in the treatment of alcohol-use disorder. In a double-blind randomised placebo-controlled trial, a single administration of ketamine, when combined with talk therapy, reduced average weekly alcohol consumption by 50% over nine months.

Market Value MDMA



MDMA was first synthesised in 1912, however its benefits in psychiatry would not be recognised until decades later. Due to a rise in recreational use, MDMA was added to Schedule 1 of the 1971 UN Convention on Psychotropic Substances in 1986. MDMA remains a Schedule 1 drug, however its possession has been decriminalised in jurisdictions across the Americas and in Europe.

Regulation of MDMA possession



	COUNTRY / STATE / CITY	AMOUNTS OF MDMA PERMISSIBLE	YEAR DECRIMINALISED
<5g	GERMANY	5.0g	1992
	SPAIN	2.4g	1983
<2g	CZECH REPUBLIC	1.2g	1990
	PORTUGAL	1.0g	2001
	OREGON	1.0g	2021
<1g	NETHERLANDS	0.5g	1976
<.5g	RUSSIA	0.3g	2004
	PERU	0.25g	1991
	MEXICO	40mg	2009

As an empathogen, MDMA instigates empathy and feelings of happiness, which contributes to its therapeutic value. It does this by increasing the availability of serotonin, dopamine and norepinephrine, with a similar chemical structure to that of mescaline and methamphetamine, and binds as an agonist to 5-HT serotonin receptors.

There have been 52 clinical trials conducted with MDMA, with over 2,000 patients enrolled to treat a number of mental health conditions, including alcohol-use disorder, major depressive disorder and post traumatic stress disorder (PTSD).

PTSD may occur following traumatic events or from accidents resulting in traumatic brain injury. In the US, 12 million adults experience PTSD each year, with 900,000 veterans receiving disability payments for PTSD from the Department of Veterans' Affairs - at a cost of US$17 billion annually.

MDMA-assisted therapy revenue savings

Cost-effectiveness is important in the coverage deliberations of; third party payers, private insurers and governmental payers such as the Veterans' Administration, Medicare and Medicaid.

A summary follows from two publications on the economics of a novel therapy for the treatment of severe PTSD. The first pertains to the cost-effectiveness of MDMA-assisted therapy. The second describes the public health impact and net savings to the health care system of scaled-up access to this therapy.

Early results

Six Phase II randomised placebo-controlled multi-site clinical trials sponsored by MAPS tested the safety and efficacy of a novel therapy-assisted MDMA. A pooled analysis of the results of these trials showed that MDMA-assisted therapy was associated with a 54.2% decrease in patients meeting criteria for PTSD at the follow-up stage.

An additional portion exhibited clinically significant improvement, though they still met the criteria for PTSD. In addition to its encouraging safety and efficacy profile, a cost-effectiveness analysis, based on the pooled Phase II data, indicated that this intervention was not only cost-effective, but would save third party healthcare payers US$103.2 million (discounted) over 30 years for 1,000 patients who are deemed to meet the inclusion criteria. Payers would break even in a little over three years.

Cost-effectiveness based on a recent Phase III trial

The publication of the first of MAPS' two Phase III trials added substantial evidence for the benefits of this new therapy. The effectiveness of this Phase III trial exceeded the pooled Phase II results, with 67% of patients no longer meeting the criteria for PTSD at the study's primary endpoint, ~8 weeks following the third experimental session.

Methods

A decision analytic model was constructed to portray; the clinical benefits, the MDMA-assisted therapy costs and the net medical costs in a hypothetical cohort of 1,000 patients. The model was designed to show the distribution, by PTSD severity, of the patients treated, between November 2018 and May 2020. In the MAPS-sponsored randomised, placebo-controlled, multi-site Phase III trial. Patients were classified and portrayed in a Markov process as being asymptomatic, or as suffering from mild, moderate, severe, or extreme PTSD.

The efficacy of MDMA-assisted therapy is portrayed as a change in the distribution of patients by severity category at the trial's endpoint as compared with the baseline. Mortality by the PTSD severity category and the medical costs were estimated from published literature. Health state utilities were calculated from EQ-5D-DL surveys completed by Phase III trial participants. The Markov simulation is annual until death,

costs and quality-adjusted life years are discounted to the present at 3% annually, with results presented for several time horizons.

Results

Projected for 30 years, in a cohort of 1,000 patients, MDMA-assisted therapy averted: 61.4 undiscounted deaths; generated 4,856 discounted quality-adjusted life years; and saved a discounted US$132.9 million in combined mental health and general medical care costs.

MDMA-assisted therapy for PTSD

MDMA-assisted therapy for PTSD is currently the only psychedelic-assisted therapy in Phase III clinical trials, with the FDA designating it as a Breakthrough Therapy.

MAPS intends to apply for market authorisation of MDMA-assisted therapy for PTSD in the second half of 2023. This could result in the regulation of psychedelic medicine as early as next year, with MAPS potentially treating patients within six months of market approval.

MDMA as Medicine

YEAR		DEVELOPMENTS
2008	»	First MDMA-assisted therapy for PTSD study completed by MAPS
2013	»	Phase II trials begin
2017	»	FDA designates MDMA-assisted therapy for PTSD as a Breakthrough Therapy
2019	»	The Ministry of Health in Israel approves compassionate use of MDMA for treatment-resistant PTSD
2020	»	MAPS raises US$30 million
2021	»	Phase IIIa trials completed in the US
2022	»	Phase IIIb trials set to complete in the US
2023	»	MDMA-assisted therapy for PSTD expected to receive FDA approval
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

In clinical trials, two-thirds of study participants, who completed a course of MDMA-assisted psychotherapy, no longer met the criteria for a PTSD diagnosis. Previous trials demonstrated that the effects of the treatment could last for up to 12 months.

Encouraged by these results, Health Canada, last year, approved real-world open-label trials of the therapy. The study hopes to identify opportunities to streamline treatments in order to reduce costs and promote its widespread adoption.

MDMA-assisted therapy for alcohol-use disorder

This year, MAPS signed a partnership with Awakn Life Sciences to explore the application of MDMA-assisted therapy to treat alcohol-use disorder in Europe.

Awakn develops and delivers psychedelic medicines to treat substance-use disorders. The company conducted the only Phase II study into the efficacy of MDMA-assisted therapy for alcohol-use disorder.

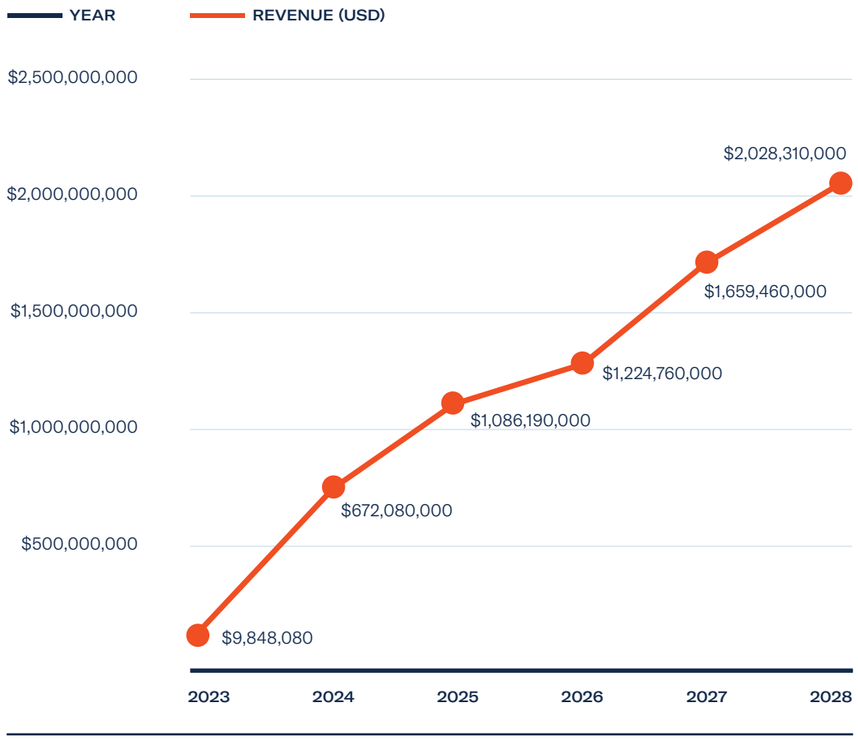
The eight-week MDMA-assisted therapy course included two 187.5 milligrams administration sessions - with psychological support provided before, during and after each session.

Nine months after the study, the average units of alcohol consumed by participants dropped from 130.6 units per week to just 18.7 units. This represented an 85% decrease.

A data licensing agreement, within the partnership, enables MAPS to support Awakn's Phase IIb and Phase III studies in Europe.

Awakn's double-blind, placebo-controlled Phase IIb trial will be conducted in the UK. In the UK, diseases related to alcohol abuse are the leading cause of death in men aged between 16 and 54, accounting for over 20% of the adult population.

Market size of MDMA-assisted therapy



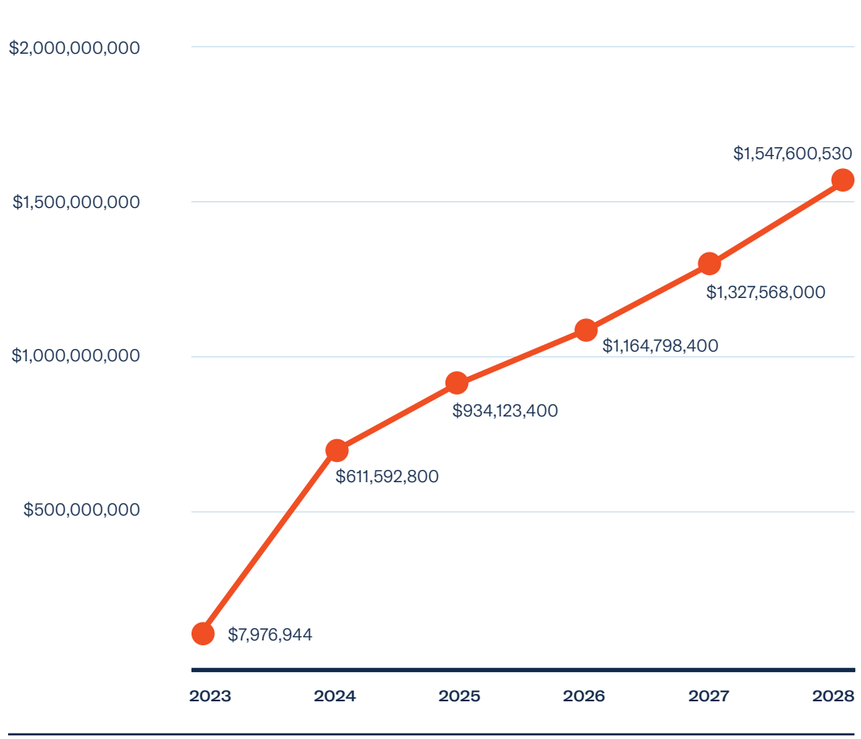
North America

In North America, MAPS' MDMA-assisted therapy for PTSD is expected to cost US$7,543 - with patients undertaking two courses of therapy a year until they are in remission.

With roughly 12 million adults suffering from PTSD in the US, and 3 million in Canada, the addressable market for MDMA-assisted therapy is considerable. However, it will be restricted by the number of trained therapists who are able to administer the treatment. MAPS hopes to train 25,000 practitioners to deliver the treatment by the end of the decade. While there are considerable opportunities for the commercial success of MDMA-assisted therapy, it may be tempered by competing psychedelic-assisted therapies and the arrival of adult-use frameworks. For instance, COMPASS Pathways' psilocybin therapy for PTSD is currently in Phase II trials, with regulatory approval on both sides of the Atlantic expected by 2028.

Assuming the price of MDMA-assisted therapy holds, and there is a linear growth rate of therapists, the market for MDMA-assisted therapy in North America could surpass US$1.5 billion by 2028.

Market size of MDMA-assisted therapy - North America



Europe

In Europe, MAPS' MDMA-assisted therapy for PTSD is expected to be regulated by the EMA and MHRA in 2024 - with the latter providing MAPS with an Innovative Licensing and Access Pathway (ILAP) Innovation Passport.Granted in January 2022, the MHRA's Innovation Passport is similar to a Breakthrough Therapy designation from the FDA. The Innovation Passport provides organisations with advice, input and collaboration throughout clinical trial design and the drug development process.

However, despite a recognition of the need for innovation in psychiatric treatments, the cost is key to their subsequent adoption. This is particularly with regard to the universal healthcare providers of Europe.

Considering a cost of US$7,543, a course of MDMA-assisted therapy for PTSD may be cheaper than a course of Spravato. Spravato was deemed not to be cost-effective by the UK's National Institute of Care and Excellence, at a price of £10,550. With an estimated 8.2 million Europeans affected by PTSD, it is expected that governments will provide, or heavily subsidise, MDMA-assisted therapy for service personnel and ex-service personnel.

This has been factored into the market modelling, which estimates that the European MDMA-assisted therapy market will be worth US$97 million in 2025 and exceed US$385 million by 2030.

Market size of MDMA-assisted therapy - Europe

The Psychedelics as Medicine Report | Market Value MDMA

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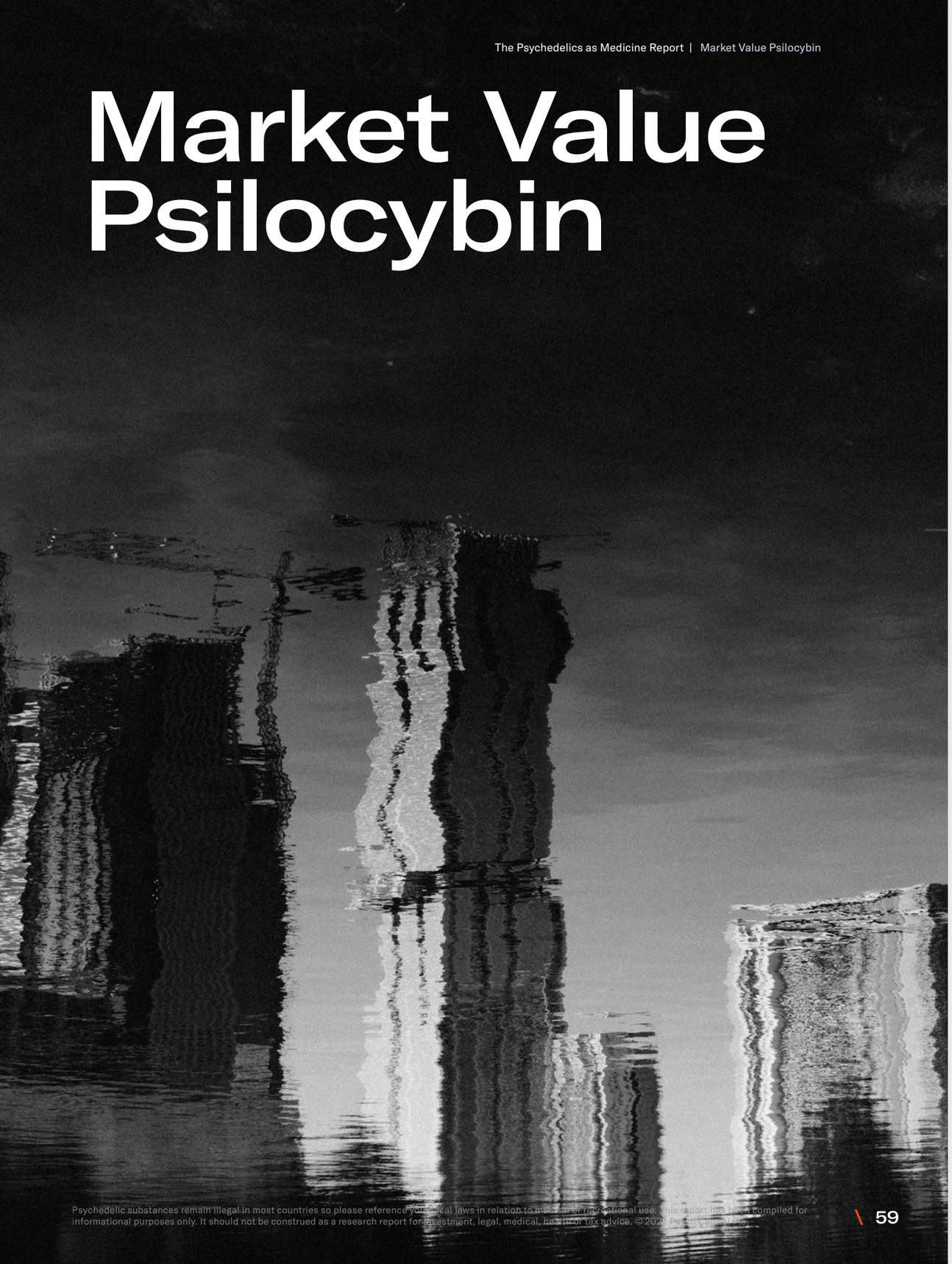
Market Value Psilocybin



Humans metabolise psilocybin into psilocin, a psychoactive compound that interacts with several serotonin receptors, including 5-HT2a and 5-HT2c. After ketamine, psilocybin is currently the most studied psychedelic medicine with over 65 clinical trials exploring its therapeutic efficacy.

COMPASS Pathways's psilocybin therapy for treatment-resistant depression is expected to enter Phase III clinical trials in 2022. These studies will be the largest clinical trials ever conducted with a psychedelic medicine, with 946 patients enrolled.

This follows the success of the UK-based organisation's Phase II trials, with topline data released in 2021. Patients who received a single 25 milligrams dose of COMPASS's proprietary psilocybin formulation, COMP360, in combination with psychological support, experienced a significant reduction in their severe symptoms of depression after three weeks, with a rapid and sustained response lasting 12 weeks.

Clinical trials and research

In addition to COMPASS's studies, clinical research with psilocybin is being conducted to treat a wide range of mental health disorders, including treatment-resistant depression, major depressive disorder, addictions and eating disorders.

There are six Phase II clinical trials underway, but only COMPASS's trial for treatment-resistant depression has progressed to Phase III. This trial's total duration is set at six weeks, and topline results are expected by the end of 2024.

Assuming positive results, the FDA could approve the novel treatment as early as 2025 - with regulation in Europe following soon after that.

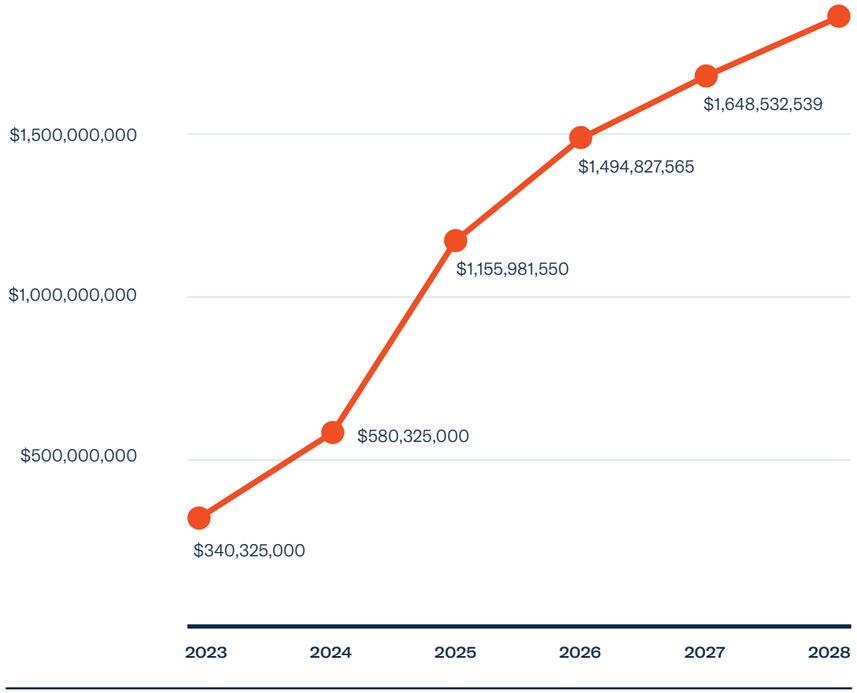
Psilocybin-assisted therapy for alcohol-use disorder

In August 2022, researchers at New York University published the largest double-blind study on psilocybin-assisted therapy in the treatment of alcohol-use disorder.

Two doses of psilocybin were administered four weeks apart, in conjunction with psychotherapy. To assess the efficacy of psilocybin-assisted therapy, researchers examined the number of heavy drinking days recorded over 32 weeks. A heavy drinking day was defined as one in which four or more alcohol drinks were consumed.

Following the course of psilocybin-assisted therapy, there was a decrease in alcohol consumption sustained for at least 28 weeks. Those given psilocybin-assisted therapy reduced heavy drinking by 83%, as compared to a 51% reduction in participants that had received a placebo.

Market size of psilocybin-assisted therapy



North America

In North America, COMPASS's COMP360 therapy is expected to be the first psilocybin-therapy to be regulated by the FDA.

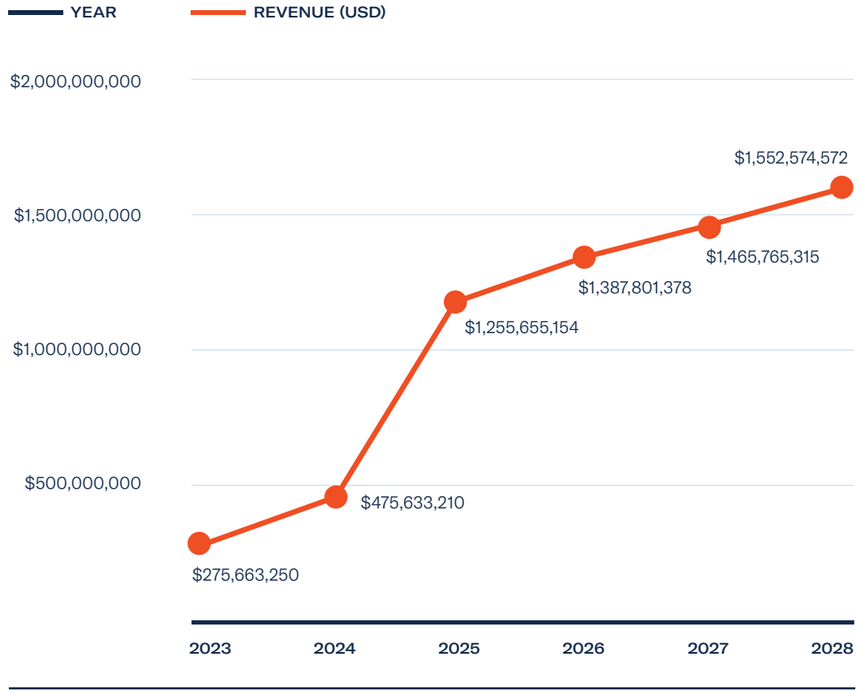
Following Phase III trials conducted in tandem, topline results are expected by the end of 2024. Assuming these studies are successful, COMP360 therapy could be available to patients with treatment-resistant depression by 2025.

Treatment-resistant depression costs healthcare providers and employers over US$30 billion in the US. Psilocybin-therapy is expected to cost US$8,250 and to be applied in the treatment of treatment-resistant depression, major depressive disorder, post traumatic stress disorder and alcohol-use disorder.

The four aforementioned indications have sizable patient populations. However, the market for psilocybin-assisted therapy will be restricted by the limited number of trained therapists and it will be affected by the arrival of adult-use frameworks.

On current projections, assuming enough therapists are trained to administer psilocybin-assisted therapy for treatment-resistant depression and major depressive disorder, the value of the North American market could reach US$1.3 billion by 2028.

Market size of psilocybin-assisted therapy - North America



Europe

In Europe, it is anticipated that psilocybin-assisted therapy for treatment-resistant depression will be approved by the EMA and MHRA in 2025. The cost of treatment will be crucial to its adoption, particularly in countries with universal healthcare.

Although expected to be cheaper than a course of Spravato, which was deemed too expensive by the UK's National Institute of Care and Excellence, psilocybin-assisted therapy will be considerably more expensive than SSRIs - although considerably more effective.

According to the EU, over 32 million Europeans suffer from chronic depression, with European economies losing US$130 billion each year in lost productivity. Against the backdrop of a deepening mental health crisis, there is an increased desire to adopt effective psychiatric treatments.

Compared to ketamine and MDMA, less stigma surrounds the consumption of psilocybin-producing fungi, due to its traditional use and availability in nature. This has been evidenced through the rise of entheogen decriminalisation in North America, and has been factored into market size modelling.

Based on current estimates, the market for psilocybin-assisted therapy in Europe is expected to be worth US$160 million in 2026. By 2028, the market for psilocybin-assisted therapies in Europe could reach US$345 million.

Market size of psilocybin-assisted therapy - Europe

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Adult-use psilocybin frameworks

Despite the manufacture, sale and possession of psilocybin in the United States being prohibited by The Controlled Substances Act, several states have implemented decriminalisation measures.

Psilocybin was initially decriminalised on a city-by-city basis, with Denver being the first in 2019. In November 2020, Oregon became the first state to regulate psilocybin services. There have since been eight bills passed regarding the creation of adult-use psilocybin programmes, of which five have been assigned to committees to discuss.

Regulatory reform to provide psilocybin services has been bolstered by successful clinical trials, which have demonstrated the compound's therapeutic efficacy. As state legislators move more quickly than medical regulators, novel treatments can be made available, without federal approval in the US.

Legislation at the local and state level can be pushed through by public advocacy, particularly when propelled by bipartisan support on issues such as, mental illness and veteran health care. This was recently seen in the widespread legalisation of cannabis.

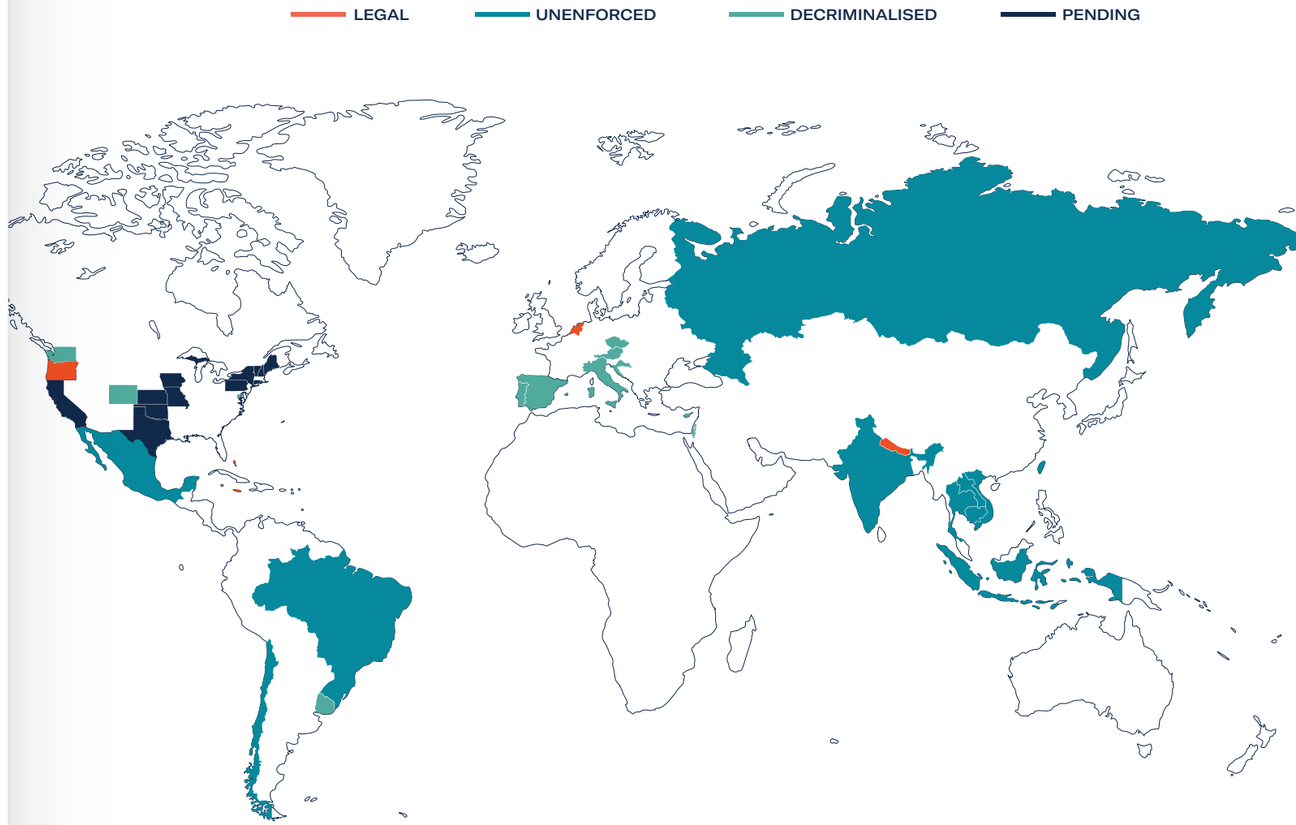
As psilocybin remains a Schedule 1 substance at the federal level, access to funding, insurance and banking services may be difficult.However, this does little to temper the burgeoning market's potential, as cannabis has not yet been federally approved and legal sales are expected to hit US$33 billion in 2023.

In Oregon, psilocybin services are expected to be available in 2023, with similar markets expected to be established in Colorado, Washington and California by the end of the decade.

To maximise addressable markets, and the subsequent economic opportunities, regulators will need to efficiently license producers, testing laboratories, service locations and facilitators.

There are a dozen states with active legislation related to the regulation of psilocybin, however only the aforementioned four states have been factored into this report's market modelling.

Regulation of psilocybin possession



LEGAL	UNENFORCED	DECRIMINALISED	PENDING
NEPAL	CAMBODIA	PORTUGAL	CALIFORNIA
NETHERLANDS***	BRAZIL	CZECH REPUBLIC	TEXAS
BAHAMAS	CHILE	AUSTRIA	MISSOURI
BRITTISH VIRGIN ISLAND	INDIA	CROATIA	IOWA
SAMOA	INDONESIA	CYPRUS	OKLAHOMA
OREGON	LAOS	ISRAEL	KANSAS
JAMAICA	MEXICO*	ITALY	NEW YORK
	RUSSIA	SPAIN	VERMONT
	TAIWAN	URUGUAY	NEW HAMPSHIRE
	THAILAND	DISTRICT OF COLUMBIA	CONNECTICUT
	VIETNAM	COLORADO	MAINE
		WASHINGTON	MICHIGAN
			PENNSYLVANIA
			RHODE ISLAND

Mushroom spores are not included in this list
**In Mexico, psilocybin-producing mushrooms are tolerated by authorities for use in religious rituals only.*
****In the Netherlands, psilocybin-producing mushrooms are illegal, but due to a legal loophole truffles are not.*

Colorado

On 8 November 2022, the Colorado electorate voted on the Natural Medicine Health Act, Proposition 122, to establish a state-wide psilocybin framework. This created the second state-wide industry in the US, after Oregon, and one that could quickly become the biggest.

Similar to Oregon's programme, adults over 21 in Colorado will be able to access psilocybin services without a diagnosis, prescription or referral.

The Act also makes allowances for at-home psilocybin services, and counties and municipalities can only limit locations through zoning restrictions - which creates a total addressable market of over three million.

Services are expected to cost US$3,000 and will be split into three sessions – preparation, administration and integration. There are goals to incentivise low-cost treatments for low-income adults, and also a fund to financially support marginalised communities to access facilitator training.

As the Natural Medicine Health Act decriminalises the personal cultivation, possession and gifting of psychoactive plants and fungi, it may present the opportunity for an unregulated market to emerge – particularly as the legislature does not outline personal possession limits. This could create challenges for the short-term profitability of licensed service providers.

However, in 2026, Colorado's regulators can expand the psilocybin framework to include; ibogaine, ayahuasca and mescaline services. Based on the state's total addressable market, psilocybin services in Colorado generate US$205 million a year.

Oregon

Oregon became the first state to vote to legalise psilocybin, and if its framework is successful, it could be replicated across the United States.

The Psilocybin Services Act, passed in November 2020, established a programme for adults over 21 to purchase, possess and consume psilocybin at licensed centres.

Participants do not need a medical diagnosis to access psilocybin services, but they must attend a preparation session and consumption must be supervised by a trained facilitator on premises which are licensed.

To protect consumers, Oregon has established product testing standards for mushroom species, psilocybin content and contaminants. Only Psilocybe cubensis mushrooms will be regulated in the programme, with other psilocybin-producing fungi and synthetic psilocybin being prohibited.

In the state's framework, psilocybin must be administered by licensed facilitators at a licensed facility. As a result, those organisations with psychedelic healthcare clinics, clinicians and therapist training programmes are well positioned to leverage their existing expertise.

Organisations that can establish themselves in Oregon, in the nation's first psilocybin programme, can generate revenue to fund drug development and placate shareholders. A first-mover advantage can also be leveraged, to scale and expand into other markets, as they emerge. Based on Oregon's total addressable market, psilocybin services in the state generate US$165 million a year.

Washington

In March 2022, Washington State legislature passed Senate Bill 5660, directing Washington State Health Care Authority to create a psilocybin work group to assess the provision of psilocybin services.

A preliminary report evaluating the socioeconomic value of a psilocybin programme must be delivered to the Washington State Governor by December 2022. Following the work group's final scheduled meeting in May 2023, a full report will be submitted to the governor by the end of 2023.

This could see an adult-use psilocybin framework in Washington as early as 2026, with the first meetings indicating the scope of the potential market. The work group signalled a desire to replicate the programme created in Oregon through Measure 109, which includes the decriminalisation of psilocybin and the imposition of a two-year development plan.

The group was also in favour of adopting regulations to expand the programme's accessibility, such as at-home administration and the consumption of low-dose psilocybin products, outside licensed service centres. The majority of the work group also believed psilocybin services should be covered through private insurance and state funding - thereby further promoting adoption and augmenting the market's potential.

Assuming the creation of a psilocybin services' market, along the guidelines discussed in the work group meetings, the total addressable market in Washington could generate US$288 million a year.

California

The creation of California's psilocybin programme is perhaps the most anticipated, due to the market's potential. The population of California is larger than that of Oregon, Washington and Colorado combined, with a substantial total addressable market creating significant commercial opportunities. Senate Bill 519 sought to decriminalise possession of psychedelic medicines, which would have laid the groundwork for the creation of an adult-use psilocybin framework. This was evidenced by reforms to enable the cultivation and transportation of spores and mycelium capable of producing psilocybin-producing fungi.

The legislation passed the Senate and moved through two committees, before being placed on hold in 2021 to secure further political support. However, this support never materialised and in August 2022 Senator Weiner announced he was no longer pursuing a bill.

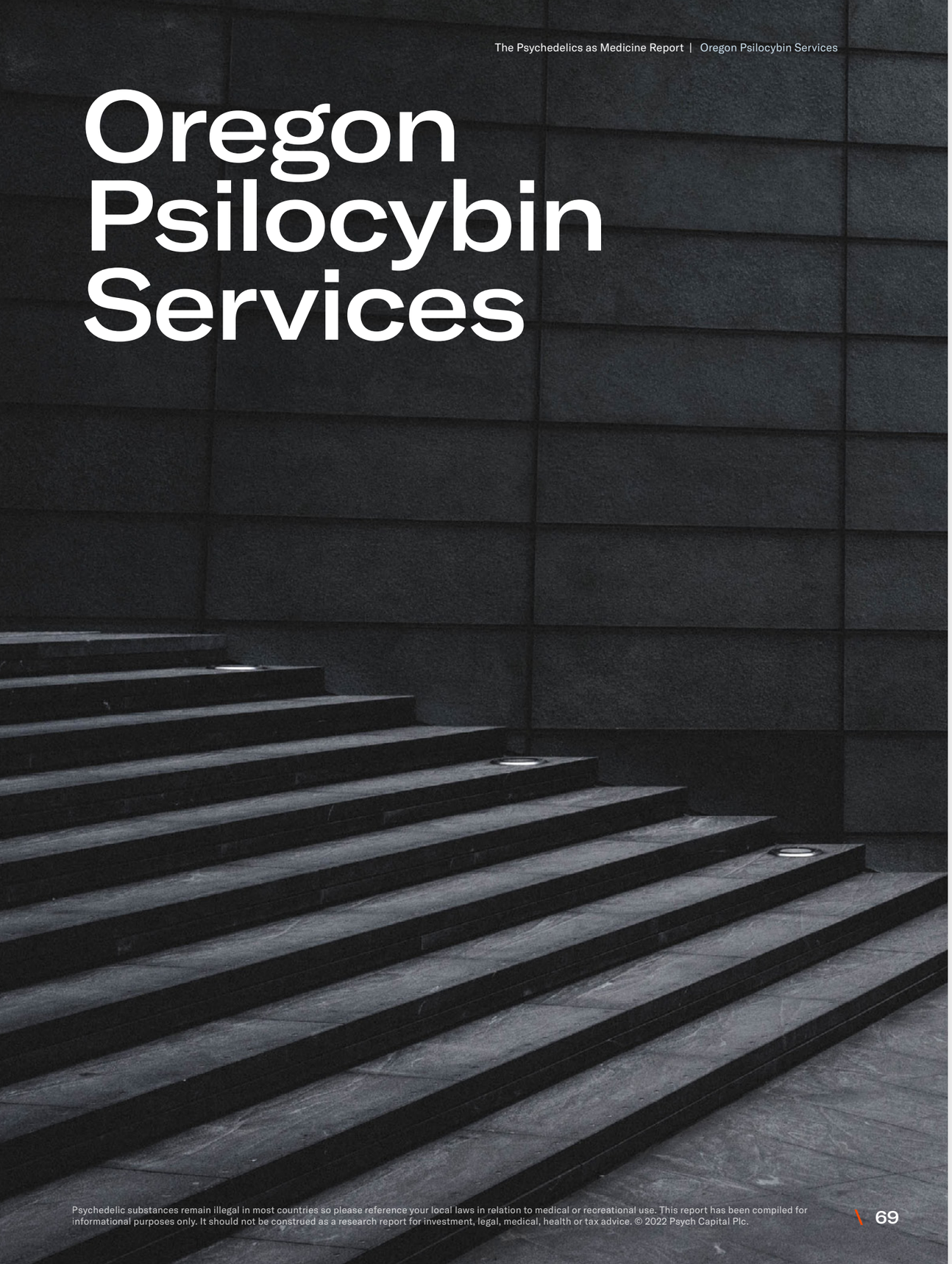
The announcement was made after a committee removed the bill's decriminalisation element, with state officials instead being directed to study the benefits of regulatory reform.

Despite the setback, the Senator has pledged to reintroduce the legislation again next year - with modifications that will hopefully enable the unadulterated bill to progress further. The scope of the amended measure is unclear, but it is believed to be a broad legalisation measure that would decriminalise psilocybin, MDMA and LSD, with possession limits designed to garner public approval.

The language of the amended bill is still not yet publicly available, but a Wiener member of staff told Marijuana Moment that he won't push to enact it as such and will instead try again to pass a broad legalisation measure next year.

If this measure instigated the creation of an adult-use psilocybin market, similar to that of Oregon, California's total addressable market could generate US$1.6 billion a year.

Oregon Psilocybin Services



The Psychedelics as Medicine Report | Oregon Psilocybin Services

Angela E. Allbee MPA
Manager, Oregon Psilocybin Services Section
Oregon Health Authority

Ballot Measure 109 (M109), the Oregon Psilocybin Services Act, creates a licensing and regulatory framework for the production of psilocybin products and the provision of psilocybin services. The Oregon Psilocybin Services (OPS) section is a new section housed within the Oregon Health Authority Public Health Division's Centre for Health Protection. OPS will begin accepting applications for licences on 2 January 2023.

M109 does not create a dispensary model like that for recreational cannabis in Oregon. People will not be able to purchase psilocybin and take products off-site with them for consumption.

Instead, a client, 21 years of age or older, may access psilocybin services. While no prescription or referral is necessary, a client will be required to complete a preparation session with a licensed facilitator before participating in an administration session. The client will only access psilocybin at a licensed service centre during an administration session in the presence of a licensed facilitator. An optional integration session will be offered to a client after the administration session.

Psilocybin services

The preparation session very much centres on client intake and on an informed consent process. This includes understanding the potential risks or potential benefits associated with psilocybin services and supporting clients in deciding whether psilocybin services are right for them. A requirement to review the client bill of rights is part of supporting a client. Finally, the preparation session is also a time to ensure that the licensed facilitator and the client are a 'good match' to move forward together.

There is a lot of safety and support planning that must be done before a client enters an administration session. Clients could be experiencing changes in their lives, so it is important to make sure clients are fully supported through the process.

In the regulations there will be a specific dosage of product which will require a minimal duration of time at a licensed service centre. Oregon Psilocybin Services is going through the rulemaking process now, which covers these and many other regulations. OPS will adopt final rules by 31 December 2022.

The third part of psilocybin services is an optional integration session. An integration session is an opportunity for clients to have an additional follow-up session with a licensed facilitator, where they could be referred to peer support networks or other community resources that may help provide additional support. This is an important time for clients to determine any next steps for either continuing with additional sessions or for them to take time to process the intervention.

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Psilocybin products

It is really important to understand that Measure 109 requires the Oregon Health Authority to prevent the diversion of psilocybin products into the unregulated space thereby avoiding interstate commerce in order to ensure public health and safety. Production limits must be set for the manufacturing and processing of psilocybin products, which further illustrates that M109 is centred on a client accessing psilocybin services, rather than on creating a consumer market for products.

Another important point is that only indoor cultivation is allowed. We know that there are over 200 species of psilocybin-producing mushrooms that grow naturally around the world. However, in the Pacific Northwest, we are beginning with just one species at the recommendation of the Oregon Psilocybin Advisory Board – Psilocybe cubensis. More information was available to the advisory board about Psilocybe cubensis and its safety and reliability at the time of making recommendations to OPS.

Oregon Psilocybin Services will continue to evaluate the inclusion of any new species as new research and information comes to light.

Indigenous communities around the world have worked with psilocybin for centuries. The Oregon Psilocybin Advisory Board and OPS have acknowledged that balancing cultural wisdom and anthropological information with scientific research is really important.

With that acknowledgement, we know that more discussions regarding psilocybin products and services will be part of the evolution of this work. Within current regulations, whole dried fungi will be allowed, as well as extracts, edible psilocybin products and also ground homogenised products.

Licensed manufacturers will have their products tested by licensed testing labs for species identification and potency based on rules already adopted earlier this year. OPS will also be able to request additional tests, if needed.

After the manufacturer has had their products tested, they will sell them to licensed service centres where products will be stored and subsequently sold to clients during administration sessions.

OPS did not want to overly burden licensees, based on the understanding that they are stepping into this work to serve Oregonians, so we are focusing on what is essential for public health and safety for rulemaking.

The roll-out of regulated psilocybin

OPS will license: manufacturers to cultivate and process psilocybin products; testing labs to test products; service centres where products can be consumed by clients during administration sessions and facilitators who will be present to support clients in a non-directive approach throughout the preparation, administration and integration sessions.

All four licence types are really important to the process moving forward in 2023. OPS has tried to expedite rules so that students can be trained before then applying for facilitator licences in January, and testing labs can become accredited in time to apply for licences in January.

Under M109, local governments may adopt ordinances to prohibit manufacturers and service centres from being licensed in their jurisdictions. While many cities and counties have adopted ordinances, these ordinances have to be referred to voters at the next general statewide election. With this in mind, many licensees will have to wait until after the election to see if prohibitions will exist in their cities and/or counties.

Building a business, especially around a Schedule 1 substance, is very difficult. Funding to support business owners is limited, which creates an access issue for those who want to be licensed under M109. In addition, the fee-based structure of the measure means that the cost of licences must cover the cost of the OPS section's work. This is another

concerning access issue for licensees. OPS will be ready to accept applications on 2 January 2023. We have been working to develop a really great licensee application system that we call the Training Programme, Licensing and Compliance System (TLC). We hope that by the second quarter of 2023 we will see service centres opening their doors.

Psilocybin services within the Oregon Health Authority

Specified in the statutory language of Measure 109 is the Oregon Health Authority's broad remit to make decisions based on public health and safety. Measure 109 is housed within the Oregon Health Authority's Public Health Division therefore, implementation will be aligned with the agency's strategic plan to eliminate health inequities as well as with Oregon's State Health Improvement Plan, Healthier Together Oregon.

Measure 109 is not a medical or a clinical model. A client can access psilocybin services for any reason, without a prescription or referral from a provider, as long as they complete a preparation session with a licensed facilitator. Even though a client may access psilocybin services for any reason, research has shown that psilocybin may be beneficial for a number of issues, including; trauma, anxiety, depression and excessive alcohol and tobacco use. We look forward to additional research on other potential benefits of psilocybin. Implementing a regulatory framework that centres on client safety and access requires our team to shift from a drug policy framework rooted in the 'War on Drugs' to a health policy approach that holds promise for healing and wellness. We want to uplift and amplify the voices of people in our communities that have not been well-served by government or institutional systems to ensure that equity, access and inclusion are central to this work.

There are many questions still remaining as Oregon implements the first regulatory framework for psilocybin services in the United States. We need to ask a number of questions. How do we reduce harm from institutional bias or adversity, trauma and toxic stress in this work? How can we increase client safety and access to services? How can this work better serve communities through a culturally responsive and trauma-informed approach?

Psilocybin is currently a federally illegal substance in the United States. As we prepare for 2023, we are working to share information about Measure 109 with members of the public who may be interested in accessing services, including information about the potential benefits and risks, while unravelling decades of stigma about psilocybin. We are working to ensure our future licensees have access to information to help create a successful launch in 2023. We are also working with the Oregon Psilocybin Advisory Board, partners and members of the public on feedback that will help shape the future of this work.

Demand for Psilocybin services

We developed and administered a community interest survey early in 2022 to better understand who was interested: in accessing psilocybin services; in becoming licensed as a manufacturer, a testing lab, a services centre, or a facilitator; or in having psilocybin facilitator training programmes approved. We sent the survey out through our distribution list and shared it on our website and had 4,421 respondents. The survey revealed that 94% of those surveyed were interested in psilocybin services. As information continues to surface about the potential benefits of psilocybin, interest is growing.

There are many clients who may benefit from a model such as Measure 109, specifically those individuals that would be better served through a culturally responsive approach. Even though Measure 109 is not a medical or clinical model, there may be opportunities for medical or clinical professionals to be licensed as facilitators and to then provide another layer of support for clients with complex needs. If a medical framework also becomes available, there would be an opportunity for both models to have a presence in Oregon,

working to serve a wide variety of people. There are many ways that clients may want to experience psilocybin services, and licensed service centres can bring these different experiences to life. We do not have details about the service centre options clients may have at this point in time, since we have not started accepting licence applications, but we do know from robust public listening sessions and feedback from interested licensees that there will be different kinds of models. Some service centres may focus on community models that work to create affordability, while others may offer longer retreat models.

Training facilitators

In May 2022, we adopted administrative rules for facilitator training programmes. Psilocybin facilitator training programmes must have the curriculum approved by the Oregon Health Authority and must be licensed by the Higher Education Coordinating Commission. The criteria for the training curriculum, adopted in May, draws upon knowledge from the unregulated space; from similar programmes that have been operating outside of the Measure 109 model, and also from recommendations from the Oregon Psilocybin Advisory Board.

If licence applicants can demonstrate that they meet all the criteria for the training programme curriculum, we will approve the training curriculum. We started accepting applications for training programmes on 6 June 2022, and so far we have approved more than 14.

We list all approved psilocybin facilitator training programmes on our website.

The cost of psilocybin services

We do not have the authority to set or regulate the cost of products or services. Measure 109 created a fee-based structure for licensing, which means the cost of the licence fees must cover the cost of the section's work.

We have been working hard to consider affordability for licensing fees without requiring additional administrative work, which would require more staff and ultimately drive up costs. We have considered ways to create reduced fees for lower income applicants to help remove barriers for licensees that want to start a psilocybin business. It is difficult for licensees, as there are no additional funds to help support start-up costs for these new businesses. We continue working to find ways to create equitable licensing fees within the statute in the hope of creating affordability for clients, as costs often trickle down to clients through the cost of products and services.

Although the legislature requires us to be self-sufficient and sustainable through licensing fees, there have been discussions within the psilocybin community about ways to create subsidies for underserved or low-income clients. Many communities in Oregon are interested in ways that philanthropy may help to ensure that the cost of services is not prohibitive.

One of the benefits of the programme will be that we have varying models for psilocybin services that may serve a diverse range of client needs. At this point we are still listening, learning and waiting to see how the work unfolds.

Obstacles to psilocybin services

One of the biggest challenges to accessing psilocybin services will be the cost. At this time, psilocybin services will not be covered by insurance, therefore, the costs of products and services will be out of pocket.

There are other challenges as well. In Oregon, local governments have the ability to prohibit psilocybin service centres or manufacturers from operating in their respective jurisdictions. Many local governments have adopted ordinances to prohibit psilocybin services, either by permanent bans or temporary opt-outs. These ordinances must be referred to voters at the next general statewide election. If voters at the next statewide election pass these ordinances, we won't be able to issue licences in those jurisdictions.

Currently, most of the ordinances that have been passed to voters are in rural Oregon. This may prohibit many rural Oregonians from accessing psilocybin services. These ordinances will be voted on in November 2022, so we are waiting to see how that unfolds and where accessibility issues may arise.

Another accessibility issue that exists in statute is that psilocybin administration sessions can only take place at licensed service centres. This presents a problem for those that want to access psilocybin services, but cannot be transported, such as those in palliative care.

Licensing psilocybin services

OPS will issue four types of licences- licenced manufacturers that will cultivate and process psilocybin products, testing labs that will test psilocybin products, service centres where products can be consumed by clients during administration sessions and facilitators who will be present to support clients in a non-directive approach throughout preparation, administration and integration sessions.

All four licence types are really important to the process moving forward in 2023. OPS has tried to expedite the training programmes and testing rules so that students can be trained and can then apply for facilitator licences in January 2023, and testing labs can become accredited in time to apply for licences in January.

OPS will be ready to accept applications on 2 January 2023. We hope that by the second quarter of 2023 we will see service centres opening their doors, but we will have to wait to see.

The pressure to succeed

The Oregon Psilocybin Services section consists of a dedicated group of professionals that bring decades of experience from many different walks of life. We really care about the outcome of psilocybin services in Oregon, and want to build something that will improve the health and wellness of our communities and serve as a model for other states.

We are a very small team right now and it has been challenging to build a new section within a state agency infrastructure that has been overwhelmed by COVID-19. There is a pressure to succeed, but there is a bigger pressure to connect with as many people as possible and get information out to the public.

We have a great responsibility to serve our communities well. We need to listen, learn and stay open to the idea of making changes along the way. Although the pressure is there, it is also an exciting and historic time. We are hoping to see positive changes in overall health and wellness in our state and beyond through safe, equitable access to psilocybin services.

Sharing Information about psilocybin services

There is a lot of information coming to light through scientific research, as well as through knowledge from indigenous communities that have worked with psilocybin for centuries. Helping to unravel the stigma about psilocybin will be important, as well as helping the public to understand the potential benefits and risks associated with psilocybin services and distinguishing between the unregulated and the regulated spaces. Education is necessary for people who want to access psilocybin through a regulated model, and we look forward to sharing information as we move past the development phase.

Overall, we are honoured to be part of this work and for the amazing partners that have come together to create dynamic solutions for safe, equitable and affordable psilocybin services in Oregon.

PSYENCE LAUNCHES PSYCHEDELIC PALLIATIVE CARE WITH UK PHASE II CLINICAL TRIAL

Dr. Neil Maresky
Chief Executive Officer
Psyence Group

Global First, Phase II Trial Approved

Psyence achieved an industry milestone in September 2022, when we received Medicines and Healthcare products Regulatory Agency (MHRA) approval to proceed with our UK Phase 2a clinical study in the context of Palliative Care and cancer. Our trial will assess the safety and efficacy of psilocybin-assisted psychotherapy, versus psychotherapy alone, for the treatment of Adjustment Disorder – an emotional and/or behavioural reaction to a stressful event – in patients with terminal diagnoses. The trial approval provides Psyence with the opportunity to create a paradigm shift in the treatment of patients suffering from terminal illness and drive significant quality-of-life improvements in this patient population, by improving the standard of care.

Our name “Psyence” combines the words psychedelic and science to affirm our commitment to producing psychedelic medicines developed through evidence-based research. We believe Psyence is a significant disruptor by developing proprietary pharmaceutical psilocybin and treatment protocols with a focus on Palliative Care. This market is currently underserved; an estimated 40 million people require Palliative Care annually, with 75% of these patients exhibiting a high burden of depression, anxiety, or psychosocial distress after diagnosis. Palliative Care and Survivorship Care targets treatment for the relief of suffering of those facing an acute or persistent medical issue whether the prognosis is deemed terminal or chronic. It includes support for psychological and spiritual distress, depression, anxiety, and in addition to the needs of patients. Palliative Care is designed to be available to patient families, caregivers, and the healthcare team. The World Health Organisation has stated that 88% of Palliative Care needs are unmet globally; the UK MHRA Phase 2 trial enables Psyence to enter the USD $28.6bn global Palliative Care market¸ which has 9.8% compound annual growth rate with a clear route to commercialisation.

We recognise that there is a significant opportunity to help improve mental health and wellbeing for millions of patients globally. Psyence is one of only a few companies exploring the therapeutic potential of naturally derived psilocybin in larger Phase 2 studies for the treatment of neuropsychiatric diseases with high unmet need. Those diagnosed with an advanced cancer diagnosis often suffer devastating mood changes, anxiety, and depression as they face their diagnosis. This suffering not only impacts the patient, it also impacts patient families. Our work introduces psilocybin together with psychotherapy, to address this anxiety and depression and, although the patient’s diagnosis remains unchanged, research from Johns Hopkins, NYU, and other well-respected medical institutions suggest that the level of existential distress can be alleviated for many months at a time. Such treatment may also help reduce patient reliance on traditional antidepressants, which often have side effects, and reduce their utilisation of the healthcare resources surrounding them.

Market leading production facility and successful exports of psilocybin mushrooms provide a foundation for our clinical drug development and commercial expansion.

In 2020, we constructed one of the world’s first commercial, federally approved psilocybin production facilities. Psyence supplies natural psilocybin to global medical and research markets. The facility, which is ISO22000 certified by the British Standards Institute (BSI) and built to FDA and GMP standards, is fully operational and scalable.

Federally Licensed GMP Facility Operational for 42+ Months

Our first exports in July 2022 included receiving import licences from Health Canada, on behalf of Psilo Scientific, and Portuguese regulators for the Cooperativa de Ensino Superior Politécnico e Universitário (CESPU) in Portugal. In October 2022, we received an import licence from the UK Home Office to supply Psyence’s Contract Development and Manufacturing Organisation (CDMO) partner in the United Kingdom.

Earlier this year we upgraded our facility to enable crude extraction and testing on site and we have since successfully exported purified pharmaceutical grade psilocybin mushroom extract to our Contract Development and Manufacturing Organisation (CDMO).

We believe this is one of the first successful legal imports of psilocybin mushroom extracts to the UK. We have also partnered with an experienced Current Good Manufacturing Practice (CGMP) compliant, full-lifecycle pharmaceutical services company in the UK. The company is a trusted partner to the world’s most innovative biotech companies and leading pharmaceutical companies.

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Our CDMO partnership is in line with our pharmaceutical product development and intellectual property strategy. Our pharmaceutical psilocybin extract will be used by the CDMO to develop standardised pharmaceutical grade psilocybin and psilocin extracts, which will be formulated into a final product for regulatory approval internationally.

We are now pursuing global partnerships to enable the supply of our pharmaceutical grade psilocybin products for preclinical research, clinical trials, and drug development.

Building world class supply and research partnerships

We are actively looking to commercially supply, partner and collaborate with companies and research organisations around the world. We encourage companies and prospective partners to get in contact with our team at supply@psyence.com to learn how we can support and supply pharmaceutical grade psilocybin to further develop research and psilocybin products internationally.

Psyence have also partnered with Clerkenwell Health, a leading UK Psychedelic Contract Research Organisation, to execute our clinical trial and take the next step in Psyence's journey in developing proprietary psilocybin drug development and treatment protocols.

A diversified business that continues to achieve significant milestones

Our clinical trial programme is only one part of the Psyence financial model. We have built a diversified business with distinct revenue streams.

Psyence Therapeutics is responsible for R & D and designing our market-leading clinical trials in the field of palliative care.

Psyence Production operates our licensed commercial psilocybin production facility in Southern Africa.

Psyence Function is focused on the development, distribution and sales of legal over-the-counter non-psilocybin containing functional mushroom nutraceuticals, GOODMIND™.

Premium range of functional mushroom products

UK & South Africa Launch and Distribution Partnershps

We launched GOODMIND™ in 2021 through our South African joint venture Good Psyence. GOODMIND™ is our premium range of non-psilocybin containing functional mushroom nutraceutical products, which are designed to nourish the mind and elevate everyday life by enhancing mental capacity and the body's ability to adapt to stress. Our product range is available online in South Africa via several leading ecommerce websites. Our functional mushroom sachets, which blend with any beverages, are also available for sale through 300 stores of one of Africa's largest coffee retail chains, Vida e Caffè.

The global Functional Mushroom market was valued at USD $25.4 billion in 2020 and is projected to reach a compound annual growth rate of 8.44% during the forecast period 2021-2026, according to a Functional Mushrooms Market 2021 report published by Research and Markets. Following the COVID-19 pandemic, the functional mushroom category experienced accelerated growth as demand for mushroom-based products grew. In response to increased global demand for this category, GOODMIND™ will expand into international markets.

In summary, Psyence is on track to deliver on the goals and strategies we set out when the business was founded, which includes our drug development program, approval of our Phase 2 clinical trial in the UK, development of our Palliative Care protocols, the continued operation and expansion of our licensed psilocybin production facility, building long term supply and research partnerships, and catering to the increased demand of psychedelic adjacent and non-psilocybin nutraceutical products such as GOODMIND™. These activities support Psyence as the anchor brand in psychedelic Palliative Care.

Supporting Medical Innovation in the UK

Dr Laura Squire OBE

Chief Healthcare Quality and Access Officer Medicines and Healthcare products Regulatory Agency

To discuss innovation in psychedelic healthcare, PSYCH spoke with Dr Laura Squire OBE, Chief Healthcare Quality and Access Officer at Medicines and Healthcare products Regulatory Agency (MHRA).

The agency regulates medicines in the UK and has supported psychedelic research through the provision of Innovative Licensing and Access Pathway (ILAP) Innovation Passports.

The MHRA has granted these passports to therapies harnessing MDMA, psilocybin and DMT. For a deeper dive into the regulatory process, PSYCH asked Dr Squire for an overview of the executive agency and its role in supporting innovation.

The MHRA is the body that regulates medicines and medical devices in the UK. We play a leading role in protecting and improving public health and we support innovation through scientific research and development.

This is an age of change, and we see ourselves as a collaborative and enabling regulator that looks for opportunities to support innovative new products and ways of working. We aim to combine a high level of scientific support and expertise with agility, to enable robust decisions in order to be reached in the shortest possible time.

To help the life sciences industry to develop effective and innovative healthcare products, we engage proactively from the earliest stages of development. For example, we advise on the design of clinical trials to support innovation while ensuring scientific rigour and participant safety as well as encouraging meaningful patient involvement.

We advise on the evidence of safety and impact that developers will need to demonstrate for each product, to help products reach patients as quickly as possible while maintaining high standards of safety and quality.

We have seen the benefits of early engagement with the MHRA and would encourage health innovators to come to us as early as possible for regulatory advice. Our Innovation Office is open to queries about innovative medicines, medical devices and manufacturing processes. It provides free and confidential expert regulatory information, advice and guidance to organisations of all backgrounds and sizes based nationally or internationally.

The MHRA works closely with public health partners across the UK, including NICE and the NHS to support an end-to-end development pathway. This integrated approach is valuable to many manufacturers as well as to patients and the healthcare system.

We have a long-standing partnership with NICE to ensure patients have access to the most innovative medicines in a timely way. We have worked together on arrangements for

licensing and appraisal of new medicines for use in the NHS, including close collaboration on developing the Innovative Licensing and Access Pathway (ILAP).

The Home Office is responsible for the controlled status of substances under the Misuse of Drugs Regulations 2001. The MHRA collaborates with their Drugs and Firearms Licensing Unit and Drugs Legislation Team to enable access to controlled medicines for legitimate purposes.

As we have outlined in our 2021-2023 Delivery Plan, our focus is on delivering meaningful health outcomes for patients and protecting public health through excellence in regulation and science.

We are changing how we work to deliver this, integrating our unique Agency assets in basic science, real-world data and regulatory innovation, undertaking ambitious reforms in how we regulate medical devices and clinical trials, and at the same time strengthening our surveillance capability, to enable UK patients to get swift and safe access to the medical products they need, including the most ground-breaking. This includes medical products to support mental health care.

We are working to maximise patient safety and quality of care in mental health. We aim to improve the use of diagnostics such as 'in vitro' diagnostics and digital health products that can help better understand the therapeutic intervention and care pathway for patients.

The MHRA and NICE have just been awarded mental health funding of £1.8 million to explore and produce guidance on regulating digital mental health tools. This project will review key aspects of medical device regulations to produce guidance that will support digital mental health in several significant areas.

The key objective is to ensure that mental health software will be proportionately regulated, meaning the public can have access to effective and safe products that can significantly help protect or improve their mental health.

Where digital mental health tools are safe and effective, they will assist in stemming the tide of mental health issues, allowing for earlier, targeted interventions and giving patients the tools to effectively manage their mental health where appropriate.

Against the backdrop of a deepening mental health crisis, there have been considerable developments in psychiatric healthcare, both in the UK and abroad. Dr Squire outlined the role of the Innovation Passport

ILAP combines the MHRA's globally recognised high standards of quality and safety with improved flexibility to reduce the time it takes innovative treatments to be available to NHS patients. The 'Innovation Passport', a new medicine designation, acts as the gateway to entry into this pathway and is awarded to innovative products submitted to the ILAP.

The ILAP covers the entire development programme with a clear ambition to speed up the time to patient access. Companies are encouraged to engage early, before they have clinical data, in order that all the benefits of enhanced interactions with the MHRA and the partners can take place.

The ILAP covers the whole life cycle of products, supporting clinical trial recruitment, adaptive inspections, and the collection of real-world data. Most important of all, it involves patients in all aspects of decision-making.

The entrance criteria for ILAP are broad and inclusive to support a wide range of products and new indications, including Advanced Therapy Medicinal Products, medicines for rare diseases and repurposed medicines.

A successful Innovation Passport designation then triggers the MHRA and partners to create the Target Development Profile document. This living document will set out a unique product-specific roadmap towards patient access in the UK healthcare system.

There has been a surge in clinical trials with psychoactive drugs, PSYCH was eager to know how the MHRA could support the adoption of psychedelic healthcare.

The MHRA helps ensure that patients have timely and safe access to treatments, including products to treat neuropsychiatric disorders, by offering scientific and regulatory advice to medicine developers. We do this through our statutory role to assess and approve clinical trial applications and marketing authorisations.

We have in place two programmes to facilitate early access to medicines, the Early Access to Medicines Scheme and the Innovative Licensing and Access Pathway, and a number of regulatory flexibilities for expedited licensing of medicines, particularly in areas of unmet medical need, such as the conditional marketing authorisation.

MDMA-assisted therapy and psilocybin therapy are expected to be regulated in 2024 and 2025. Assuming similar timelines for other treatments with Innovation Passports, there could be three psychedelic compounds used to treat mental health disorders - MDMA, psilocybin and DMT.

There is significant work undertaken to support mental health and wellbeing through advances in neuroscience and drug discovery, as patients still have significant unmet therapeutic needs in this area.

The MHRA supports innovation through ILAP, as well as broad regulatory and scientific advice, to facilitate the development of new treatments for a wider variety of psychiatric and behavioural conditions, with a particular focus on treatments tailored to the specific needs of individual patients.

This should lead to increased availability of safe and effective treatment options to improve cognition, function and social outcomes for people with neuropsychiatric disorders.

Therapists in Psychedelic Healthcare

The Psychedelics as Medicine Report | Therapists in Psychedelic Healthcare

Access to therapists is critical to the adoption of psychedelic-assisted therapy, and ensuring market access is crucial for the industry to realise its potential.

A shortage of trained therapists has been cited as an obstacle to the scalability of psychedelic healthcare, with organisations creating therapist training programmes and protocols to expand patient access.

Over 800 healthcare practitioners have undergone MAPS' therapist training programmes, with the organisation hoping to train 20,000 psychedelic-assisted therapists by the end of the decade.

In June, MAPS negotiated with the FDA to lift a hold on a MAPS-sponsored Phase II study of MDMA-assisted group therapy. This would enable six patients to undergo psychedelic-assisted therapy with one therapist, significantly expanding the treatment's addressable market.

Following the FDA's expected approval of MAPS' MDMA treatment next year, the organisation will have six years of data exclusivity. During this time, MAPS needs to treat as many patients as possible in order to maximise the return on its investment.

MAPS aims to build a network of 24,000 psychedelic therapists and to treat 500,000 patients before the end of 2029. In which time, MAPS could generate over US$7 billion through MDMA-assisted therapy and training services.

MAPS hopes its MDMA-assisted therapy will be regulated in Europe in 2024, where data exclusivity extends to eight years. However, in Europe's publicly funded healthcare systems, cost is king. This heightens the importance of group therapy and innovations, such as shorter-acting tryptamines, which would reduce the price of treatments for payees.

By the end of 2023, there could be 1,000 therapists trained to deliver MDMA-assisted therapy. If group therapy proves effective, these 1,000 therapists could treat 6,000 patients, greatly expanding the treatment's accessibility. Another means to expand patient access is by reducing the reliance on therapists, through the development of psychedelic treatments with shorter durations.

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TRAINING PSYCHEDELIC-ASSISTED THERAPISTS

Dr Ben Sessa
Head of Psychedelic Medicine, Awakn Life Sciences

Psychiatrist Dr Ben Sessa, Head of Psychedelic Medicine at Awakn Life Sciences, specialises in addiction services and psychedelic-assisted therapy.

PSYCH spoke with Dr Sessa regarding Awakn's business model, its therapist training programmes and the potential of psychedelic healthcare on the NHS.

At Awakn we have two things we do. Research and Development and commercialisation.

From an R&D perspective, the goal is to repurpose drugs to treat Alcohol-Use Disorder, (AUD), in combination with our proprietary therapy. On that front, we have a completed a Phase IIb study using ketamine-assisted therapy for the treatment of AUD and are progressing this into a Phase III trial very soon. We have just received approval of a grant from the UK government to cover 66% of the costs of the Phase III trial, which is a fascinating development.

We will also be delivering the trial within the NHS infrastructure, which really shows the NHS's intent to try and adopt the treatment. The reason they are both such great supporters of the research is because of its efficacy. The trial resulted in patients experiencing, on average, 86% abstinence at six months post treatment versus 2% before the trial, which means that study participants went from being sober on average seven days a year to being sober on average 314 days a year. That is approximately a three and a half times greater success rate than the standard care, which is incredible.

We have also completed a Phase IIa trial with MDMA-assisted therapy for AUD and are assessing our options on how best to progress this.

In R&D we also have some early stage clinical studies into behavioral addictions and gambling disorder in particular, which is investigating ketamine as a treatment. Finally, we have a New Chemical Entity programme - which looks at new compounds to treat addiction.

The second thing we do is commercialisation. We take the amazing work that the R&D team has done, then we hone, fine tune it and then deliver it in our clinics. There are bricks and mortar clinics on the high street where people can go and get psychedelic therapy. We have three clinics open in Bristol, Oslo and London, with a view to opening another 10 to 15 over the next four or five years.

At the moment, ketamine is the only legally available tool because it's the only licensed psychedelic medicine. Other medicines such as psilocybin, MDMA, DMT and LSD all show tremendous promise, but they're not medicines with a capital M; they are research chemicals. They can only be used in research until they get licensed.

The final part of commercialisation is our licensing partnerships, where we out-license our ketamine-assisted therapy treatment to clinic operators in North America, arming them with a proven more effective treatment.

Awakn conducts training programmes to teach therapists the required protocols with regard to psychedelic medicines. To qualify for the course, applicants must already be a licensed clinician, such as a psychologist, a nurse or a doctor.

What we have at Awakn is an online training module programme, which is based on 12 online modules, two hours each. The participant works their way through each session, answering quizzes, and then gets a certificate at the end of it.

The 12 modules cover MDMA, psilocybin and ketamine, plus an introduction and a summary. They're available online through a platform by signing up.

Then there is face-to-face lecture delivery from professionals at Awakn for small groups. This is the main training that we offer in-house to our staff. One day, we may be able to roll out this training to other people who aren't working for us. At the moment, because we're opening new clinics and recruiting, we've only delivered that training programme to our own staff, as we need to know they're up to date.

Recently we announced our first two license partners in the US and Canada. We provide them with all the tools and training necessary to deliver the Awakn protocol of ketamine-assisted therapy for AUD. So, as well as building physical clinics, which is great, but very expensive, the other model we have is that we license our evidence-based treatments to existing clinics, who are not using ketamine or who are maybe using ketamine without psychotherapy.

As we speak, Owain Winfield, our KARE lead and psychotherapist at Awakn, is in North America delivering the first of our training sessions. The training sessions delivered this month consist of two-and-a-half days of training, from qualified clinical psychologists, to licensed psychologists and therapists from clinics in the US and Canada.

They take the form of workshops with face-to-face lectures, which run through the KARE programme we're licensing. KARE stands for Ketamine in the Reduction of Alcoholic Relapse, and is our ketamine-assisted psychedelic therapy programme for people with alcohol-use disorder.

The training programme goes through KARE in great detail. They not only learn how to deliver ketamine in the drug sessions, but they also learn the underpinning psychological model.

They get two-and-a-half days of training from our experts and undergo a period of

supervision of four clinical cases supervised by our training staff. The therapists who get trained and start using our treatments will be closely supervised to check that they're carrying them out in the same way.

We also have supervision for individual disciplines in these clinics. So, nurses will supervise nurses, pharmacists will supervise pharmacists, doctors will supervise doctors, so it's discipline led.

Contracts to train Awakn's protocols in North America represent global expansion for the UK-based company. PSYCH was interested to learn about the organisation's strategy and emerging commercial opportunities.

We hope they're going to be the first of many. There are two main population targets for us to license our treatments. One would be existing alcohol services that don't do anything with ketamine, such as inpatient rehab units and community teams working with alcoholics. We could teach them how to use ketamine-assisted psychotherapy with their patients.

Another target population would be existing ketamine clinics. There are between 600-1200 ketamine clinics in the States, but the vast majority just use the drug as an antidepressant. There's no psychotherapy or support. You go home and then the antidepressant drug starts to work. These places are marginally useful, but they don't do any psychotherapy.

They're already completely 'au fait' with ketamine, but we'll be teaching them how to do ketamine-assisted psychotherapy. So, we have two different populations. One is alcohol units doing psychotherapy without ketamine, and the other is ketamine units doing ketamine without psychotherapy.

Typically, ketamine is prescribed off-label and administered intravenously. In response to clinical evidence of its efficacy, there is a growing demand for ketamine-assisted therapy.

I can remember speaking to a UK-based ketamine clinic about six years ago where they were doing ketamine infusions. They would say to the patient when they hooked them up to the infusion, 'We're going to give you the drug now. I'm really sorry, you will feel a bit weird for a couple of hours but, don't worry, it'll soon pass. Then you can go home and the antidepressant will start working.'

I remember saying to them that the psychedelic experience, which you consider just as this irritating side effect, can be a very valuable experience with the right skill and guidance. You can work with that therapeutically.

The psychedelic experience is not just an irritating side effect. I think more people are moving towards the idea of not giving ketamine as an antidepressant, but using ketamine in the same way as we would use other psychedelic medicines like MDMA or psilocybin, as part of a more effective course of psychotherapy.

What is really important about the KARE programme, and indeed all of our psychotherapy protocols, whether using ketamine or MDMA -assisted therapy, is that they all have a mixture of non-drug and drug sessions.

For example, on the KARE protocol you take ketamine on three occasions, but this is sandwiched in-between non-drug sessions, which are really important.

You start with a non-drug face-to-face psychotherapy session for preparation, during which psychotherapists build a relationship with the patient. This builds up an agenda for the sorts of things they want to address, before they have a guided drug session. After that, patients have a non-drug integration session to talk about the drug session.

The following week, there will be another guided drug session followed by another non-drug integration session. So, the totality of the course is three drug sessions, alongside six non-drug preparation and integration sessions.

On the subject of ketamine's use as a classic psychedelic medicine like MDMA, PSYCH asked Dr Sessa about Awakn's New Chemical Entity programme. A derivative compound has been developed with the potential for a quicker onset, which could promote better integration into existing healthcare frameworks.

We'd like to aim for a two-hour experience. One of the many ways ketamine is very useful is that it is short acting when given by intramuscular injection. You are kind of up and down within 90 minutes and that makes it very clinically deliverable because you can do a session in the morning and a session in the afternoon.

With MDMA we've done research and it is an eight-hour session. It is arguable that you need an eight-hour session, but it's worth experimenting as to whether we could produce a shorter-acting MDMA-like analogue that would be more clinically deliverable, economical and therefore potentially more attractive to providers like the NHS.

MDMA-assisted therapy for PTSD is expected to be regulated in Europe by 2024. MAPS hopes to train 25,000 practitioners to deliver the treatment by the end of the decade.

PSYCH asked Dr Sessa if the number of trained therapists could cause a bottleneck in the roll out of psychedelic healthcare.

It is certainly a concern. Which is why MAPS is on a very rigorous therapist training programme at the moment. It has been very difficult to train as a psychedelic therapist as you could only really train psychedelic therapists if you had a psychedelic study to carry out.

There are only several dozen studies going on around the world. I'm a trained psilocybin therapist because I trained with COMPASS Pathways and I am an approved MDMA therapist, because I trained with MAPS.

In the UK the only people trained to use psilocybin or MDMA are the few lucky people who have done similar studies. So, that does indeed induce a bottleneck the minute the drug gets licensed, because there are only a select number of licensed therapists.

However, there is not much point in training thousands of MDMA and psilocybin therapists in the UK today as they cannot use it. It will all be about timing over the next few years and getting people trained ready. That way, the minute the drug is licensed, they can hit the ground running.

It is a very strange situation in that we are expecting the floodgates to open when MDMA gets licensed. We need to train therapists, but at the moment there is nowhere for therapists to train unless they are taking part in a research study.

There are long waiting lists for cognitive behavioural therapy on the NHS. With ketamine-assisted therapy having proven effective in clinical trials, PSYCH asked about the treatment's integration into public healthcare.

At conferences, people will ask, 'Why does Awakn have to be private? Why isn't ketamine-assisted psychotherapy available on the NHS?' Don't ask me; there is nothing we want more than Awakn's protocols on the NHS. We would have queues around the block if we could provide treatments to NHS patients.

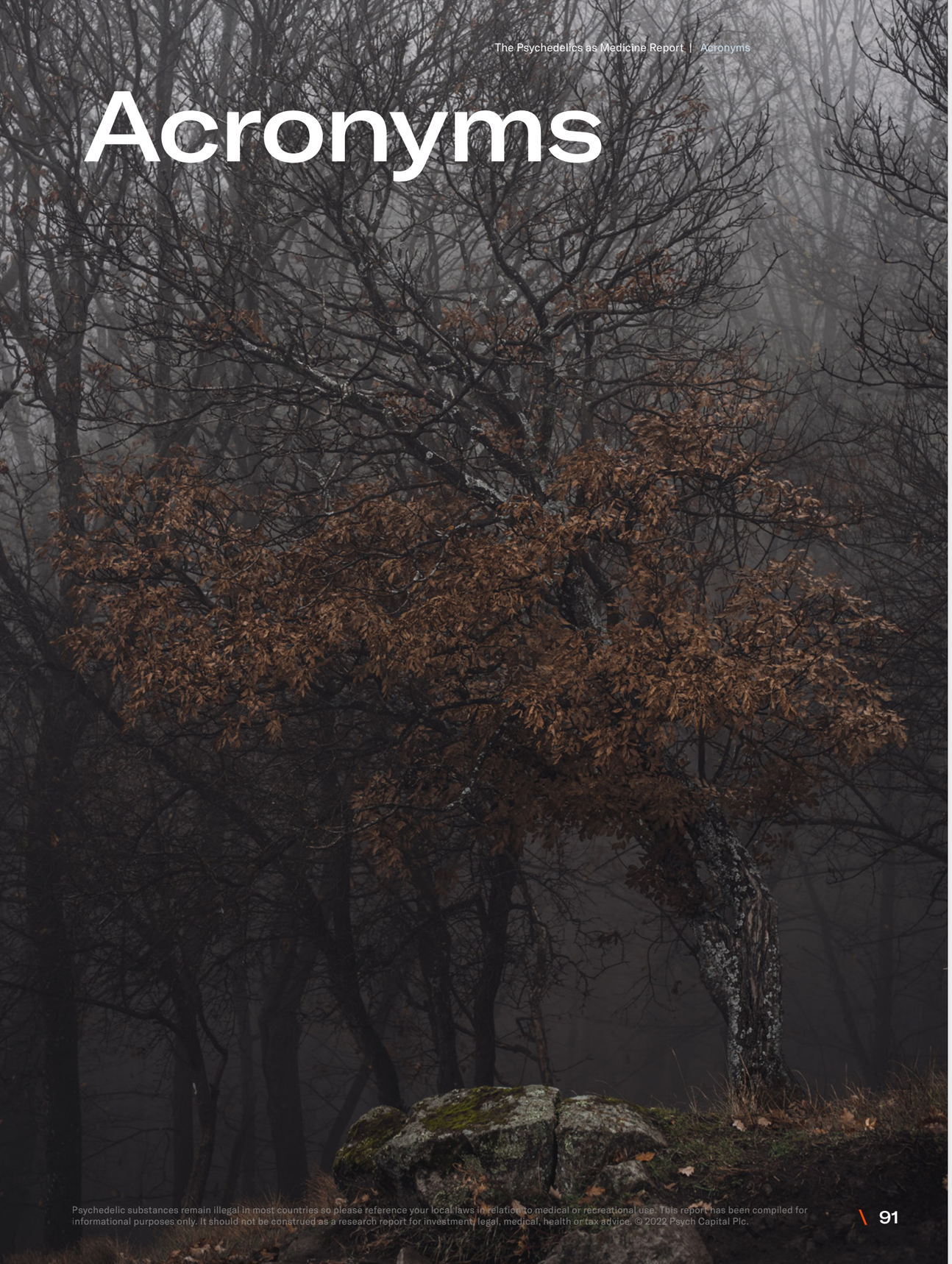
The NHS is a slow beast. It takes a long time to decide what to fund, so it is normal that innovative treatments are available privately first. I have no doubt that in the future psychedelic medicine will be available for free on the NHS for a few reasons – it is safe, it's effective and it is cheap.

It may sound expensive, when a patient has to pay £6,000 themselves. But, as I often say in my talks, there is nothing more expensive than an untreated psychiatric patient.

Psychiatric patients who don't get better don't work and are often on disability benefits. If we can deliver an eight-week course of ketamine-assisted psychotherapy for £6,000 and the patient gets better and gets back to work, then that is very cheap.

As an addiction consultant, I've lost count of the number of times I've put patients into expensive six-month alcohol rehabilitation programmes costing £50,000 and on the last day they walk out straight into the pub. The current treatments for addictions on the NHS are very poor with poor outcomes and are, consequently, very expensive.

The figure, £6,000, may sound expensive, but it actually makes total economic sense. I'm quite convinced that the NHS will put these medicines into public healthcare because psychedelic-assisted therapies make sense economically. That is why the NHS are such great supporters of the work we are doing and why they will play such a critical role in our Phase III studies.



Acronyms

FDA	Food and Drug Administration
WHO	World Health Organisation
MAOIs	monoamine oxidase inhibitors
DMY	Dimethyltryptamine
5-MeO-DMT	O-methyl-bufotenin
LSD	Lysergic acid diethylamide
MDMA	3,4-methylenedioxy-methamphetamine
TRD	treatment-resistant depression
BTD	Breakthrough Therapy designation
MAPS	Multidisciplinary Association for Psychedelic Studies
PTSD	post-traumatic stress disorder
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence
UN	United Nations
NHS	National Health Service
SI	suicidal ideation
MADRS	Montgomery–Åsberg Depression Rating Scale
UE	European Union
CRO	contract research organisation
VA	Department of Veteran's Affairs

NIH	National Institutes of Health
CIHR	Canadian Institutes of Health Research
CIMH	Central Institute of Mental Health
MDD	major depressive disorder
AUD	alcohol-use disorder
QALYs	quality -adjusted life years
REBUS	Relaxed Beliefs Under Psychedelics
NDAs	non-disclosure agreements
FTO	Freedom To Operate
PTAB	Patent Trials and Appeals Board
IP	intellectual property
EMA	European Medicines Agency
OPS	Oregon Psilocybin Services

The Psychedelics as Medicine Report | Acronyms

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