
# PSYCHEDELICS 2021

## A YEAR IN REVIEW

A five-part review of psychedelics in 2021: from drug policy reform and research highlights, to pop culture and controversy.

# INTRODUCTORY REMARKS

## "JUST AS THE NUMBER OF MOLECULES UNDER INVESTIGATION HAS, WELL, MUSHROOMED; SO TOO HAVE THE AILMENTS THAT RESEARCHERS AND DRUG DEVELOPERS SEEK TO TARGET."

Given that Psilocybin Alpha was launched in Spring 2020, this past year marked our first full year of reporting on the psychedelics space. It's also the first year that I was able to meet so many folks in person for the first time, which was a welcome change from Zoom.

These days I am increasingly reflecting on just how inappropriate the name Psilocybin Alpha has become. When I started writing about psychedelics nearly two years ago, psilocybin was at the forefront of clinical research into the 'true' psychedelics, and the subject of early investor interest. Today, psilocybin is just one of a whole host of molecules under investigation, with derivatives and entirely new chemical entities increasingly the subject of drug development efforts.

Just as the number of molecules under investigation has, well, mushroomed; so too have the ailments that researchers and drug developers seek to target. While neuropsychiatric diseases such as depression and PTSD represent a beachhead for psychedelic research, we're increasingly seeing a move toward other areas of medicine that are also characterised by high unmet needs, such as neurodegenerative diseases. We should be cautious, however, with overstating the 'promise' of psychedelics to treat such diseases: while psychedelics appear to work in a transdiagnostic manner, much of the research is in early stages.

2021 brought a great deal of validation to psychedelic-assisted therapies, most notably via the stellar results of MAPS' Phase 3 MDMA-assisted therapy for PTSD study.

This psychedelic research is taking place amidst an increasingly warm context, which includes: federal grants in the U.S. and Australia; increased psychedelics production quotas in the U.S.; a fast-track designation for a DMT therapy in the UK; a flurry of new psychedelics research centres; Bills passed that mandate State-level research into psychedelics; amendments to Canada's Special Access Programme and further Section 56 exemptions allowing access to psilocybin-assisted therapy; and many, many other positive signals.

But, just as we see outsized expectations from participants in clinical trials (which can lead to outsized disappointment among patients who fail to respond), we certainly saw high expectations of publicly-listed psychedelics stocks, which instead performed terribly this year. There is a clear disconnect between fundamentals, such as company news and data readouts, and stock prices, as investors struggle to value these unusual ventures. But, psychedelics startups continued to succeed in their fundraising efforts in 2021, with little signs of slowing.

As the psychedelics space continues to change in both size and composition, some have rightfully expressed concerns about new influences, such as the increasing attention paid to profitability and defensibility by psychedelics companies. Controversies have also emerged from more established sides of the psychedelic ecosystem, with sexual abuse allegations surfacing long overdue conversations.

In this review series, we'll look at a number of key areas of activity for psychedelics in 2021, before sharing some trends and events to keep an eye on in 2022. Of course, this is not exhaustive: either in content, or in terms of the voices represented. As always, we welcome your comments.

**JOSH HARDMAN**
Founder and Editor

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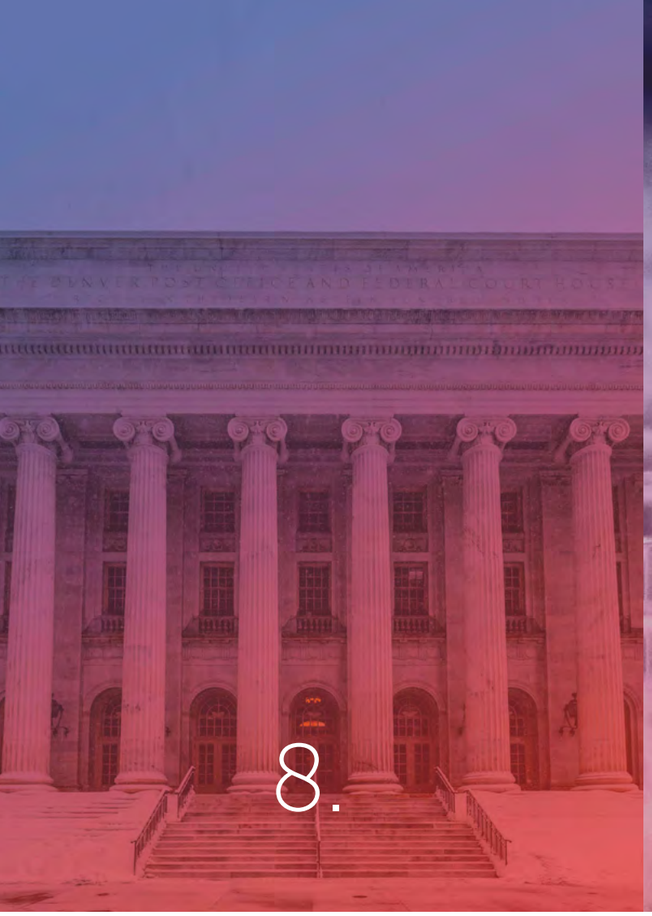
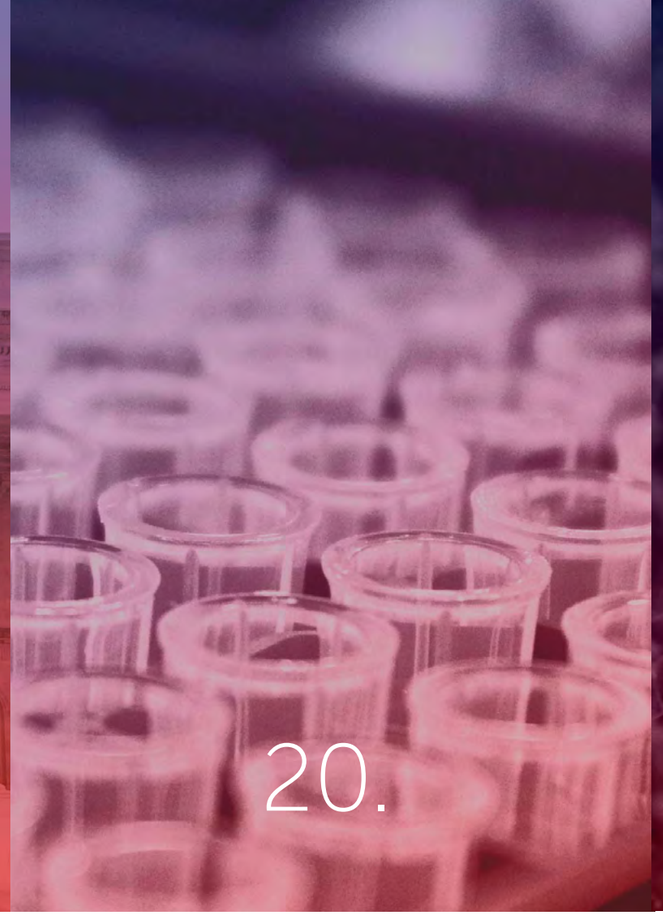
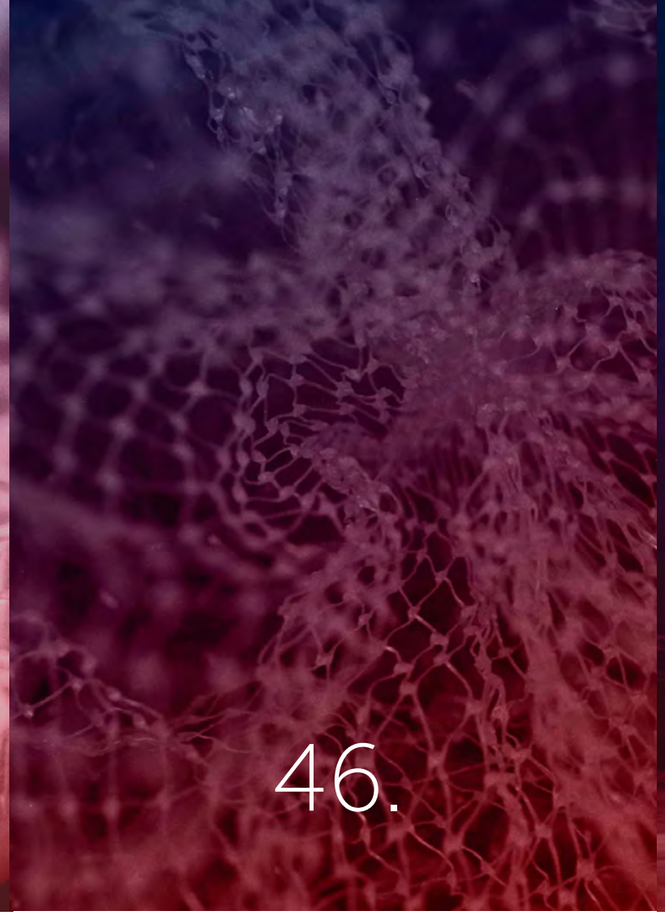
with research support from Noah Smith

With thanks to Michael Haichin, Graham Pechenik, and Sean Clancy for their feedback





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SECTION
**ONE**

# PSYCHEDELIC DRUG POLICY REFORM IN 2021

1

# 1.1 - FOREWORD

While this Review focuses on 2021, it's difficult to contextualise the levels of psychedelic drug policy reform witnessed this year without appreciating the gravitas of events in late 2020. 2020 was a groundbreaking year for psychedelics decriminalisation and legalisation efforts, with the U.S. leading the pack with significant activity at both the local and state level. The twin successes of Oregon's Measure 109 and Washington, D.C.'s Initiative 81, to create legal access to psilocybin-assisted therapy and to decriminalise psychedelics, respectively, propelled psychedelics decriminalisation and legalisation efforts to the mainstream.

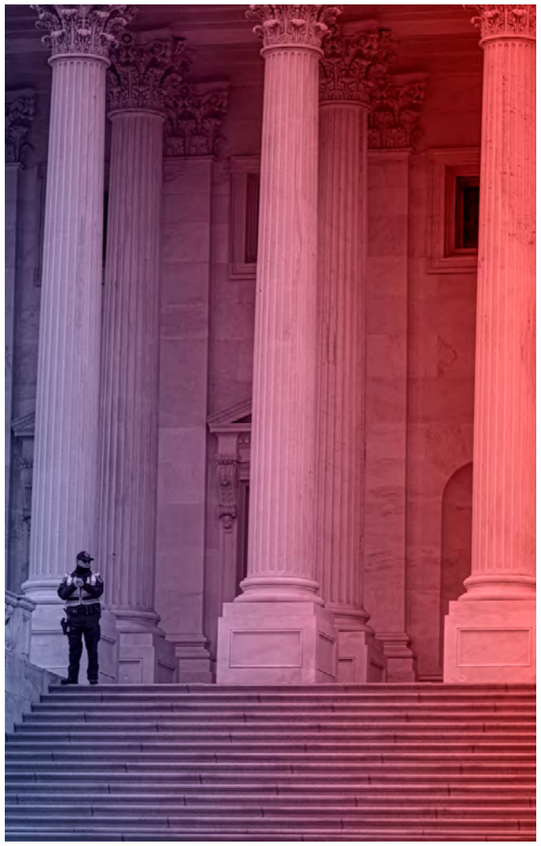
Here at Psilocybin Alpha, our readership increased in quantity and diversity almost overnight following these successes at the ballot box. In response to these initiatives we were now being contacted by—and seeing subscribers from—journalists of all stripes; entrepreneurs looking to launch biotechs or retreats; investment banks looking to keep tabs on the emerging industry; therapists hoping to offer this new modality as part of their practice; and more.

We also observed psychedelic companies, and their executives, scramble to find a line and toe it. Many chose to publicly celebrate Oregon's Measure 109, with Field Trip' Ronan Levy exclaiming, "what an incredible accomplishment," when discussing the results with Psilocybin Alpha. Other executives have been more hesitant to condone the Measure, while others still have been accused of drumming up opposition to the measure.

As individuals and companies try to find their feet in this rapidly changing legal and public opinion landscape, the pace of drug policy reform efforts has not slowed in 2021. The aforementioned Initiative 81 came into effect in D.C., with psychedelics de facto decriminalised, and Oregon Psilocybin Services, housed within the Oregon Health Authority, is making progress toward implementing Measure 109 through the two-year development process that ends December 31, 2022.

Beyond progress updates on these two landmark initiatives, 2021 saw a flurry of policy reform efforts across the world. As advocates and decision-makers pressed for changes to antiquated drug policies, ending the prohibition and criminalization of psychedelic drug use appeared in political agendas all over the world.

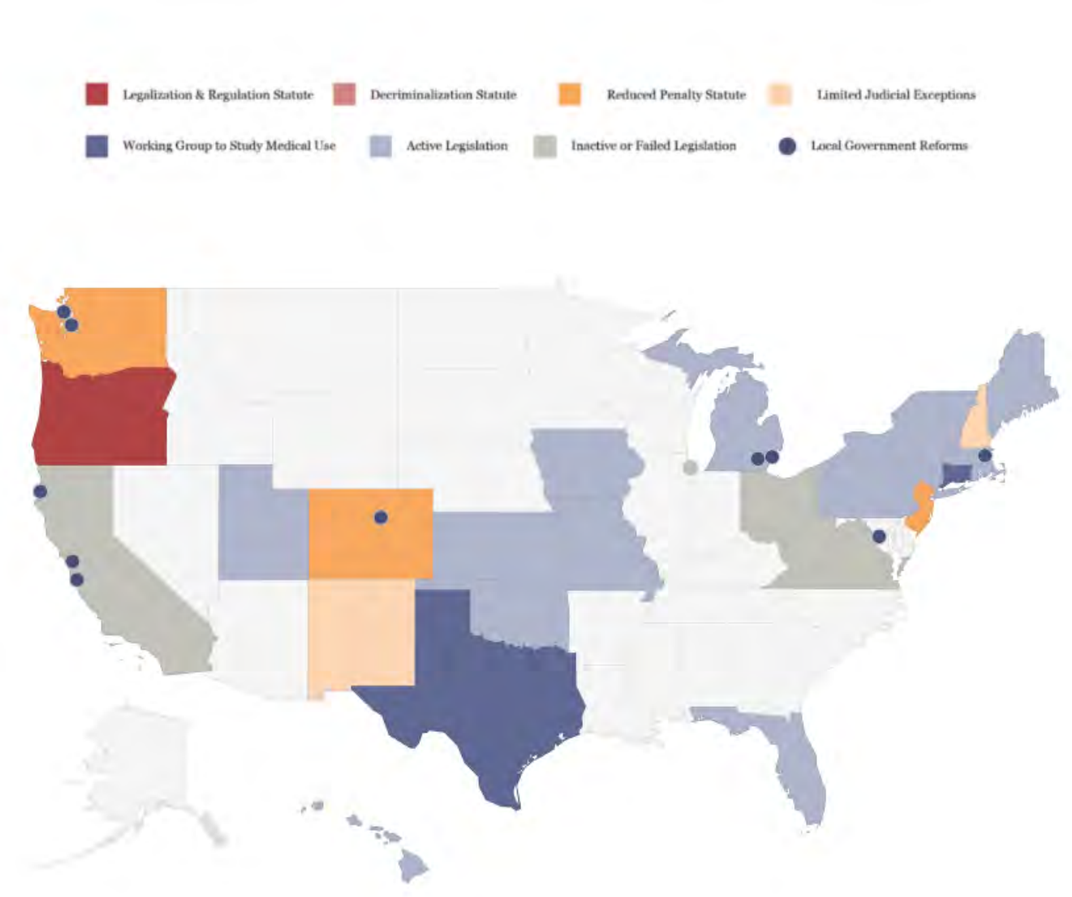
**Here are some of 2021's most significant developments from the U.S., Canada, UK, and Australia.**



# 1.2 - THE UNITED STATES

This year we have seen an explosion of psychedelic drug policy reform initiatives in the U.S. that follow a variety of templates: some call for decriminalisation of psychedelics in some manner, others for legalisation. Others, still, call for state-funded research into psychedelic-assisted therapies or other specific actions.

Perhaps the best way of conveying the sheer volume and diversity of efforts underway is to review our Psychedelic Legalization & Decriminalization Tracker, produced in collaboration with Calyx Law and Emerge Law. A majority of the efforts visualised in the tracker were initiated in 2021.



## TEXAS BILL MANDATES STATE RESEARCH INTO PSYCHEDELICS

While liberal states and cities have no doubt led the charge, as was the case with marijuana, some initiatives have a surprisingly bipartisan flavour. Take Texas, for example. Former GOP Governor Rick Perry joined Democrat Alex Dominguez to back House Bill 1802, which was enacted into law on June 18th, came into effect on September 1st and expires in two years.

HB 1802 requires the Department of State Health Services to evaluate the therapeutic efficacy of psychedelics including MDMA and psilocybin for the treatment of depression, anxiety, PTSD, migraine and other conditions. The report, which is to be submitted by December 1, 2022, is to involve a clinical trial of psilocybin for PTSD in veterans, with $1.4m in funding allocated.

In November, Perry appeared on stage alongside Tim Ferriss and Rick Doblin at a gala in support of Veterans Exploring Treatment Solutions (VETS), a non-profit dedicated to assisting U.S. veterans seeking psychedelic-assisted therapies. This appearance drives home just how important the narrative surrounding veterans is to some corners of the psychedelic renaissance, and has certainly been central to building a bipartisan agenda around their acceptance.

We highlight Texas' HB1802, and Rick Perry's involvement, for two reasons. Firstly, and as aforementioned, because it succeeded in a decidedly Republican state, and was openly supported by prominent Republicans like Rick Perry. It's also forming a model for other Republican states, such as Florida, where politicians have now introduced similar bills (SB348 and HB193). Secondly, it's not a decriminalisation or legalisation initiative, but rather an effort to mandate state governments to support research into psychedelic therapies.

In response to the success of the Bill, the Center for Psychedelic Research and Therapy was launched at the University of Texas at Austin's Dell Medical School. We spoke to the Co-Director, Dr. Greg Fonzo, who explained that the centre will "advance the application of psychedelics for the treatment of mental health disorders through impactful clinical research."

Emphasising the centre's focus on veterans, Fonzo explained that the first of its kind in Texas facility will aim to "improve the health of those suffering from severe depression, anxiety and PTSD through psychedelic-assisted psychotherapy and research focused heavily on military veterans and adults affected by early childhood trauma."

Why might people feel the need to mandate this research at the State level? Well, Alexandria Ocasio-Cortez's attempt to lift barriers on federal research into psychedelics via an amendment was defeated for a second time this year in a 285-140 vote. But, it's important to compare this margin of defeat to when the amendment was put to vote in 2019, when it was defeated 331-91. "I am undeterred," explained Ocasio-Cortez, "I'll keep bringing it up until the times catch up."

**The Verdict:** Texas House Bill 1802, which requires the State's health agency to evaluate the therapeutic efficacy of psychedelics, is remarkable for a number of reasons, not least its success in a firmly Republican state. It also propelled the launch of a new Center for Psychedelic Research and Therapy at the University of Texas at Austin, and has provided a cookie cutter template for like-minded states such as Florida

## CALIFORNIA MOVES CLOSER TOWARDS DECRIMINALISATION

The most populous state in the U.S. captured a great deal of attention with the introduction of Senate Bill 519 (SB 519) which would decriminalise the possession of some psychedelic drugs in the golden state.

Notably, and importantly, the bill explicitly excludes peyote, and as such both peyote and mescaline will remain illegal in the state. The reasoning for this exclusion is to ensure that the endangered plant remains available for use in Native American spiritual practices.

We followed the early passage of SB 519 closely as it passed a number of key California State Assembly Committees, including the Committee on Public Safety where it passed by a 5-3 vote. Senator Scott Wiener, who authored the Bill, claimed that psychedelics are "fixing people's brains," and was supported by witnesses including veterans group Heroic Hearts and MAPS' Ismail Ali.

The Bill didn't proceed unscathed, however, and was watered-down by a number of amendments conceded by Wiener. Perhaps most notably, a clause that mandated the expungement of historic convictions related to the possession of psychedelics was removed from the Bill. Ketamine was also removed from the Bill, at the request of the Committee on Public Safety.

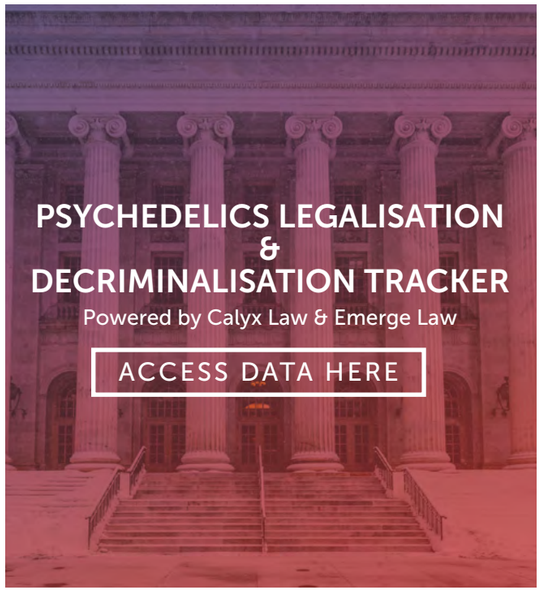
Then, in late August Senator Wiener announced that the Bill had been put on pause. The Bill is still "alive & well," the Senator explained on Twitter, but it has been paused until 2022. The Senator explained that, "over the next year [a] coalition of veterans, parents, healthcare professionals and others will continue to work hard to earn the support of Assembly Members."

**The Verdict:** SB 519, which would decriminalise many psychedelics in California, drew a great deal of attention this year. While the Bill has now been put on pause, the fact that it passed a number of key Assembly Committees is a feat in itself, and many will be closely watching SB 519 as it is reintroduced for consideration in 2022.

## A WEALTH OF OTHER INITIATIVES

Events in Texas and California are but two examples. Over the past year, U.S. states and municipalities have proposed, introduced, and voted on a range of laws governing psychedelics. Decriminalisation and legalisation initiatives were undertaken across 20 states, many of which prioritised the need to reduce or eliminate criminal penalties for psychedelic possession and increase access for therapeutics purposes.

Visit our Psychedelics Legalisation & Decriminalisation Tracker to stay up-to-date with the latest developments on this front.



Beyond state-level efforts, many reform advocates found success at the local level. According to Emerge Law's Sean Clancy, "targeted local government measures with smaller footprints achieved more political success" in 2021.

**The Verdict:** What a year it's been for psychedelic drug policy reform in the U.S. On the whole, we agree with Emerge Law's Sean Clancy, who told Psilocybin Alpha: "2021 revealed mixed success among a small handful of state lawmakers who aimed at psychedelic drug decriminalization or legalization – in contrast, targeted local government measures with smaller footprints achieved more political success."

## 1.3 - CANADA

### HEALTH CANADA GRANTS FURHTER SECTION 56 EXEMPTIONS

In 2021, Health Canada continued to affirm its commitment to providing psilocybin access exemptions to patients in need. Most recently, Canada's new Minister of Health granted his first three exemptions for psilocybin under Section 56. This (admittedly modest) batch of exemptions was particularly important, not just because it signalled the incoming Health Minister's openness to the process, because they were granted to patients who are not palliative, or in receipt of a terminal diagnosis.

We spoke to TheraPsil, a Canadian non-profit that works closely with physicians and patients to advocate for compassionate access to psilocybin. To date, the organisation has helped 47 individuals access psilocybin for a number of therapeutic needs via the Section 56 exemption route.

Spencer Hawkswell, TheraPsil's CEO, told us that "2021 was a year for the Canadian history books." According to Hawkswell, 81 Canadians were granted access to legal psilocybin therapy in 2021. 62 of these were patients (47 of which were supported by TheraPsil) and 19 were health care practitioners (all of which were supported by TheraPsil).

Despite these successes, Hawkswell was keen to note that these cohorts represent a relatively small number of those who might benefit from psilocybin therapy. "While the successes of the past year are certainly to be celebrated, so many Canadians still wait months for their exemptions and all 81 Canadians who have/had exemptions were forced to find their psilocybin mushrooms underground/illicitly," he explained.

**The Verdict:** These case-by-case exemptions are certainly important for the individuals that received them, but long wait times and the relatively small number of recipients indicate the insufficiency of such a piecemeal process. Nonetheless, the willingness of Health Canada to grant such exemptions, including the country's new Minister of Health, demonstrates a pragmatic stance by the regulator, which will hopefully be reflected in further reforms in the coming months and years.

### HEALTH CANADA SPECIAL ACCESS PROGRAM TO ALLOW CONSIDERATION OF PSYCHEDELICS AND OTHER RESTRICTED DRUGS

Just days after we spoke with TheraPsil's CEO, news broke that Health Canada will amend its Special Access Program to allow for drugs like MDMA and psilocybin to be considered.

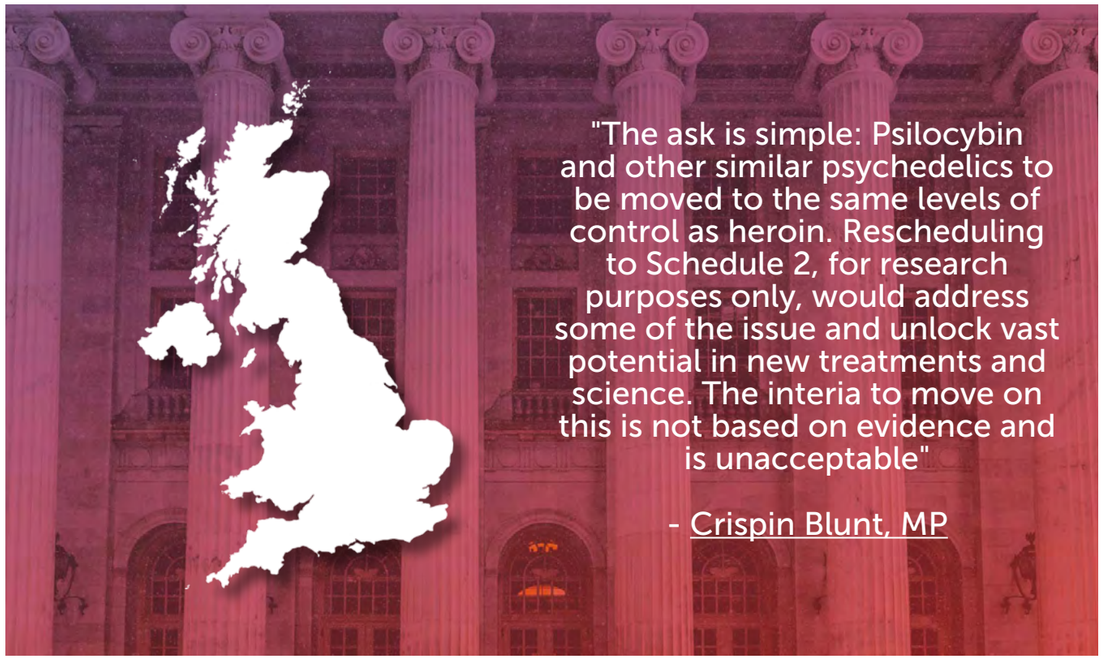
We covered this news in late 2020, when Health Canada first signalled its intent to make such an amendment. Just as 2021 drew to a close, and just over a year after our first reporting on the matter, Numinus broke the news that the amendments will come into effect on January 5th, 2022.

In 2013, an amendment to the Food and Drug Regulations (section C.08.010) saw restricted drugs—including psychedelics like MDMA and Psilocybin—explicitly excluded from the SAP. Under this amendment, clinical trials were the only route through which patients could access these drugs. The new amendment restores potential access to restricted drugs. This could afford Canadians access to potentially life-saving medications and therapies prior to their formal approval and routine provision.

Once the relevant subsection is repealed on January 5th, restricted drugs will be treated in the same manner as all other controlled substances when considered under the SAP, that is: practitioners can request these drugs for patients with serious or life-threatening conditions where other therapies have failed, aren't suitable, or aren't available in Canada.

This reversal does not guarantee that restricted drugs will be approved via a SAP application, but rather that they will be treated in the same manner as all other controlled substances.

**The Verdict:** This amendment represents the latest in a string of progressive moves by Health Canada, and will allow psychedelics to be considered for access via the Special Access Program (SAP). However, much will remain open to debate, such as the point at which other therapies are deemed to have 'failed' or to not be 'suitable,' which are prerequisites for an SAP application.



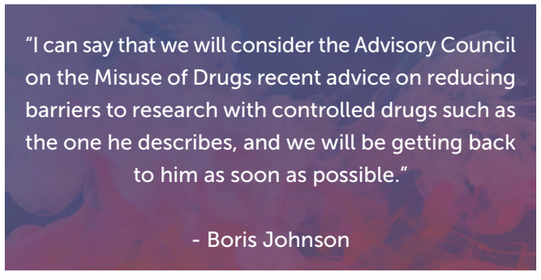

# 1.3 - THE UNITED KINGDOM

## BORIS JOHNSON CONSIDERS RESCHEDULING PSILOCYBIN

In October 2021 news broke that UK Prime Minister Boris Johnson is set to "consider calls to legalise magic mushroom drug psilocybin" (BBC). The BBC headline, which featured the word 'legalise,' overstates the proposed change, which is a rescheduling rather than legalisation.

During Prime Minister's Questions (a weekly fixture in UK Parliament where MPs pitch questions to the PM), conservative MP Crispin Blunt urged Johnson to reschedule psilocybin to enable further research into the drug's therapeutic potential.

In response to the question, the Prime Minister said that he would get back to Blunt "as soon as possible." His full response to Blunt was as follows:




Speaking to the Express in September, Crispin Blunt claimed that the Prime Minister had assured him in May that psilocybin would be rescheduled. However, no such action has yet occurred.

Regardless, the fact that these debates are playing out on the floor of the UK Parliament is remarkable, and promising. But, the Conservative Drug Policy Reform Group (CDPRG) warns that continued engagement with Ministers is necessary in order to secure the rescheduling. Speaking to Psilocybin Alpha, CDPRG's Timmy Davis said:


**The Verdict:** There's plenty of misplaced hype here, which isn't helped by shoddy editorial standards at the BBC. What is being proposed is a rescheduling, not legalisation, of psilocybin in the UK, which would reduce barriers to research. Action by the Home Office to enact such a rescheduling is long overdue, according to insiders who claim the Prime Minister approved the action in principle earlier this year. application.

## A POST-BREXIT FOCUS ON R&D SPENDING AND STREAMLINING MAY FAVOUR PSYCHEDELICS COMPANIES

Tom McDonald, CEO of London-based psychedelics company Clerkenwell Health, told Psilocybin Alpha that while the aforementioned movement to reschedule psilocybin "is gaining traction within civil society", "the real action is within the regulatory bodies of the state."

Alluding to broader strategic initiatives underway in post-Brexit Britain, McDonald explained that the UK government has embarked on "the fastest increase in R&D spending ever."

"The clinical trial system as well as the broader innovation system is being transformed, as is the regulator, to become an enabler of innovation," McDonald noted. "These changes create an increasingly frictionless pathway that will allow developers of psychedelic drugs to undertake speedier and more cost--effective research processes in the UK."

This is certainly evidenced in recent actions by regulators such as the Medicines and Healthcare products Regulatory Agency's (MHRA), which issued new guidance on the use of real-world data in clinical trials, and the National Institute for Health and Care Excellence (NICE) which issued its first update to guidelines on the treatment of depression for over a decade this year.

In concrete terms, we have seen these innovations in UK drug development regulations manifest in a fast-track designation for Small Pharma's DMT therapy candidate, which is discussed later in our Research and Clinical Trials section.

**The Verdict:** As the UK seeks to find its edge in a post-Brexit world, nurturing its biotech industry has emerged as a clear focus. This bodes well for psychedelic researchers and companies, who may benefit from streamlined drug development routes such as the Innovative Licensing and Access Pathway (ILAP) and pragmatic approaches to research and clinical trials such as the employment of real-world data.

## 1.4 - AUSTRALIA

### AUSTRALIAN REGULATORS REJECT PSILOCYBIN AND MDMA RESCHEDULING

In late 2020, a proposal was submitted to the Australian Therapeutic Goods Administration (TGA), the regulatory body in charge of the country's drug scheduling, to reclassify psilocybin and MDMA from prohibited substances to controlled medicines. Following two rounds of consideration, the TGA ultimately rejected the rescheduling efforts in mid-December, citing the emergent nature of evidence and explaining that "the therapeutic value... has not been established."

**The Verdict:** We would have been surprised if the TGA had taken the decision to reschedule psilocybin and MDMA at this stage, which would be out of kilter with other similar countries. However, this has put the issue firmly on the national agenda in the land down under.

### FEDERAL GOVERNMENT CARVES OUT $15M FOR PSYCHEDELIC RESEARCH

It's not all bad news for psychedelics advocates in Oz, though. Just weeks after the proposal was initially rejected in Spring 2021, the federal government announced a $15m grant program to support research into psychedelics, including MDMA-assisted psychotherapy.

**The Verdict:** This capital injection into psychedelic research was welcomed by researchers. Beyond its cash value, it sends a strong message that Australia is open for psychedelics research.

SECTION
**TWO**

# PSYCHEDELIC RESEARCH & CLINICAL TRIALS IN 2021

2

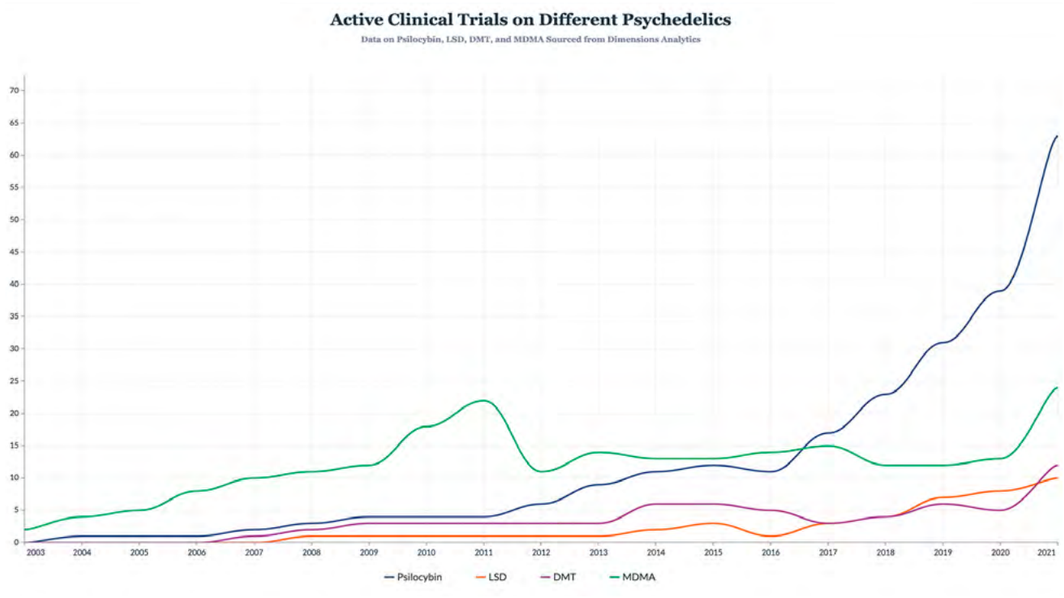
# 2.1 – FOREWORD

The resurgence of research into psychedelics has continued to thrive over the past year. Dozens of trials and hundreds of studies have been published in 2021, expanding the depth and scope of scientific inquiry in this flourishing space.

If published findings from this past year are a reliable indicator of what is to come, these investigations will foreseeably expand our fundamental understanding of psychedelics and point to new, promising avenues of exploration.

However, we must also appreciate the methodological challenges inherent in psychedelic research, as well as the broader fields within which such research is nested.

It's worth reminding ourselves of the lengthy timescales involved in drug development, with clinical trials regularly taking in excess of six years to complete.



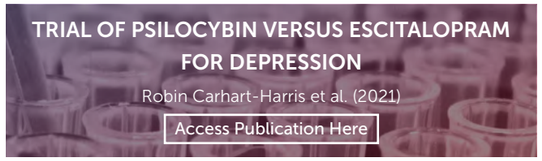

As such, it's worth looking at studies announced and approved in 2021, and considering when we may expect to see data readouts from such work.

Just as the funding environment for psychedelic research has heated up significantly in recent years, regulators are also demonstrating an increasingly warm attitude to such work. Toward the end of this section we review some key regulatory developments in 2021, and profile a handful of new psychedelics research centres.

As you will see as you leaf through this report, psychedelic research is showing no signs of slowing. One of the most prolific psychedelics researchers, Robin Carhart-Harris, predicts "more of the same" in 2022, and data confirms that we're witnessing the most productive period of psychedelic research (at least that which is conducted in recognised institutions).

**To begin, here are some of 2021s most notable publications...**

# 2.2 – PSILOCYBIN GOES HEAD-TO-HEAD WITH SSRI ANTIDEPRESSANT




In April 2021 results of a Phase 2 trial evaluating psilocybin-assisted therapy compared with psychotherapy and escitalopram, a common SSRI antidepressant, in the treatment of major depressive disorder (MDD) were published in the New England Journal of Medicine. This was the first randomised, controlled study of psilocybin for the treatment of MDD.

Publication in NEJM—one of the oldest and most prestigious medical journals—is, in itself, a significant moment for psychedelic research. The study was also covered widely in mainstream media outlets, including NBC; Scientific American; BBC; Rolling Stone; and the Guardian.

However, the results didn't—at least on the face of it—appear to meet the lofty expectations of many. This is partly due to the study's design, including the measure of depression that was chosen as the primary outcome in the study's pre-registration. Speaking to Psilocybin Alpha, Psilera Bioscience's Co-Founder and CEO Chris Witowski explained, "by primary endpoints [sic] there was no difference in efficacy, however, when you look at other endpoints there seem to be better outcomes trending towards psilocybin."

We featured exclusive expert commentary from Stanford School of Medicine's Boris Heifets in an April Bulletin, in which he further explained some of these "very unfortunate (and unlucky) design features" that make this study "difficult to interpret."

However, despite these methodological misfortunes Witowski explained that, "there is still promise for psilocybin in the treatment of depression but more studies are needed to prove this in the eyes of regulators; the best way to do this and increase access is through top-quality science and clinical research."

The trial was also profiled in a BBC documentary, somewhat unimaginatively titled, The Psychedelic Drug Trial.

**The Verdict:** Despite some prima facie shortcomings, a closer look at this study shows that psilocybin-assisted therapy outperformed the (standard of care) SSRI antidepressant on a number of measures. Its publication in the prestigious journal NEJM, and its widespread reporting in mainstream media, marks a significant moment for psychedelic research in itself.

# 2.3 – MAPS PUBLISHES RESULTS FROM PHASE 3 TRIAL OF MDMA-ASSISTED THERAPY FOR PTSD


One of the year's most anticipated publications came in May, when MAPS released results of its MAPP1 Phase 3 trial investigating MDMA-assisted therapy (MDMA-AT) in the treatment of PTSD.

The trial, which enrolled 90 participants, found that 88% of individuals who underwent MAPS' MDMA-AT

protocol experienced clinically meaningful reductions in PTSD symptoms. Perhaps even more remarkable was the fact that 67% of participants in the treatment arm no longer met the criteria for a PTSD diagnosis 2 months post-treatment, versus 32% of those in the placebo group.

In a view shared by many, MAPS' Founder Rick Doblin characterised these results as "outstanding." So remarkable, in fact, that Science magazine shortlisted the nonprofit's work for its 2021 Breakthrough of the Year, dubbing MDMA-AT "a psychedelic PTSD remedy".

In terms of safety, there were no serious adverse events in the MDMA group. Rather, the two serious adverse events recorded were both in the placebo group. Non-serious adverse events, meanwhile, occurred to a greater extent in the placebo group than the MDMA group.

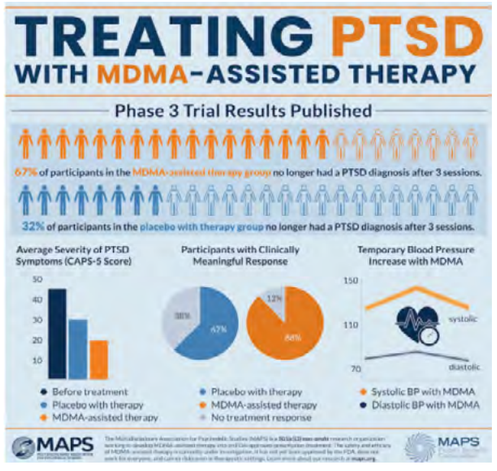
The study received a great deal of mainstream media attention, including a major write-up in the New York Times: A Psychedelic Drug Passes a Big Test for PTSD Treatment. Other write-ups include those from the BBC, TIME, Fast Company, and a second piece from the New York Times.

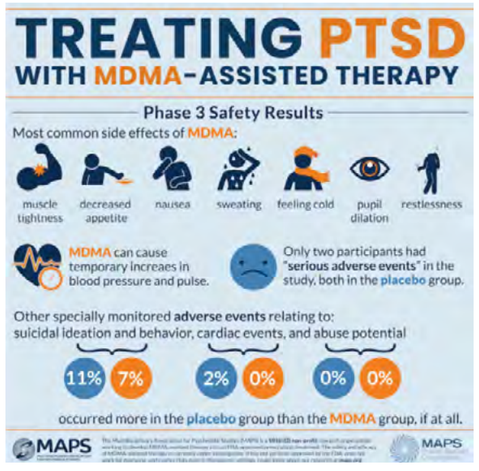
This is about as excited as I can get about a clinical trial," said Gül Dölen, a neuroscientist at Johns Hopkins University School of Medicine, who was not involved in the research. "There is nothing like this in clinical trial results for a neuropsychiatric disease."

It's been no small feat to get this far, Rick Doblin reminded Psilocybin Alpha. "MAPS trained over 800 therapists [in 2021]," he explained. "We still need to supervise each new therapist as they work with their first PTSD patient, and we still need to arrange for those therapists who want to volunteer to receive MDMA themselves in a therapeutic setting as part of their training."

There's plenty of work ahead, too. In our Looking Ahead to a Psychedelic 2022 section, we discuss the next steps in MAPS' path to approval with Doblin himself.

**The Verdict:** Our Pharmaceutical Advisor Michael Haichin summed up these results succinctly: "Both the efficacy and safety results are pretty astounding. Now, MAPS will hope to reproduce these results in its second Phase 3, before presenting data to the FDA for a potential approval of MDMA-AT as early as 2023.




Some important findings in the publication can be found below:

**There is no obvious impact of past SSRI usage.**
Importantly, the study found that there was "no obvious impact of SSRI history on the effectiveness of MDMA." This is a reassuring finding, especially in the context of a study published in 2020 that suggested past antidepressant usage reduces the efficacy of MDMA-assisted psychotherapy for PTSD. It's not clear why we see a discrepancy between these findings, but we may expect deeper analysis following MAPS' second Phase 3 trial. We discuss studies published in 2021 that further elaborate the potential interactions between SSRIs and psychedelics below.

**Diversity and Representation.**
As a field, we still have a significant amount of work to do in terms of representation in clinical trials of psychedelics. Just 2 participants in this trial were black or African American, representing just over 2% of the sample size. For context, according to the US Census Bureau around 12.4% of the U.S. population is black or African American.

A significant body of literature (e.g., Roberts et al., 2010) shows that lifetime prevalence of PTSD is higher in minority groups than Whites, but that minority groups are less likely to seek treatment. While, like many clinical trials, MAPS' study falls short of representing society in an equitable manner, it is hoped that MAPS will be in a position to deliver MDMA-Assisted Therapy to a diverse range of individuals, should it be approved. MAPS is prioritising this in their second Phase 3 trial, and in their therapist training efforts. Comments from MAPS PBC at Horizons 2021 reinforced the fact that this is high on their agenda.

**Overnight Stay vs. Evening Discharge.**
The study also found that whether or not a participant had an overnight stay following treatment had no effect on the success of the protocol. This was achieved by allowing participants at two study sites to be discharged in the evening, as opposed to being kept at the site overnight.

Haichin points out that the ability to eliminate the overnight stay from the treatment protocol would have a significant impact on cost-effectiveness. However, he also points out that 10/14 participants that requested further integrative visits were in the MDMA arm, indicating that the amount of psychotherapy in the current model may be insufficient for some.

**The Blinding Problem.**
As with most, if not all, psychedelic studies, the elephant in the room is the ability of the researchers to adequately prevent participants from guessing what treatment they received, and potentially influencing the results (more in this later, where we discuss a number of methodological stumbling blocks that were further highlighted in 2021).

Previous MDMA research used low-dose MDMA instead of an inactive placebo in the comparator group, which improved blinding but made participants' PTSD worse. Since the use of low-dose MDMA made it easier to find a treatment difference (and would be unethical to give), MAPS decided—in partnership with the FDA—that an inactive placebo group was more appropriate for both Phase III trials.

"However, although blinding was not formally assessed during the study, when participants were contacted to be informed of their treatment assignment at the time of study unblinding it became apparent that at least 10% had inaccurately guessed their treatment arm. Although anecdotal, at least 7 of 44 participants in the placebo group (15.9%) inaccurately believed that they received MDMA, and at least 2 of 4 participants in the MDMA group (4.3%) inaccurately believed that they had received placebo."

In other words, almost 90% of participants guessed whether they received MDMA-assisted psychotherapy or not. Because of this, critics will say the trial is essentially open-label, where the given treatment is known and treatment effects tend to be overestimated.

## 2.4 – PSILOCYBIN THERAPY FOR TREATMENT-RESISTANT DEPRESSION: COMPASS PATHWAYS' PHASE IIB RESULTS


In June, COMPASS Pathways announced that it had finished administering psilocybin therapy to all patients enrolled in its Phase 2b clinical trial. The company had been investigating the safety and efficacy of psilocybin therapy for treatment-resistant depression (TRD) since March 2019. The study, which enrolled over 200 patients, was the largest clinical trial for psilocybin therapy in history.

The population targeted by this psychedelic intervention are those with treatment-resistant depression (TRD). These individuals, of which there are thought to be at least 100 million worldwide, have failed to respond to at least two existing antidepressant treatments.

In anticipation of the results we published a Special Issue, 2b, or not to be? Preparing for COMPASS Pathways' Data Readout, in which we explored the significance of the forthcoming results and aimed to provide a primer on their interpretation.

Not a week later, while we were attending Microdose's Wonderland conference in Miami, the company published topline results from the study on November 9th.

The results of the trial were generally positive, finding that a 25 mg dose of the company's synthetic psilocybin (COMP360), alongside 'psychological support', produces a statistically significant and clinically relevant reduction in depression symptom severity.

Summarising the findings, COMPASS CEO George Goldsmith said, "a high dose of psilocybin works immediately, the day after, for a large number of people, and continues to work."

This appears borne out in the topline data, which showed that at least twice the number of patients in the 25 mg group demonstrated response to the therapy and remission from their treatment-resistant depression at weeks 3 and 12 compared with the 1 mg group.

However, many expressed concern about the serious adverse events reported in the study, which involved 12 patients and were more common in the 25 mg COMP360 group than in the 10 mg or 1 mg arms.

Goldsmith suggested that some of the most concerning adverse events were among non-responders, who were perhaps despairing at the therapy's inability to help them (especially in the context of such hype and promise). On this topic, readers may find Tehseen Noorani's piece on The Pollan Effect of interest. It's also worth remembering that TRD sufferers are a very vulnerable group of people, with suicidal ideation, for example, not uncommon.

In this trial, COMPASS Pathways attempted to standardise their psilocybin-assisted therapy protocol as far as possible across its trial sites and individuals: a significant undertaking given the heterogeneity of psychedelic-assisted therapies.

Overcoming the incongruities between the idiosyncratic psychedelic-assisted therapy modality and the objectivity and standardisation demanded by the clinical trial regime is certainly no small feat. In fact, it was a significant contributor to the downfall of psychedelic research in the first place (see Oram, 2014; Bonson, 2017; or, Hall, 2021 for a broader overview).



For much deeper analysis on these results, including contextualisation of the serious adverse events and efficacy data, read our Special Issue: Deconstructing COMPASS Pathways' Phase 2b Results (>3,000 words).

READ OUR SPECIAL ISSUE HERE

Upon publication of the results, COMPASS' stock price took a tumble and dragged much of the sector down with it. CMPS had been climbing since October, closing in on $50 for the first time since February.

How might we explain this: a rational reaction to the publication of topline results, or a buy the rumour, sell the news moment? Remember, many psychedelics stocks are characterised by an unusually high level of retail investor ownership compared to other small-cap biotech companies, which may explain some of the apparent irrationality.

**The Verdict:** This Phase 2b trial is the largest randomised controlled double-blind trial of psilocybin in the world, enrolling 233 patients across North America and Europe. Despite concern surrounding adverse events, some of which were serious, COMPASS' psilocybin-assisted therapy protocol appears to be effective in a significant proportion of participants, with at least twice the number of patients in the high-dose (25 mg) group entering remission from treatment-resistant depression at weeks 3 and 12 versus the main comparator group (1 mg). When considering these results, it's worth remembering that the population targeted in this trial are treatment-resistant. COMPASS will now meet with the FDA to discuss the design of its Phase 3 trial.

## 2.5 – MICRODOSING: LITTLE DOSES, LITTLE EVIDENCE?

Anecdotal evidence has suggested that even sub-perceptual doses of psychedelics can produce a number of therapeutic or wellbeing-enhancing benefits. From general wellness benefits, to improved creativity and attention, microdosing psychedelics has garnered a substantial amount of public attention.

These positive reports have led to high expectations and hopes that clinical evidence might one day legitimise the practice in the eyes of regulators and practitioners. To this end, many researchers have been evaluating the practice.

**Here's what their efforts taught us about microdosing in 2021...**

### IMPERIAL COLLEGE LONDON RESEARCHERS FIND ANECDOTAL BENEFITS OF MICRODOSING "CAN BE EXPLAINED BY THE PLACEBO EFFECT"


In March, a group of researchers at Imperial College London published the largest placebo-controlled trial on psychedelics to date, which used an innovative citizen science approach to explore microdosing. The researchers concluded that the "anecdotal benefits of microdosing can be explained by the placebo effect."

The research design was certainly interesting: 191 participants were asked to incorporate placebo

control into their microdosing routine. However, it's important to note that this was not supervised: instead, the study was self-blinded with participants instructed to place placebo and active capsules into envelopes with QR codes, before drawing the envelopes at random.

While this study is, of course, not comparable in rigour to a randomised controlled trial (RCT), the authors claim that their novel self-blinding approach allows them to reach the following conclusion:

> "...Our study validates the positive anecdotal reports about the psychological benefits of microdosing (significant improvements from baseline in a broad range of psychological measures); however, our results also suggest that these improvements are not due to the pharmacological action of microdosing, but are rather explained by the placebo effect (lack of significant between-groups differences)."

The study was covered broadly in the media: the Guardian; FT; Science; Wired; Forbes; and others. It also encouraged a great deal of conversation and debate within the psychedelics community, especially from those who claim to have found, or witnessed, benefits from the practice.

## STUDY FINDS CORRELATION BETWEEN MICRODOSERS AND LOWER LEVELS OF ANXIETY AND DEPRESSION

**ADULTS WHO MICRODOSE PSYCHEDELICS REPORT HEALTH RELATED MOTIVATIONS...**
Rootman, J et al. (2021)

Later in the year, in November, a microdosing study published in Scientific Reports caused a stir among microdosing advocates and skeptics alike.

The publication, titled Adults who microdose psychedelics report health related motivations and lower levels of anxiety and depression compared to non-microdosers, was co-authored by a mix of researchers at the University of British Columbia and those with other affiliations, including mycologist and microdosing advocate Paul Stamets.

The observational study found that:

> "those who [microdose] appear to be slightly less symptomatic of depression and anxiety than their peers who report similar mental health concerns but do not microdose..."

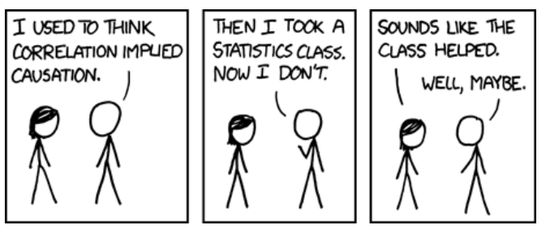
The study also sought to understand the motivations of microdosers, with health and wellness-related motives proving to be the most prominent.

Interestingly, and perhaps frustratingly, the paper was reported with headlines such as:

**New study finds 'microdosing' psychedelics can be effective in treating anxiety, depression**

UBCO study finds psychedelic microdosing improves mental health
Psychedelics used to combat anxiety and depression, not to get high

But, this reporting implies that causality was identified through the study: i.e., that the practice of microdosing causes, or leads to, lower levels of anxiety and depression. However, this was neither what the observational study sought to, or did, demonstrate.




Source: Big Data Made Simple.

Perhaps the most important thing to note here is that identifying a correlation between microdosing and better mental health does not imply that microdosing has caused a better mental state.

A co-author of the study reiterated that the purpose of the study was not to establish causality, noting that it would not be possible via an observational approach.

There were other concerns surrounding this study, including the omission of any discussion around placebo or expectancy effects, which we would expect to see in this type of study.

Read our late November Bulletin for a more detailed exploration of the study. Also note that Paul Stamets, a co-author of the paper, announced that a second microdosing study is due to be published in 2022.

## PREPRINT STUDY SUGGESTS "EXPECTATION EFFECTS UNDERLIE AT LEAST SOME OF THE ANECDOTAL BENEFITS" OF MICRODOSING

**MICROEVIDENCE FOR MICRODOSING WITH PSILOCYBIN (PREPRINT)**
Cavanna, F et al. (2021)

A preprint of a study by Cavanna et al. published in December delivered another blow to microdosing. Researchers recruited 34 individuals who planned to microdose with psilocybin mushrooms and employed a double-blind placebo-controlled design to investigate the effects of microdosing on subjective experience, behaviour, creativity, perception, cognition and brain activity.

While the researchers found that reported acute effects were significantly more intense among microdosers than those consuming placebo (which, the researchers note, could be explained by unblinding), for other measurements the group observed trends toward cognitive impairment, reductions in certain brain activity, or null results.

The researchers conclude:

> "Our findings support the possibility that expectation effects underlie at least some of the anecdotal benefits attributed to microdosing with psilocybin mushrooms."

## STUDY FINDS MICRODOSING PSILOCYBIN DID NOT AFFECT ANXIETY OR DEPRESSION COMPARED WITH PLACEBO

**PSILOCYBIN MICRODOSING DOES NOT AFFECT EMOTION-RELATED SYMPTOM AND PROCESSING**
Marschall, J et al. (2021)

Another double-blind placebo-controlled microdosing study emerged in December, which sought to investigate whether microdosing psilocybin across the space of three weeks modulated emotion processing, altered interoceptive awareness, and reduced symptoms of anxiety and depression.

The researchers ultimately found that "psilocybin microdosing did not affect emotion processing or symptoms of anxiety and depression compared with placebo." However, the researchers were stymied by the fact that most participants had tried psychedelics previously, and many easily broke the blinding. As has been recommended for many psychedelics studies, research in a substance-naive population may be more fruitful

## BEYOND THE 'BENEFITS': POTENTIAL RISKS ASSOCIATED WITH MICRODOSING

Speaking to Psilocybin Alpha, Dr. Kelan Thomas (Associate Professor of Clinical Sciences at Touro University California College of Pharmacy and Board Certified Psychiatric Pharmacist) noted:

> "While psychedelic macrodoses have consistently demonstrated benefits for mental health in clinical trials, the current evidence available from double-blind randomized placebo-controlled microdosing trials show minimal positive benefit beyond the placebo response, suggesting that anecdotal reports of microdosing efficacy may be due to positive expectation effects. Pharmacology and toxicology researchers have also expressed concern over the potential risk of long-term chronic LSD and psilocybin microdosing to cause valvular heart disease due to 5-HT2B receptor binding affinity."
>
> - Dr. Kelan Thomas

Thomas has prominently sounded alarm around the potential dangers of microdosing, including in a presentation titled "Safety First: Microdosing's Possible Benefits and Potential Risks," and in a pair of articles on Chacruna Chronicles.

It's also worth noting that several FDA-approved medications that are agonists of the 5-HT2B receptor, such as fenfluramine/phentermine ('fen-phen'), have been withdrawn due to the risk of valvular heart disease. However, there is a dearth of longitudinal research on microdosing, and the doses involved are (unsurprisingly) small, so no firm conclusions can be drawn.

It's also worth noting that participants in microdosing studies thus far are generally healthy individuals. As such, some may argue that the likelihood of seeing an improvement in wellbeing is lower, due to a relatively high baseline.

So, we shouldn't write-off the possibility that microdosing may be beneficial to those diagnosed with depression or anxiety, for example, just yet.
It's also possible that we might see differences in the efficacy of microdosing across different molecules. Perhaps microdosing LSD will demonstrate a different safety and efficacy profile to, say, psilocybin. Companies like MindMed are certainly hoping this will be the case. The company is sponsoring trials of LSD microdosing, including via its recently announced study of low-dose LSD effects on sleep and cognitive measures.

**The Verdict:** This year, a number of studies have called the purported benefits of microdosing into question. We shouldn't write off microdosing entirely, though. Further research, especially that with a focus on participants with clinical diagnoses of mental health disorders, may still be fruitful.



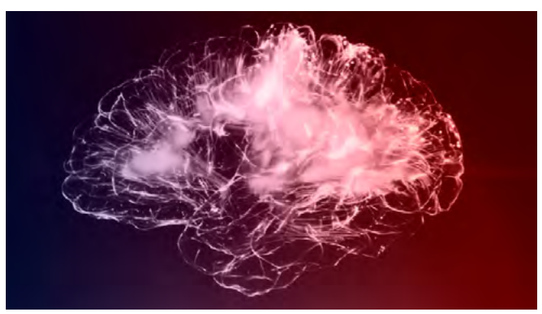
## 2.6 – PSYCHEDELICS INDUCE NEUROPLASTICITY AND NEUROGENESIS?

Recent foundational scientific research has brought investigators closer to understanding how psychedelics might elicit their purported therapeutic effects.

While the full pharmacological profiles of drugs like psilocybin, LSD, and DMT are not yet fully understood, the past year saw many important breakthroughs that have helped push that understanding forward. Recent discoveries appear to add support to the theory that much of the therapeutic potential of psychedelics can be attributed to their ability to elicit structural and functional changes in the brain via mechanisms like neuroplasticity and neurogenesis.

Should psychedelics act as a catalyst for neuroplasticity and neurogenesis, these compounds may prove to be viable treatments for disorders beyond those falling within the realm of mental health, such as neurodegenerative disorders.

In 2021's most popular study on psychedelics and neuroplasticity (according to Altmetrics; see more studies ranked by attention later in this section), researchers from Yale set out to understand what effects psilocybin had on structural plasticity in vivo, how quickly these changes might occur, how enduring the effects may be, and whether the drug's hallucinatory effects are related to structural remodelling.



Commenting on the group's approach, co-author Dr. Alex Kwan, Associate Professor of Psychiatry at Yale School of Medicine, told Psilocybin Alpha:

> "Although there have been hints of psilocybin promoting neural plasticity, we were able to visualize and track the plasticity over many days in a live brain for the first time. The approach is powerful, and opens up new ways to screen compounds, by looking at how they directly affect neural circuits."
>
> - Dr. Alex Kwan

Through their innovative efforts, the Yale researchers found that a single dose of psilocybin can quickly lead to structural changes in the medial frontal cortex of mice. Shao et al. demonstrated that the administration of psilocybin resulted in the increased growth and formation of dendritic spines. Evidence suggested that a number of these new spines lasted long enough to develop into functional synapses, some of which were found to persist 34 days after administration. Together, their results added to the growing body of research that points towards neuroplasticity as an impetus for many of the therapeutic benefits psychedelics are believed to produce.

The researchers also attempted to shed light on the relationship between hallucinatory effects and neuroplasticity. To achieve this, they administered ketanserin, a serotonin 5-HT2A receptor antagonist, before administering psilocybin. The researchers found that psilocybin continued to elicit some of its neuroplastic effects, despite a roughly 30% reduction in available 5-HT2A receptors (the primary receptor on which psilocybin acts to generate hallucinogenic effects) in the mice treated with ketanserin. While these results seem to suggest that neuroplasticity might not depend on psilocybin's hallucinatory effects, Shao et al. maintained that due to the differences between humans and mice, further studies will be needed to evaluate this relationship in humans. Nonetheless, their discoveries add to an exciting conversation around psilocybin's therapeutic mechanisms.

Studies being conducted by researchers and companies alike continue to contribute to our understanding of the relationship between psychedelics, neuroplasticity, and derived therapeutic benefits. Recent results from an in vitro preclinical trial by Algernon Pharmaceuticals (which, it should be noted, are neither published nor peer-reviewed) suggested that even a sub-perceptual (non-hallucinogenic) dose of N, N-Dimethyltryptamine (DMT) could result in a rapid growth of neural connections in the brain. The company hopes to one day leverage these effects to treat patients recovering from the neurodegenerative impacts of strokes.

Another 2021 study found that the in vivo administration of the non-hallucinogenic (according to animal studies) ibogaine analogue tabernanthalog led to dendritic spine formation as well. This work is being commercialised by Delix Therapeutics in partnership with the National Institute on Drug Abuse (NIDA).

So what might some of the implications of these findings be? As the researchers iterated, these neural modifying effects may help explain some of psilocybin's purported antidepressant benefits. Like others in the field, including Delix Therapeutics' David Olson, Kwan sees the promotion of neural plasticity as a key mechanism of action behind psychedelics' apparent therapeutic effects.

> "We are now seeing hundreds, if not thousands, of novel psychedelic-like compounds. For me, a key question is how to screen them and prioritize the most promising candidates for human studies? I believe neural plasticity is key, and a step towards identifying changes in the brain that are unique to psychedelics and that drive the beneficial actions."
>
> - Dr. Alex Kwan

A number of popular 2021 publications have proposed that psychedelics could one day be used as treatments for Alzheimer's and brain injuries (perhaps working via other mechanisms beyond neuroplasticity: see Szabó et al., 2021, for example). Should the emerging evidence continue to support the theory of psychedelic-induced neuroplasticity in humans, these compounds may be applied to a much broader range of psychiatric and neurodegenerative treatment indications.

**The Verdict:** Researchers are still attempting to prove out the underlying mechanisms of psychedelics' apparent therapeutic effects, and have made significant headway in 2021. The promotion of neuroplasticity and neurogenesis continues to be a popular thesis, which gained further evidence through a number of impressive studies this year. If true, this could explain the apparent transdiagnostic efficacy of psychedelics, and broaden its potential clinical applications.

**Selected psychedelics and neuroplasticity & neurogenesis publications from 2021:**

- Psilocybin induces rapid and persistent growth of dendritic spines in frontal cortex in vivo
- DMT Increases Growth of Rat Neurons by 40 Percent, New Data Shows (Algernon)
- An analog of psychedelics restores functional neural circuits disrupted by unpredictable stress
- A Single Dose of Psilocybin Increases Synaptic Density and Decreases 5-HT2A Receptor Density in the Pig Brain
- Psychedelics and Neuroplasticity: A Systematic Review Unraveling the Biological Underpinnings of Psychedelics
- Therapies to Restore Consciousness in Patients with Severe Brain Injuries: A Gap Analysis and Future Directions
- From Psychiatry to Neurology: Psychedelics as Prospective Therapeutics for Neurodegenerative Disorders

## 2.7 – FURTHER CLARITY ON INTERACTIONS BETWEEN SSRIS AND PSILOCYBIN

Given that many of the populations targeted by psychedelic-assisted therapies are attempting to find relief via other pharmacological agents, such as SSRI antidepressants, it's important that we understand the interaction between these common drugs and psychedelics.

Beyond avoiding potential issues with safety or reduced efficacy, deepening our understanding of drug interactions of this kind may help increase the accessibility of psychedelic-assisted therapies. If it's found that SSRIs and psychedelics do not generate adverse effects when co-administered, this could allow psychedelic-assisted therapies to be provided as an adjunct therapy as opposed to a monotherapy. This wouldn't require participants in the therapy to taper off SSRIs, which can be a daunting and tumultuous process for those who have been chronically taking antidepressants.

It's not surprising, then, that for-profit companies are keen to produce such data.

In December, COMPASS Pathways shared unpublished results of a single-arm open label study of 19 patients taking SSRI antidepressants alongside its COMP360 psilocybin therapy. The company found that a single 25 mg dose of COMP360 resulted in comparable treatment outcomes to patients in the company's Phase 2b trial (mentioned above), in which patients were required to taper off their SSRIs. These findings will likely inform the company's Phase 3 trial design, for which it is set to meet with the FDA in the new year with an eye to commencing the trial in Q3 2022.

MindMed, via its collaboration with the Liechti Lab, also published results from an SSRI and psilocybin interaction study. The research also appears to refute received wisdom that chronic administration of serotonergic antidepressants (such as SSRIs) dampen the subjective effects of psychedelics (e.g. Bonson and Murphy, 1996, in the case of LSD).

The MindMed sponsored study pretreated participants with the SSRI escitalopram for 14 days (7 days at a 10 mg dose, followed by 7 days at a 20 mg dose), or placebo pretreatment, and then administered 25 mg of psilocybin.

The study found that pretreatment with escitalopram had "no relevant effect on positive mood effects of psilocybin but significantly reduced bad drug effects, anxiety, adverse cardiovascular effects, and other adverse effects of psilocybin compared with placebo pretreatment."

But, is a 14 day stepped pretreatment representative of real-world SSRI usage? The Psychedelic Pharmacists Association asked, "Is 14 days of pretreatment sufficient to draw conclusions about the need for antidepressant tapering and cessation before psilocybin administration?"

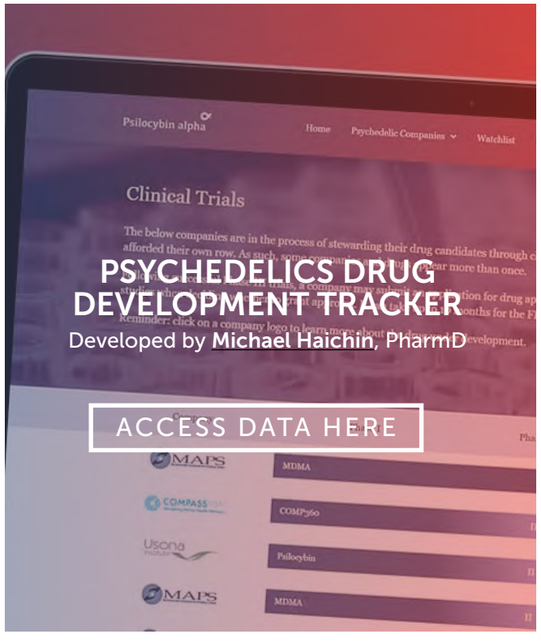
The authors of the study noted this limitation themselves, explaining that, "escitalopram pretreatment lasted only 14 days, which may have been too short to produce more chronic neuroadaptations and changes in receptor expression that can alter the response to psilocybin."

**The Verdict:** If the co-administration of SSRI antidepressants and psychedelics is found to be safe and effective, it would be a boon for psychedelics companies. This would reduce the barrier to entry for patients who (along with their healthcare providers) may be hesitant to wean themselves off SSRIs, and would take psychedelic-assisted therapies from monotherapies to adjunct therapies, greatly expanding their markets. It's not surprising, then, that companies are sponsoring research to try and demonstrate such safety and efficacy. But, these studies are far from conclusive due to limitations that include their small size and short pre-treatment periods. As is often the case: further research is needed.

## 2.8 – APPRECIATING METHODOLOGICAL ISSUES

Throughout the course of recapping some of these central studies of 2021, it should have become apparent that psychedelic research is fraught with methodological challenges. Some of these are inherent to the broader field of psychotherapy and pharmacology, but others are unique to psychedelics. These include outsized expectancy effects (due, in part, to increasing 'hype') and, perhaps most obviously, the difficulty (impossibility?) of designing a genuinely placebo-controlled trial, given that it's pretty obvious to most people if they're having a 'trip'.

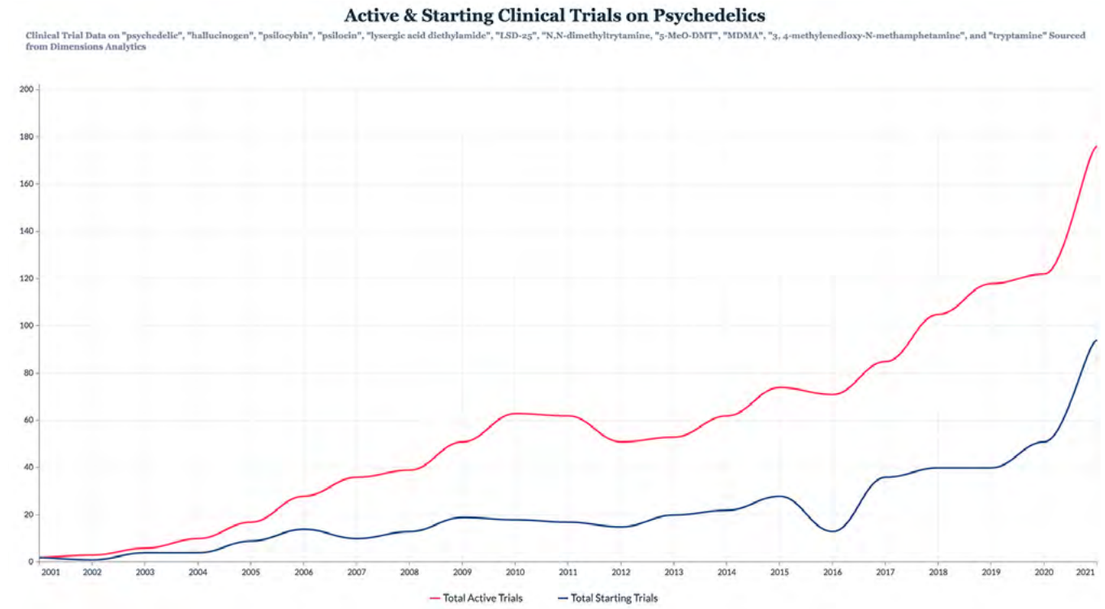
Those interested in reading more about these methodological issues will likely enjoy a recent preprint publication by Aday et al., which provides recommendations for improving the methodological rigor of psychedelic clinical trials.

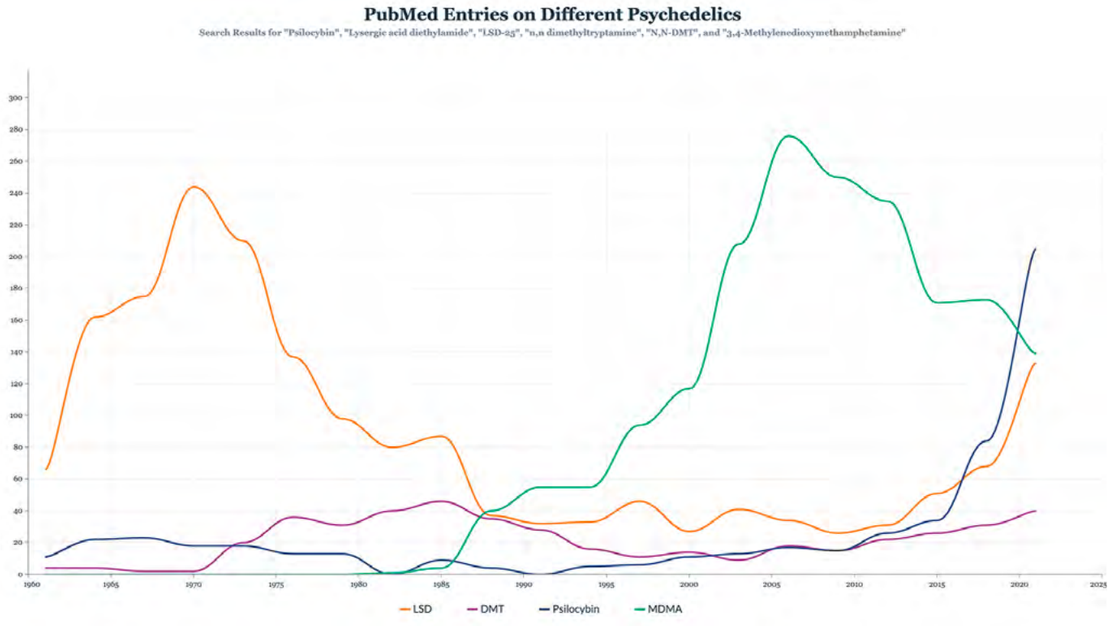



## 2.9 – NEWLY APPROVED & ANNOUNCED STUDIES

As interest continued to grow throughout 2021, investigations into the effects, mechanisms, and therapeutic potential of psychedelics proliferated. Companies at various stages of development announced the approval and initiation of dozens of new trials studying psychedelics for an increasingly wide range of treatment indications, and investigators at academic institutions and research centres across the globe helped push the number of ongoing investigations to new heights. Researchers are working diligently to bolster and challenge our current understanding of psychedelic science.

Over the next few pages you will find a sample of sponsor or investigator led trials that were announced, approved, or initiated in 2021.



## COMPANY-SPONSORED TRIALS THAT WERE APPROVED OR BEGAN IN 2021

**TRYP Initiates a Phase 2 Trial of Psilocybin for Binge Eating Disorder** [December 23, 2021]

In October of 2021, TRYP Therapeutics announced that the FDA had placed a clinical hold on its Phase 2 trial of psilocybin in the treatment of binge eating disorder. The company subsequently amended its IND application with the FDA. On December 23, TRYP announced that it had received notice from the FDA that the clinical hold had been lifted. The study will evaluate both the safety and feasibility of treating patients diagnosed with binge eating disorder using psilocybin. [NCT05035927]

**MindMed Initiates a Phase 2a Proof-of-Concept Trial of LSD for ADHD** [December 17, 2021]

On December 17, 2021, MindMedicine announced that it had begun enrollment for a Phase 2a trial evaluating repeated low doses of LSD as a treatment for ADHD. The company will collaborate with both Maastricht University and the University Hospital at Basel. Through the study, researchers will gather information on changes in ADHD symptoms, dosing regime, therapeutic mechanisms, and other effects of low doses of LSD.

**TRYP Receives FDA Approval for a Phase 2a Trial of Psilocybin for Fibromyalgia** [December 6, 2021]

In December of 2021, TRYP Therapeutics announced that it had received FDA approval to study its TRP-8802 psilocybin candidates as a potential treatment for fibromyalgia. The trial, which is slated to begin in 2022, will evaluate whether or not psilocybin-assisted psychotherapy can help treat chronic pain symptoms in patients diagnosed with fibromyalgia. [NCT05128162]


**Cybin and the University of Washington Initiate a Phase 2 Trial of Psilocybin for COVID-Related Distress** [December 1, 2021]

On November 30, 2021, Cybin announced that the FDA had authorized advancement of an investigator-initiated Phase 2 trial studying psilocybin-assisted psychotherapy in the treatment of frontline clinicians suffering from COVID-related distress. The co-funded trial will occur at the University of Washington in Seattle. Investigators will use Cybin's EMBARK model of psychedelic-assisted psychotherapy to inform its use in future company-sponsored trials. [NCT05163496]

**DemeRx (atai) Initiated Part 1 of a Phase 1/2a Trial of DMX-1002 for OUD** [September 21, 2021]

On September 21, 2021, atai life Sciences announced that its platform company DemeRx had dosed its first patients in the first part of a Phase 1/2a trial investigating DMX-1002 (ibogaine) as a treatment for opioid withdrawal syndrome. The company announced that this Phase 1 part of the trial will evaluate the safety, tolerability, pharmacokinetics, and efficacy of its DMX-1002 oral ibogaine formulation. [NCT05029401]

**Small Pharma Initiates Part 2 of a Phase 1/2 Trial of DMT for MDD** [September 21, 2021]

On September 21, 2021, Small Pharma announced that it had completed the first phase of its Phase 1/2a clinical trial studying SPL026 (DMT) as a treatment for major depressive disorder (MDD). The company subsequently initiated the second Phase 2a proof-of-concept segment of the trial to assess the efficacy, safety, and tolerability of its intravenous DMT drug candidate in conjunction with psychotherapy. [NCT04673383]

**COMPASS Pathways Announces a Phase 2 Trial of Psilocybin for PTSD** [November 3, 2021]

On November 3, 2021, COMPASS Pathways announced a new Phase 2 trial investigating COMP360 psilocybin therapy as a potential treatment for PTSD. The company intends to enroll 20 patients to assess the safety, tolerability, and efficacy of its psilocybin therapy protocol. This announcement followed the completion of the company's flagship Phase 2b trial of psilocybin therapy for treatment-resistant depression (TRD).

**Mydecine Announces a Phase 2/3 Trial of MYCO-001 for Smoking Cessation** [September 7, 2021]

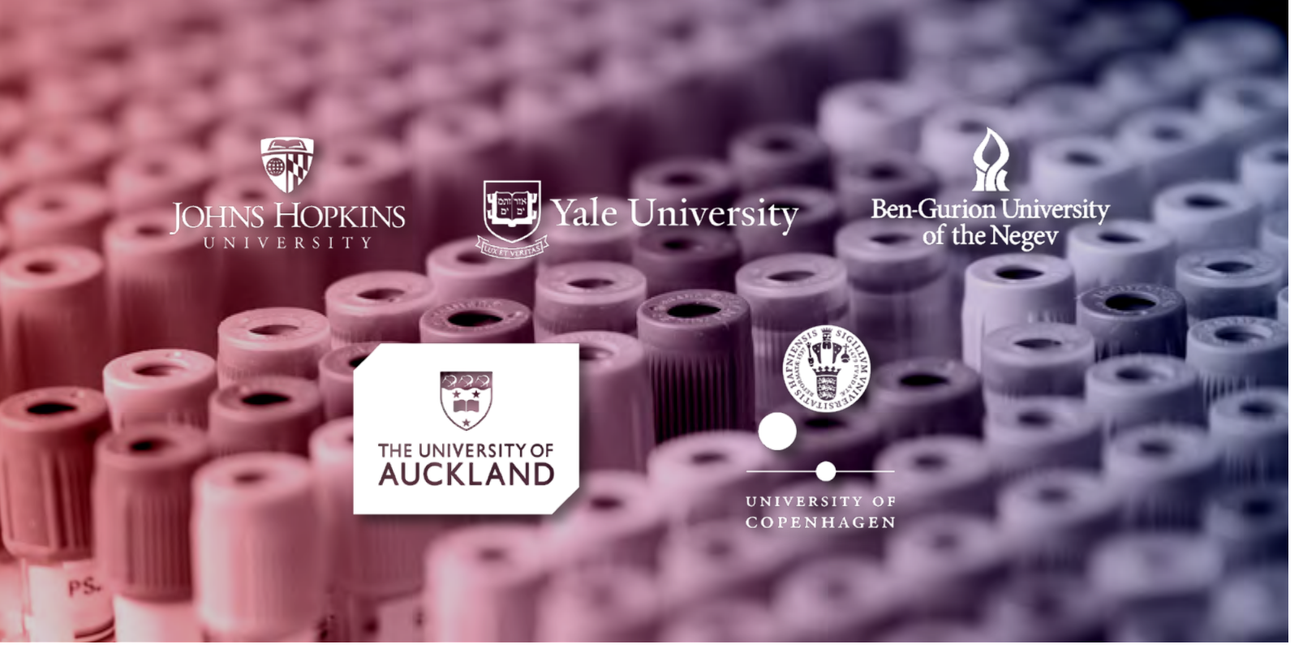
On September 7, 2021, Mydecine announced its intent to initiate a new Phase 2/3 studying its MYCO-001 psilocybin drug candidates for nicotine dependence. The company will collaborate on the trial with Johns Hopkins researcher Dr. Matthew Johnson. Through the study, researchers will assess the efficacy of using MYCO-001 in conjunction with a smoking cessation treatment program to treat nicotine dependent patients.

**Braxia Initiates a Phase 2 Trial of Psilocybin for TRD** [August 27, 2021]

In August of 2021, Braxia Scientific announced the initiation of a Phase 2 trial studying psilocybin for treatment-resistant depression (TRD). Braxia will collaborate on the study with the Usona Institute to assess the safety, feasibility, and efficacy of varying doses of psilocybin in patients diagnosed with treatment-resistant depression. [NCT05029466]

**Beckley Psytech Initiates a Phase 1b of Psilocybin for SUNHA** [September 14, 2021]

On September 14, 2021, Beckley Psytech announced that it had begun dosing patients in its previously approved Phase 1b trial of low-dose psilocybin for Short-lasting Unilateral Neuralgiform Headache Attacks (SUNHA). The trial will investigate the safety, tolerability, and efficacy of different ascending doses of psilocybin in patients diagnosed with SUNHA. [NCT04905121]




## INVESTIGATOR-INITIATED TRIALS THAT WERE APPROVED OR BEGAN IN 2021

**Trial of LSD Microdosing for Creativity and Brain Activity at the University of Auckland**

This randomised controlled trial will study the effects of LSD microdosing on healthy adult males. The study will assess the effects that LSD microdosing has on a number of personality and creativity measures. Researchers will also measure brain activity before and after the administration of LSD. [ACTRN12621000436875]

**Phase II Trial of Psilocybin for Co-occurring MDD and AUD at Johns Hopkins University**

This double blind, placebo controlled study will evaluate the therapeutic effects of psilocybin in patients suffering from both major depressive disorder (MDD) and alcohol use disorder (AUD). Primary measures include reductions in depressive symptoms and amount of alcohol consumption. [NCT04620759]

**Phase I Trial of Psilocybin for Headache Disorders at Yale University**

This Phase I trial will study repeated dosing of psilocybin as a potential treatment for migraines. The trial will recruit 24 participants who will receive varying dose combinations of psilocybin and placebo. Primary measures in the trial include migraine frequency, intensity, and duration. [NCT04218539]

**Phase I/II Trial of Psilocybin for Severe OCD at Beer-Sheva Mental Health Center**

This open label, Phase I study will evaluate the safety, efficacy, and feasibility of psilocybin-assisted psychotherapy for the treatment of severe obsessive compulsive-disorder (OCD). 15 patients suffering from OCD who had failed at least one prior treatment will be enrolled. [NCT04882839]

**Phase II Trial of Psilocybin for AUD at Copenhagen University Hospital Rigshospitalet**

This trial, sponsored by Anders Fink-Jensen, MD, DMSci, will evaluate safety of using psilocybin in patients suffering from alcohol use disorder (AUD). Secondary measures will focus on feasibility, pharmacokinetics, several subjective effects, and changes in alcohol cravings, self-efficacy, and mindfulness. [NCT04718792]



## 2.10 – AN INCREASINGLY WARM REGULATORY ENVIRONMENT FOR PSYCHEDELIC RESEARCH

Following a near half-century nadir in psychedelic research, the field is booming. This is helped, in part, by an increasingly warm regulatory environment: from federal funding and increases in production quotas for research purposes, right through to further fast-track designations and research partnerships with federal agencies.

Below, we highlight some of the key signals of bureaucratic amenability toward psychedelic research.

### DEA INCREASES PSYCHEDELICS PRODUCTION QUOTAS

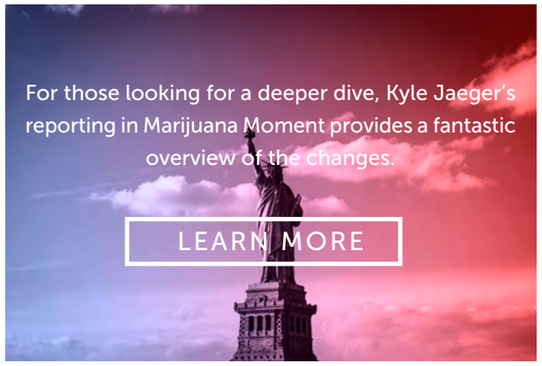
The U.S. Drug Enforcement Administration (DEA) sets annual quotas for the legal production of controlled substances for research purposes, including psychedelics like psilocybin, DMT and MDMA.

The federal agency has increased these quotas—both intra-year quotas for 2021, and for the current year, 2022—multiple times in the latter half of 2021, with drugs like psilocybin seeing enormous boosts to production levels.

In an early September 2021 bulletin we reported on the DEA's proposal to significantly increase the production quota for research psilocybin for 2021. Then, in mid-October, we covered the Administration's proposal to greatly increase psychedelic production quotas for the present year, 2022.

Take psilocybin, for example. In its earlier proposed increases to the 2021 quotas, the DEA expressed plans to increase psilocybin production to 1,500 grams (1.5 kg), which represented a fifty-fold increase from the 30 g federal quota. On Monday 15th November, a notice published in the Federal Register revealed that the agency has boosted this in-year quota increase yet again, with the final adjusted aggregate production quotas allowing for 6,000 grams (6 kg) of psilocybin and 3,500 grams (3 kg) of psilocin to be produced in 2021. In December, that number was increased even further to 8,000 grams (8 kg).

**The Verdict:** Supply of scheduled substances has been a bottleneck for researchers in many fields, not least psychedelics. Moves by the DEA, which governs the production quotas of scheduled substances for research in the U.S., to increase the availability of psychedelics for research purposes are a positive development that should reduce friction.



## BIDEN-HARRIS ADMINISTRATION RECOMMENDS REDUCING BARRIERS TO RESEARCH FOR SCHEDULE I SUBSTANCES

In a press release published in September the White House explained that Regina LaBelle, Acting Director of National Drug Control Policy, presented to Congress the Biden-Harris Administration's recommendations that primarily related to reducing the supply and availability of illicitly manufactured fentanyl-related substances (FRS).

However, if one looks beyond recommendations related to FRS, the piece explains the Administration's ambition to "establish a simplified process that would align research registration for all Schedule I substances [...] more closely with the research registration process for Schedule II substances."

The press release goes on to explain that, "the Biden-Harris Administration strongly supports expanding the research of Schedule I substances to help advance evidence-based public policy."

Given that psychedelics are Schedule I substances in the United States, these recommendations to Congress could make research into psychedelics such as psilocybin and DMT more straightforward than at present, especially when combined with DEA quota increases.

**The Verdict:** This is another positive signal from the highest echelon of the U.S. government for researchers and companies looking to explore the potential therapeutic applications of Schedule I substances.


## FEDERAL GRANT AWARDED TO JOHNS HOPKINS RESEARCHERS TO STUDY PSILOCYBIN FOR SMOKING CESSATION

In September 2021, prominent psychedelic researcher Matthew W. Johnson announced (via Twitter) that he has received a grant from the National Institute on Drug Abuse (NIDA) to study psilocybin for the treatment of tobacco addiction.

According to Johnson, this is the first grant from the U.S. Government dedicated to investigating the therapeutic effects of a classic psychedelic in over a half-century, marking a "new era in legitimacy" for psychedelic science.

We spoke to Sandeep Nayak, Post-Doctoral Research Fellow at Johns Hopkins' Center for Psychedelic & Consciousness Research, about this development.

"It's hard to overstate the importance of federal funding for psychedelic research," Nayak noted. Commenting on the changing research funding landscape, he went on to add that, "this is a huge step towards normalizing this line of work which has been mostly funded by philanthropy and now nascent drug companies."

Beyond the grant itself, which amounts to nearly $4m, this government funding "legitimizes the research and makes it much more feasible for researchers to build careers working on psychedelics," Nayak added, noting that, "it's also a clear sign of how much public opinion has shifted."

The Johns Hopkins researcher, who is working alongside Matthew W. Johnson on this research, believes this isn't the last we will see of government funding for psychedelic research: "This funding is significant on its own, but I anticipate it will be the first of many." Finally, he noted that this trend is not limited to the U.S., "there are now government funded psychedelic trials in Germany and Canada, and likely we'll see this expand greatly in coming years." As we mentioned in our first Year in Review section, the Australian government carved out $15m for psychedelic research, which is supporting seven trials.

**The Verdict:** This is a watershed moment for psychedelics research, representing the first grant from the U.S. government in over half a century to investigate the therapeutic potential of a classic psychedelic. As Dr. Johnson himself said, this is a "new era in legitimacy" for psychedelic science, and we should expect governments across the world to follow (or, continue following) suit.

## NATIONAL INSTITUTE ON DRUG ABUSE PARTNERS WITH PSYCHEDELICS COMPANIES

Two psychedelic drug developers, Delix Therapeutics and CaaMTech, are among a growing crop of companies to score cooperative R&D agreements with U.S. federal agencies.

In the case of CaaMTech, the company has entered into a Cooperative Research and Development Agreement (CRADA) with the Designer Drug Research Unit (DDRU) at the National Institute on Drug Abuse (NIDA) Intramural Research Program (IRP). That's a lot of jargon, but the company told Psilocybin Alpha that the purpose of this agreement is to screen CaaMTech's library of tryptamine compounds using a number of in vitro and in vivo assays.

According to a CaaMTech spokesperson, "previous work in this area has been frustrated by a lack of access to pure, well-characterized compounds." As such, the aim of the CaaMTech-DDRU collaboration is to "supply much-needed data about the fundamental biological activity of tryptamine compounds, making it possible to develop safer and more effective next-generation psychedelic drugs."

In December, Boston-based Delix Therapeutics announced its own partnership with NIDA. Research will be conducted under NIDA's Addiction Treatment Discovery Program (ATDP), which works to screen promising therapies that may be more effective than the standard of care for substance use disorders.

Delix's non-hallucinogenic (in animal models) drug candidates, such as DLX-7, appear to reduce alcohol- and heroin-seeking behaviour in preclinical studies. The company will hope to have these findings validated through further study, with initial data from NIDA's research on the candidate expected in early 2022.

**The Verdict:** Delix has gained a great deal of attention in 2021, and enters 2022 with the goal of proving out the potential of its 'non-hallucinogenic' compounds in the treatment of conditions including substance use disorders. CaaMTech, meanwhile, has taken a stealthier approach, and appears to have been filing patents prolifically. The fact that both companies have struck partnerships with the National Institute on Drug Abuse (NIDA) once again demonstrates the increasing openness to, and interest in, psychedelic research by national agencies.

## DMT THERAPY RECEIVES FAST-TRACK DESIGNATION IN UK

In October, London-based Small Pharma announced that it had been granted a fast-track designation from a UK regulator for its DMT lead candidate. The UK Medicines and Healthcare products Regulatory Agency (MHRA)–the country's equivalent of the FDA–granted Small Pharma's SPL026 candidate an Innovation Passport Designation via a relatively new Innovative Licensing and Access Pathway (ILAP) program.

In a similar manner to the FDA's fast-track designation, the ILAP aims to accelerate time to market and facilitate patient access to emerging novel treatments. The ILAP connects other key stakeholders in the drug development and roll-out process, including the country's National Health Service (NHS) and the National Institute for Health and Care Excellence (NICE). The program was touted as a way to encourage the development of innovative medicines in the UK post-Brexit.

Psilocybin Alpha understands that Small Pharma's DMT candidate is the first psychedelic to receive this designation since they began being issued in Spring 2021.

Speaking to Psilocybin Alpha, Small Pharma's Chief Medical and Scientific Officer Dr. Carol Routledge explained that the designation allowed for the company to receive "specialist advice throughout the drug development process," and that the Innovation Passport "has the potential to enable a speedier, more efficient development process for SPL026," the company's lead candidate.

SLP026, the company's DMT-assisted therapy, entered clinical trials for major depressive disorder (MDD) at the start of this year, with topline results expected H1 2022.

Investors seemed optimistic, too, with the company's share price jumping c.60% on the news after months of steady decline. This was short-lived, however, with the stock price slowly bleeding toward pre-news levels.

**The Verdict:** As the UK seeks to make its mark in a post-Brexit milieu, becoming a haven for drug development has become a clear priority, with the ILAP program (which approximates the FDA's Fast Track Designation) representing a cornerstone of this new strategy. The fact that Small Pharma's DMT candidate has been one of the first recipients of such a designation is a positive signal of UK regulators' evidence-based approach to catalysing drug development: a good sign for all psychedelic research and trials taking place in the UK, not just Small Pharma's.

# 2.11 – NEW PSYCHEDELICS RESEARCH CENTRES

2021 saw the number of prestigious institutions with psychedelic research centres continue to swell. Below are just a few of the new centres launched this past year...

## NIKEAN FOUNDATION PROVIDES $5M TO LAUNCH CENTRE FOR PSYCHEDELIC PSYCHOTHERAPY IN TORONTO

In September, we helped break the news of the launch of the Psychedelic Psychotherapy Research Centre at Toronto's University Health Network.

A $5m donation from the Nikean Foundation, founded in 2019 by Canadian tech entrepreneur Sanjay Singhal, provides founding capital for the new centre.

Linda Medeiros, Director of Operations at Nikean Foundation, told Psilocybin Alpha that the creation of this centre "was a giant leap forward in Canadian history." Medeiros went on to say, "the partnership with the University Health Network validated the need for systemic change in mental healthcare and the urgent need for new tools to meet unmet therapeutic needs."

Importantly, Nikean supports those organisations conducting research in accordance with an Open Science approach rooted in principles of cooperation and accessibility. This is in contrast to the operating principles of many for-profit actors, especially in drug discovery and development, who tend to focus on confidentiality and defensibility (through various forms of IP, for example).

Medeiros was keen to highlight this point, telling us that, "as we emerge into this psychedelic renaissance, it is crucial that we promote collaboration and Open Science methods to move this field forward together for the greater good of humanity."

**The Verdict:** This centre will likely constitute a new hub for psychedelics research in Toronto, which is already home to a number of psychedelics researchers, companies and investment funds. Nikean Foundation's commitment to collaboration, codified in Open Science methods, is also of interest.


## HARVARD LAW SCHOOL'S PETRIE-FLOM CENTRE LAUNCHES RESEARCH INITIATIVE ON PSYCHEDELICS AND THE LAW

In June, the Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics at Harvard Law School announced a new research initiative that will promote safety, innovation, equity and access in psychedelics research, commerce, and therapeutics.

The Project on Psychedelics Law and Regulation, or POPLAR, is the first academic initiative offering a clear focus on psychedelics law, regulation and ethics.

In our coverage of the launch we spoke to Mason Marks, Senior Fellow at the Center and Project Lead of POPLAR.

Beyond legislative measures, the debate around intellectual property in the psychedelics space is set to be a "major focus" of POPLAR, which will "analyze the role of biopiracy in psychedelics commercialization and the ethics, validity, and social utility of patents on psychedelics related inventions," Marks explained.

**The Verdict:** The launch of the POPLAR research initiative marks the first academic initiative with a specific focus on the legal, regulatory and ethical contexts of psychedelics, and the present renaissance. It also looks set to further increase the salience of debates around intellectual property in the space.

## UNIVERSITY OF WISCONSIN MADISON LAUNCHES PSYCHOACTIVE RESEARCH CENTRE AND MASTER'S PROGRAM

This year, the University of Wisconsin Madison approved a new Transdisciplinary Center for Research in Psychoactive Substances, and launched the first psychedelic master's program in psychoactive pharmaceutical investigation, which is led by Dr. Cody Wenthur.


We spoke to the Director of the Center, Dr. Paul Hutson, who explained that the Center will expand its current portfolio of translational and Phase I, II, and III clinical research into psychedelics, as well as "embracing members from across the UW Madison campus" from a variety of disciplines including, "historians, anthropologists, and ethnobotanists, as well as the expected biomedical scientists and clinicians."

According to Hutson, the Master's program was well subscribed in the Fall of 2021, "and anticipates expansion in the coming years that will include internships in many of the new global psychedelic pharmaceutical companies.

**The Verdict:** This new centre hosts what was widely touted as 'the first psychedelic master's program,' which appears to already have become a popular offering.

**The Broader Verdict:** What started as a small crop of research centres at prestigious universities such as Imperial College London and Johns Hopkins has turned into a global trend, with tens of new institutions joining the fray this year. What's interesting is the increasingly interdisciplinary nature of these centres and their research programs. While the earlier centres have a core focus on scientific and clinical research, the new crop of psychedelics research centres are focusing on other facets of the field: from law to journalism.

## 2.12 – TOP PUBLICATIONS BY ATTENTION

Hungry for more? We pulled the top 15 articles of the year, according to Altmetric. We covered some of these above, but not all...

**1.** Trial of Psilocybin Versus Escitalopram for Depression
(Altmetric Score: 2,875) [April 15, 2021]

**2.** A 'Trip' to the ICU: Intravenous Injection of Psilocybin
(Altmetric Score: 2,554) [January 1, 2021]
See our Pharmaceutical Advisor Michael Haichin's Viral Tweet On This Subject

**3.** MDMA-Assisted Therapy for Severe PTSD: A Phase 3 Study
(Altmetric Score: 2,216) [May 10, 2021]

**4.** How Ecstasy and Psilocybin Are Shaking Up Psychiatry
(Altmetric Score: 1,721) [January 27, 2021]

**5.** Psilocybin Induces Rapid and Persistent Growth of Dendritic Spines in Frontal Cortex In Vivo
(Altmetric Score: 964) [April 15, 2021]

**6.** Self-Blinding Citizen Science to Explore Psychedelic Microdosing
(Altmetric Score: 729) [April 15, 2021]

**7.** Racial Justice Requires Ending the War On Drugs
(Altmetric Score: 666) [January 7, 2021]

**8.** Psychedelic-Inspired Drug Discovery Using An Engineered Biosensor
(Altmetric Score: 551) [May 13, 2021]

**9.** Ketamine for the Treatment of Mental Health and Substance Use Disorders: Comprehensive Systematic Review
(Altmetric Score: 400) [December 23, 2021]

**10.** Adults Who Microdose Psychedelics Report Health Related Motivations and Lower Levels of Anxiety and Depression Compared to Non-Microdosers
(Altmetric Score: 389) [November 18, 2021]

**11.** Lysergic Acid Diethylamide (LSD) Promotes Social Behaviour Through mTORC1 In the Excitatory Neurotransmission
(Altmetric Score: 387) [February 2, 2021]

**12.** Acute Effects of Psilocybin After Escitalopram or Placebo Pretreatments In A Randomized, Double-Blind, Placebo-Controlled, Crossover Study in Health Subjects
(Altmetric Score: 384) [November 7, 2021]

**13.** Psychedelic Therapy: A Roadmap for Wider Acceptance and Utilization
(Altmetric Score: 348) [October 4, 2021]

**14.** First Study of Safety and Tolerability of MDMA-Assisted Psychotherapy In Patients With Alcohol Use Disorder
(Altmetric Score: 342) [February 18, 2021]

**15.** Psychedelics and Other Psychoplastogens for Treating Mental Illness
(Altmetric Score: 340) [October 4, 2021]

SECTION
**THREE**

# PSYCHEDELIC COMPANY HIGHLIGHTS IN 2021

3

## 3.1 – FOREWORD

If public company valuations are anything to go by, it's been a difficult year for the psychedelics sector. Many companies in the space have seen their share prices slashed, with ETFs like PSYK down over 50% since inception.

But, a focus on public companies (of which there are now around fifty) and their share prices alone obscures a great deal of successes that have occurred in 2021 for psychedelics companies: from promising data readouts to significant private financing rounds.

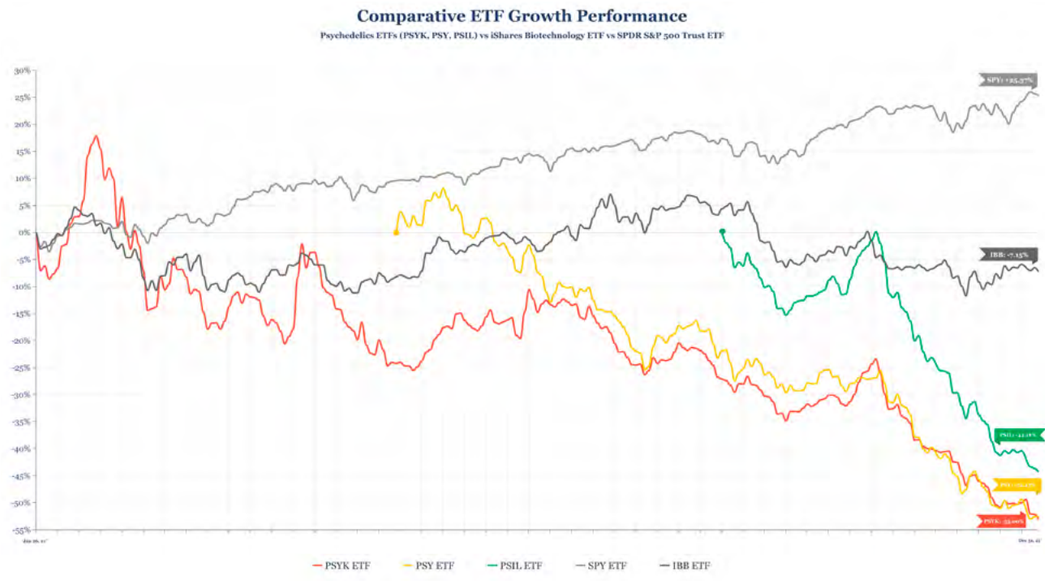
**Here are some of the year's most notable financings and public markets moments...**

## 3.2 – A BASKET OF PSYCHEDELICS: NEW PSYCHEDELICS-FOCUSED ETFS

The past year saw the creation of three ETFs focused on tracking the performance of companies operating in the psychedelics space.

On January 26, Horizons launched the world's first psychedelic-focused ETF in Canada under the ticker symbol PSYK. Subsequently, Defiance would move to establish its US-listed PSY ETF to track companies operating in the psychedelic, cannabis, and ketamine spaces. Finally, in September AdvisorShares established its US-listed actively managed PSIL ETF.

Representative of the psychedelics market in general these ETFs have performed poorly this year, underperforming the broader stock market significantly, and seeing greater downside than the biotech sector.




## 3.3 – OVERVIEW OF CAPITAL FLOWS INTO THE SECTOR

According to our data, which tracks around 100 of the leading public and private psychedelics companies, nearly $2 billion was invested in the psychedelics sector in 2021 across more than 60 financing events.

This remarkable volume of capital continued to disproportionately accrue to companies engaging in drug discovery and development, with atai Life Sciences' Series D ($157m) and GH Research's Series B ($125m) representing the sheer scale of financings in this segment of the value chain.

However, we are seeing investment in other areas of the emergent psychedelics value chain begin to tick upward, with digital therapeutics and adjunct technologies of increasing interest to investors (e.g., MINDCURE's $23m bought deal; Osmind's $15m Series A).


## 3.4 – CAPITAL ALLOCATION AND COMPANY TRENDS

### INCREASINGLY CROWDED DRUG DEVELOPMENT PIPELINES: CERTAIN MOLECULES ATTRACT MORE CAPITAL THAN OTHERS

At the molecular level, it's clear that certain psychedelics are attracting more funding than others. Investment in companies developing 5-MeO-DMT was strong in 2021, with the Irish company GH Research securing a $125m Series B in April. The round was led by two U.S.-based pharmaceutical investment firms: RA Capital and RTW Investments. The company has kept its cards close to its chest, but we know that its three drug candidates are all 5-MeO-DMT based.

In August, UK-based Beckley Psytech announced the closing of its own Series B, bringing in c.$80m to accelerate its drug development pipeline. 5-MeO-DMT features again, with the company hoping to harness it in the treatment of undisclosed neuropsychiatric indications.

Take a look at our Psychedelics Drug Development Tracker to see other molecules and indications that are receiving outsized attention from drug developers.

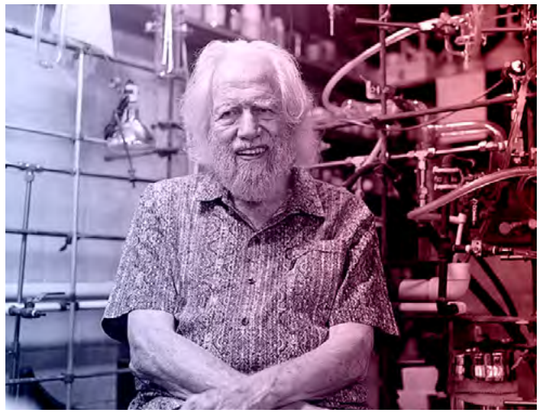
We're also seeing a clear trend in the move beyond 'known' psychedelics, and toward a plethora of analogs, derivatives, and new chemical entities. These include the so-called 'non-hallucinogenic psychedelics,' which are discussed in more detail later in this section.

## COLLABORATIONS WITH NATIONAL INSTITUTES BOOST INVESTOR CONFIDENCE

As we mentioned in our Psychedelic Research and Clinical Trials in 2021 section, the National Institute on Drug Abuse (NIDA) has partnered with a number of psychedelics companies. NIDA has also hosted virtual events showcasing research into psychedelics, further demonstrating its interest and active involvement in the space.

Two such companies were Delix Therapeutics and CaaMTech, both of which closed significant rounds in 2021. The former closed a $70m Series A, while the latter raised $22m via its own Series A.

Are such collaborations with National Institutes fueling investor confidence in psychedelics companies?



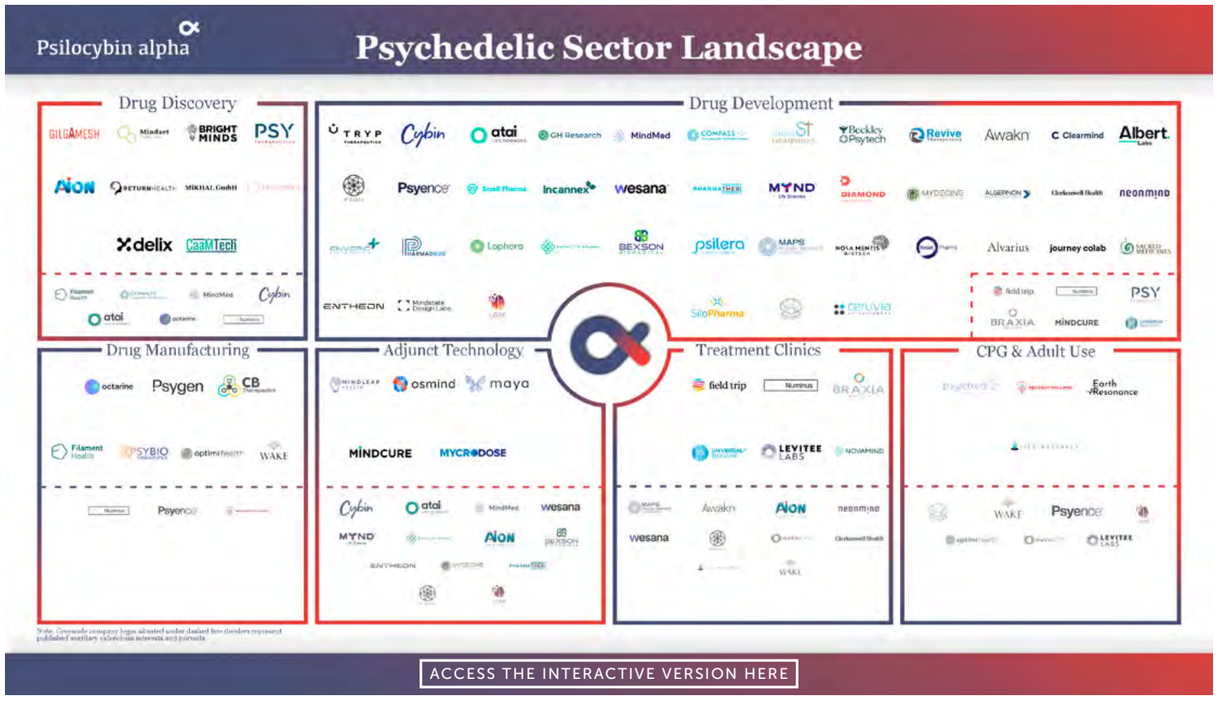
## EMERGING FROM THE PSYCHEDELIC 'UNDERGROUND'

As the 'psychedelic renaissance' reaches a fever pitch, many individuals and organisations who have been involved in psychedelics for a long time are now considering whether, or how, to benefit from this recent influx of interest and investment. Despite some hesitancy, a number of groups from what may be characterised as the psychedelic 'underground' have now forayed into the commercial side of today's psychedelics space.

The Alexander Shulgin Research Institute (ASRI) is a fine example of this trend. The Institute was founded, albeit informally, by legendary chemist and psychedelics enthusiast Alexander ("Sasha") Shulgin in the 1980s.

Shulgin was known for his hands-on research methodology, which involved self-experimentation with psychoactives, after which he tested them with small groups of friends. Two years after publishing PiHKAL (now canonical, alongside TiHKAL) the DEA raided Shulgin's lab and forced him to give up his licence. A DEA spokesperson characterised the tomes as "pretty much cookbooks on how to make illegal drugs."

After Shulgin passed in 2014, his research colleagues Paul Daley and Nicholas Cozzi helmed the Institute, which has now synthesised and supplied compounds for psychedelics research across the globe. ASRI was formally incorporated in April 2021 by Shulgin's widow, Ann, and recently raised a $6.95m Seed Round to continue its work in developing the legacy of Sasha's work.




## GROWTH OF DIGITAL THERAPEUTICS, DELIVERY TECHNOLOGIES & DRUG DISCOVERY TECH

Innovative technologies have become an increasingly interwoven element of drug development and treatment delivery more broadly. Over the course of 2021, many companies operating in the psychedelic space took steps to incorporate and leverage new technological tools with a wide range of scientific and therapeutic applications.

These tools aren't just on the patient-facing side. In 2021, companies committed substantial resources to the acquisition and development of technologies to support novel drug discovery efforts, for example. Supported by AI-powered drug discovery platforms, drug developers in the space are creating catalogues of novel derivatives and analogues based on many classical psychedelic compounds and therapeutic targets.

While companies such as Mydecine announced (further explained in a buzzword-heavy press release) new technology-driven drug discovery programs in 2021, others such as Enveric, CaaMTech, and Delix continued to leverage existing discovery technologies to identify the next generation of psychedelic compounds

**Drug Discovery Technology-Related Press Releases from 2021:**

- atai Life Sciences Partners With CB Therapeutics to Launch TryptageniX (December 9, 2021)
- Mydecine Unveils AI Drug Discovery Program (June 16, 2021)
- MindMed Partners With MindShift AG (February 11, 2021)

In 2021, many drug developers began investigating new drug delivery technologies that might one day be paired with approved psychedelic drugs. The use of different drug delivery technologies is expected to allow companies to overcome many challenges related to drug bioavailability, time to onset of effects, drug metabolism, duration of effects, and more.

Companies are looking to leverage, among others, nasal, intravenous, sublingual, subcutaneous, and oral drug delivery technologies for a variety of psychedelic candidates. A 2021 collaboration between MindMedicine and Nextage, for example, will see the two companies focusing on delivering ibogaine derivatives using a brain targeting liposome technology.

**Drug Delivery Technology-Related Press Releases from 2021:**

- Mycrodse Therapeutics & Nova Mentis Sign Collaborate to Advance Drug Delivery System (October 19, 2021)
- Bexson Biomedical Launches New Subcutaneous Delivery Technology Program for Psychedelics (August 12, 2021)
- atai Life Sciences Launches InnarisBio (July 28, 2021)
- MindMed Collaborates With Nextage Therapeutics (May 24, 2021)
- BetterLife Files Patent for Novel Subcutaneous Implant (April 29, 2021)
- Cybin Signs Drug Development Agreement With Catalent (March 22, 2021)
- IntelGenx Announces Strategic Partnership With atai Life Sciences (March 15, 2021)

The unique nature of psychedelic-assisted psychotherapy will foreseeably create a demand for assistive technologies that can support patient preparation, monitoring, treatment integration, and more.

As the first generation of drugs move closer to approvals, many companies have begun to develop new digital therapeutics platforms that will be used to support future psychedelic therapies. While some drug development companies intend to build new in-house digital technologies, others have acquired or partnered with technology-focused companies that are already creating digital therapeutics tailored for these emerging treatments.

**Digital Therapeutics-Related Press Releases from 2021:**

- atai Life Sciences Launches PsyProtix (November 11, 2021)
- MINDCURE Joins Digital Therapeutics Alliance (September 16, 2021)
- Cybin Announces Digital Therapeutics Strategy (July 13, 2021)
- Mydecine Announces Launch of Mindleap 2.0 (July 13, 2021)
- atai Life Sciences Acquires Majority Stake in Psyber (April 7, 2021)
- MindMed Acquires HealthMode (February 26, 2021)
- Cybin Partners with Kernel (January 11, 2021)

## EXPANDING NETWORKS OF TREATMENT CLINICS, THERAPIST TRAINING & PATIENT ACCESS

Over the course of 2021, for-profits and nonprofits alike were hard at work setting the foundation for the delivery of future psychedelic therapies. Many companies continued to create or expand networks of specialized clinics that may be used for psychedelic--assisted psychotherapies if and when approved.

To address the growing demand for therapists equipped to deliver these unique treatments, many new training programs for prospective therapists are proliferating across the world. Over the past year, we have also seen nonprofits such as TheraPsil continue to successfully advocate for greater patient access to psychedelics (read more in our Psychedelic Drug Policy Reform in 2021 section). These efforts are central for the realization of accessible and impactful psychedelic therapies.

**Here are some notable developments on this front from 2021:**

- TheraPsil Helps 47th Patient Access Psilocybin In Canada (December 13, 2021)
- Fluence Raises $1.6m to Meet Demands for Psychedelic Therapy Training (November 4, 2021)
- Cybin Launches EMBARK Psychedelic Facilitator Training Program (October 28, 2021)
- Field Trip Expands Clinic Network to Seattle, Vancouver, and Fredericton (October 19, 2021)
- Beckley Psytech & Fluence Partner to Created Psychedelic Therapy Training Program (April 20, 2021)
- TheraPsil Hosts Health Canada-Approved Experiential Psilocybin-Assisted Therapy Training Program (March 2, 2021)
- NYU Langone Launches Center for Psychedelic Medicine Dedicated to Research and Professional Medical Training (February 24, 2021)
- ATMA Journey Centers Opens Psychedelic Therapy Clinic in Calgary (February 16, 2021)

## A FOCUS ON RECIPROCITY AND PHILANTHROPY?

Throughout 2021 questions of ethics, reciprocity and philanthropy continued to be pointed at for-profit psychedelics companies, with many arguing that as a sector we should aspire to do better than the conventional biotech and pharmaceutical playbook.

A number of psychedelics companies and investors actioned this call, but whether or not these moves were tokenistic or genuine and substantial is up to the reader to decide.

**atai Life Sciences** announced the launch of atai Impact in October, which is "committed to advancing education, expanding access and supporting the wider ecosystem of mental health care." The program announced its first major initiative two months later, establishing a Fellowship Fund in Psychedelic Neuroscience with Massachusetts General Hospital's Center for the Neuroscience of Psychedelics.

Other companies have sought to bake reciprocity and equity into their cap tables. **Panacea Plant Sciences**, for example, has reserved 32% of its equity for Indigenous Groups and related 401(c)3 organisations, with these preferred shares benefitting from a 10x dividend rate over common shares. This affords the aforementioned cohorts a potential source of revenue, as well as voting rights.

Other companies and funds have made similar commitments, such as **Woven Science** which is dedicating 10% of its equity to El Puente, "a foundation for access and benefit-sharing," and **Journey Colab** which dedicates 10% of its founding equity to the Journey Reciprocity Trust..

**Note: the above are just a selection of trends from 2021, it wouldn't be possible to catalogue them all here.**

# 3.5 – MORE COLLABORATION BETWEEN COMPANIES AND ACADEMIC INSTITUTIONS

Over the last year, we have seen a number of organisations engaging in collaborations, including company-company partnerships and academic partnerships. Here are some of 2021's most notable partnerships and collaborations.

## COMPANY - COMPANY PARTNERSHIPS & COLLABORATIONS

**atai Partners With CB Therapeutics to Launch TryptageniX (December 9, 2021)**
In December, atai announced that it had launched a new platform company focused on discovering and synthesising new drug candidates in partnership with CB Therapeutics. The platform, named TryptageniX, hopes to leverage bioprospecting for the discovery of novel compounds and biosynthesis as a means of production.

**COMPASS Pathways Acquires MiHKAL GmbH, a Portfolio of Novel Psychedelic Compounds (September 14, 2021)**
In September, COMPASS Pathways announced that it had entered into an agreement with Matthias Grill Ph.D. and MiHKAL GmbH to acquire MiHKAL's catalogue of purportedly novel psychedelic and empathogenic compounds. In addition to the IP acquisition, COMPASS and Matthias Grill will continue to work together in an effort to develop new psychedelic drug candidates..

**Clerkenwell Health and Octarine Bio Ink Partnership (September 8, 2021)**
In September, Clerkenwell Health, a contract research organisation (CRO), and Octarine Bio, a drug manufacturer, announced a partnership focused on delivering and supporting psychedelic clinical trials in Europe. The companies hope that this partnership will allow contracting investigators to conduct clinical trials with access to both a reliable supply of psilocybin (via Octarine's biosynthesis process) and specialised CRO resources.

## COMPANY - ACADEMIC PARTNERSHIPS & COLLABORATIONS

**Mydecine Signs Five-Year Research Collaboration Agreement With Johns Hopkins (August 18, 2021)**
In August of 2021, Mydecine announced that it had entered into a 5-year collaborative research agreement with Johns Hopkins. The research will initially focus on using psilocybin as a potential treatment for smoking cessation before expanding to other therapeutic areas. Mydecine subsequently announced a Phase 2/3 trial in partnership with Johns Hopkins researcher Dr. Matthew Johnson evaluating its MYCO-001 psilocybin candidate as a treatment for nicotine addiction.

**COMPASS Pathways Partners With King's College London & South London and Maudsley NHS Foundation Trust (SLaM) (July 5, 2021)**
In July of 2021, COMPASS Pathways announced that it had partnered with King's College London and SLaM to advance research on COMPASS's psychedelic therapies for treating indications such as post-traumatic stress disorder (PTSD) and anorexia nervosa. The partnership will also focus on training therapists to deliver psychedelic-assisted psychotherapies, integrate digital therapeutics, and developing "new models of care for mental health in the UK."

## COMPANY - COMPANY PARTNERSHIPS

Here are some other notable 2021 partnerships and collaboration between different psychedelic companies

**Revive Therapeutics & PharmaTher Sign Research Collaboration**
November 3, 2021 Press Release

**Nova Mentis & Mycrodose Therapeutics Partner to Co-Develop Drug Delivery System**
October 19, 2021 Press Release

**MindMed Joins Clinical Trial Transformation Initative**
October 13, 2021 Press Release

**MINDCURE Joins Digital Therapeutic Alliance**
September 16, 2021 Press Release

**Wesana Commits $1.5 Million to Exploring Viability of MAPS' MDMA-Assisted Therapy to Treat TBI**
September 14, 2021 Press Release

**Cybin Partners With Greenbrook TMS**
July 6, 2021 Press Release

**MindMed Joins Digital Medicine Society**
August 3, 2021 Press Release

**Beckley Psytech Parters With Fluence to Create Psychedelic Therapy Training Programme**
April 20, 2021 Press Release

**Otsuka Collaborates With Perception Neuroscience (atai) to Develop PCN-101**
March 16, 2021 Press Release

**Cybin Partners With Kernel to Leverage Its Neuroimaging Technology**
January 11, 2021 Press Release

## COMPANY - ACADEMIC PARTNERSHIPS

Here are some other notable 2021 partnerships and collaboration between companies and academic institutions

**CaaMTech Partners With the University of Wyoming to Study Psychedelics for Addiction**
November 16, 2021 Press Release

**Silo Pharma Enters Sponsored Research Agreement With Columbia University**
October 27, 2021 Press Release

**PharmaDrug Collaborates With Johns Hopkins on DMT Study**
August 25, 2021 Press Release

**TRYP Therapeutics Partners With the University of Michigan to Evaluate Psychedelic Formulations**
July 7, 2021 Press Release

**Wesana Partners With the University of South Carolina for TBI Research**
June 24, 2021 Press Release

**Silo Pharma Collaborates With UCSF On Psilocybin Research**
June 8, 2021 Press Release

**BetterLife Enters Research Agreement With Carleton University On Depression Studies**
March 8, 2021 Press Release

**Atai Collaborates With Massachusetts General Hospital to Study Psychedelic Mechanisms of Action**
January 26, 2021 Press Release


## 3.6 – YOUR FAVOURITE PSILOCYBIN ALPHA BULLETINS

We covered many of the above trends via our weekly Bulletins throughout 2021. Here's some of your favourite segments from our 2021 catalogue....

### DECONSTRUCTING COMPASS PATHWAYS' PHASE 2B RESULTS

This deep dive was, by a wide margin, our most popular Bulletin of the year. Following the publication of COMPASS Pathways' Phase 2b topline data, there was a great deal of confusion around their interpretation (we covered this in the preceding section).

Here, we sought to begin contextualising the preliminary safety and efficacy data from this influential trial, and ended by summarising the next steps for COMPASS.

### DISPATCH FROM HORIZONS: PERSPECTIVES ON PSYCHEDELICS

Horizons conference in New York City, which also featured a Business Forum, was an agora for healthy debate, discussion, and reflection. Following our return, we shared a summary of some of the key topics covered, which included: funding and business models for psychedelic ventures; legal and regulatory matters, including IP; accountability and ethics; the scale-up and roll-out of psychedelics; research and science; and much more.

### NO DATA PROTECTION IN CANADA FOR KETAMINE'S CHEMICAL COUSIN, ESKETAMINE (SPRAVATO)

In this Bulletin, we covered Canada's Federal Court of Appeals' decision to uphold a refusal to grant data protection for Janssen's Spravato (esketamine) product.

While this is, on the surface, a very 'in the weeds' topic, we used it as an opportunity to discuss enantiomers, cost-effectiveness, and data exclusivity more generally, as well as making some broad comments regarding implications for psychedelics companies.

### MINDMED INITIATES PHASE I TRIAL OF IV DMT

In late July we reported on MindMed's Phase I trial of intravenous DMT, using it as an opportunity to explore the other DMT drug development efforts that were underway at the time, notably Small Pharma's pipeline.

"As we have commented before, there is increasing competition across molecules, indications, and value chain segments. As such, we should expect to continue seeing smaller companies pivot accordingly."

**Pivot or perish will likely be a theme in 2022.**

### REMS PATENTS: THE NEXT FRONTIER IN THE PSYCHEDELICS PATENT SKIRMISH?

This deep dive on REMS Patents was one of our most technical (and speculative) pieces of the year, which presented an overview of Risk Evaluation and Mitigations Strategies (REMS) programs, the potential for elements of them to be patented, and the implications that both of these facts may have on psychedelics.

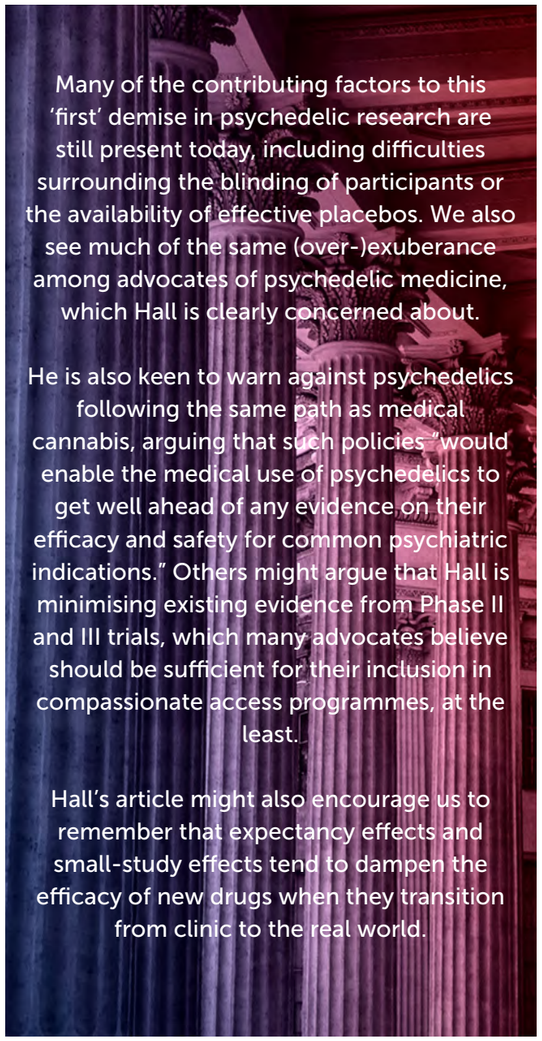
In short, we asked: "could the patenting of REMS programs be the next frontier in the apparent psychedelics IP skirmish?"

### WAS IT ALL LEARY'S FAULT? THALIDOMIDE, RCTS, SANDOZ AND 'THE END' OF PSYCHEDELIC RESEARCH

Here, we covered a journal article by Wayne Hall that complicated a common narrative: one which suggests the passage of the Controlled Substances Act (CSA) in 1970, and the resultant scheduling of psychedelics alongside heroin and cocaine, singularly marked the end of any meaningful clinical research into psychedelics.

Hall foregrounds a confluence of factors that contributed to the abandonment of psychedelic research in psychiatry, which may be parsed out into three (interrelated) strands: a tightening of controls on pharmaceutical research; the ascendant primacy of the Randomised Control Trial; and, Sandoz cutting the supply of psychedelics like LSD.

We ended by asking whether lessons from the past have been learned and assimilated into the psychedelic renaissance.



# 3.7 – MAJOR IPOS AND UPLISTINGS

We covered many of the above trends via our weekly Bulletins throughout 2021. Here's some of your favourite segments from our 2021 catalogue....

## MINDMED'S NASDAQ UPLISTING

In September 2020, then-CEO JR Rahn disclosed that the company had applied to uplist on the NASDAQ stock exchange. On April 23rd, 2021, following many months of anticipation, MindMed announced that its listing application had been approved.

On April 27th, the company's shares began trading on the NASDAQ under the ticker MNMD, with the company's share price reaching $6.97 before falling to $4.92 at close, up over 180% compared to just a few days prior.

MindMed's successful uplisting made it the second publicly-traded psychedelic drug developer to achieve this milestone.



## ATAI LIFE SCIENCES' IPO

On April 20th, 2021, after more than 2 years as a private company, atai set the stage for its eventual IPO with the filing of a preliminary prospectus.

The registration statement outlined the company's goal of raising $100 million through its initial public offering. The company's subsequent prospectus amendment would reveal a target valuation of roughly $2.3 billion.

On June 18th, 2021, the company began trading under the ticker "ATAI" and became the third psychedelic drug developer to list on the NASDAQ. atai's share price reached a high of $22.91 and closed out its first day of trading at $19.45, with the IPO raising roughly $231.6 million.

Many investors hoped that this high-profile IPO would buoy the broader sector, but this failed to be the case as most psychedelics traded lower throughout the month.

Note: We appeared on the Business Trip podcast to discuss atai's IPO in June 2021.

## FIELD TRIP UPLISTINGS

In 2021 Field Trip Health successfully uplisted to both a major Canadian and American exchange. Field Trip had previously traded on the Canadian Securities Exchange (CSE) since going public in October of 2020. In late May, the company announced that it had gained approval to list on the Toronto Stock Exchange (TSX). Field Trip would subsequently achieve its first uplisting milestone of the year at market-open on June 7, 2021.

A little over a month later, the company would announce that it had received conditional approval to graduate from the OTC markets onto the NASDAQ Global Select Market, listing on July 29th.


## CYBIN UPLISTING

Like many other companies in the sector, Cybin underwent an exchange uplisting of its own in 2021. However, unlike the companies before it, on July 22 Cybin announced that it had received conditional approval to uplist onto the New York Stock Exchange (NYSE) as opposed to the NASDAQ. As of market open on August 5, 2021, Cybin would become the first psychedelic-focused company to list on the NYSE.


## GH RESEARCH IPO

On April 20th, 2021, the Irish drug development company GH Research filed a draft registration statement confirming its intent to IPO. The company would subsequently announce the pricing of its estimated $160 million initial public offering, and on June 25th GH Research would begin trading on the NASDAQ.

The company's share price would climb to a high of $24.19 before settling at $19.25 by market close. GH Research announced that it had raised roughly $184 million through its IPO.

## 3.8 – PSYCHEDELIC COMPANIES INCLUDED IN MAJOR INDICES

As a result of some of the past year's high-profile IPOs and exchange graduations, many companies became eligible for inclusion in major indices.

NASDAQ and NEO-listed MindMed announced on March 19th, 2021, that the company had been included in both the FTSE Russell Global Micro-Cap and FTSE Total-Cap indices. On June 25th, 2021, MindMed would be included in the FTSE Russell 3000 index. At the same time, NASDAQ-listed Seelos Therapeutics announced that it had been included in the Russell 2000, Russell 3000, and Russell Microcap indices. In December 2021, both atai Life Sciences and COMPASS Pathways were selected to be included in the NASDAQ Biotechnology Index.

Institutions and investment managers often create index funds and ETFs that track the performance of major indices such as those previously mentioned. As a result, many prominent investment management corporations such as Blackrock's iShares and ProFunds Group's ProShares have since included atai, COMPASS, MindMed, and Seelos in various related funds.

## 3.9 – MAJOR PRIVATE FINANCINGS

A considerable amount of the capital that flowed into psychedelics companies last year did so via private financings. As a result, many of these companies have secured the capital needed to support and expand their drug discovery, development, and delivery efforts for the foreseeable future.

Below you can see a recap of some of 2021's most notable private financings...

**atai Life Sciences (now public) - $157m Series D**
- Apeiron Investment Group, Thiel Capital, Woodline Partners, [...]
- Development of drug candidate pipeline and enabling technologies

**GH Research (now public) - $125m Series B**
- RA Capital, RTW Investments, BVF Partners, [...]
- Clinical development of 5-MeO-DMT candidate for TRD, among others

**Beckley Psytech - $80m Series B**
- Integrated, Prime Movers Lab, Adage Capital Management, Palo Santo [...]
- Clinical development of low-dose psilocybin (SUNHA) 5-MeO-DMT (TRD & other undisclosed neuropsychiatric indications)

**Delix Therapeutics - $70m Series A**
- ARTIS Ventures, RA Capital Management, OMX Ventures, [...]
- Development of non-hallucinogenic psychoplastogens (see case study for more).

**Gilgamesh Pharmaceuticals - $27m Series A**
- Prime Movers Lab, Noetic Fund, Gron Ventures, [...]
- Development of new chemical entities

**CaaMTech - $22m Series A**
- Noetic Fund
- Advance compounds from its library into clinical trials

**Alexander Shulgin Research Institute (ASRI) - $7.2m Seed Round**
- Noetic Fund
- Seed financing to advance discovery and development efforts


## CASE STUDY: INVESTORS BACK DELIX THERAPEUTICS' ATTEMPT TO SKIP THE TRIP

Boston-based Delix Therapeutics closed a $70m Series A financing in September 2021, with the aim of advancing 'non-hallucinogenic' psychedelics.

The company's thesis, which is largely borne out of co-founder David Olson's research, hinges on the idea that many psychedelics promote neuroplasticity. Olson believes that these neuroplasticity-promoting properties (which we discussed in more detail in the previous section of this Review) may be isolated from psychedelic properties of a molecule, leaving a non-hallucinogenic 'psychoplastogen'.

Delix is not alone in seeking to develop non-hallucinogenic psychedelics. MindMed has a program around 18-MC, and appointed Bryan Roth to its Scientific Advisory Board in the same week that Delix announced their Series A. Roth's research focuses on engineering drugs that are, "maximally helpful to patients while minimizing discomfort in the treatment process," explaining that "not all patients are comfortable with their treatment program requiring hallucinatory trips."

If these researchers and companies are able to corroborate preclinical signals of efficacy in using non-hallucinogenic psychedelics to provide therapeutic benefits, the impact could be enormous. Imagine if a cheaper, non-hallucinogenic product approximates the benefit of a 'true' psychedelic-assisted therapy: surely payers would prefer it. And, surely it would be easier to scale, with a take-home drug representing significantly reduced labour intensity versus classic psychedelic-assisted therapy?

This potential is captured in the below table, which appears in a journal article co-authored by Olson.

| | Traditional Antidepressants | Ketamine and Psilocybin | Non-Hallucinogenic Psychoplastogens |
|---|---|---|---|
| Fast-Acting? | No | Yes | Yes* |
| Long-Lasting? | No | Yes | Yes* |
| Scalable? | Yes | No | Yes** |
| Cost-Effective? | Yes | No | Yes** |

It was certainly promising enough to convince the investors in Delix's Series A, which included ARTIS Ventures, RA Capital and OMX Ventures, a founding investor. It also earned the company a place in Fierce Biotech's 2021 Fierce 15 list.

But, the non-hallucinatory nature of these molecules, and their efficacy in treating a range of diseases, is yet to be borne out in human trials, and is situated within a much broader debate of whether the subjective effects of a psychedelic are necessary to derive therapeutic benefits. Indeed, not a single clinical trial has been conducted with non-hallucinogenic psychoplastogens as of today.

Yaden and Griffiths, for example, contend that "underlying neurobiological-based mechanisms are undoubtedly necessary but likely not sufficient to confer full beneficial effects." It also gets at a more philosophical question as to whether non-hallucinogenic psychedelics ignore the broader social or spiritual 'purpose' of psychedelics that at least some folks ascribe.


## CASE STUDY: VINE VENTURES CREATES SPV TO HELP FUND MAPS' FINAL PUSH TOWARD MDMA-AT APPROVAL AND ROLL-OUT

In December, Vine Ventures' Ryan Zurrer announced The Regenerative Financing Vine, a $70m Special Purpose Vehicle (SPV) that intends to fund patient access infrastructure and research for MAPS' MDMA-assisted therapy (MDMA-AT) for PTSD.

According to details released by MAPS and Vine Ventures (who have pledged a minimum of $13m to the SPV), this model "fully maintains both MAPS' nonprofit mission and governance and MAPS Public Benefit Corporation's (MAPS PBC) public benefit drug development and post-approval activities."

Thus far, MAPS' research has been funded via $130m in philanthropic donations over its 35-year history. This SPV represents a shift away from this donation--only approach, funding the next stretch of MAPS MDMA-AT for PTSD work via an investment vehicle.

Speaking to Lucid News, Doblin expressed feeling, "in some ways a sense of massive failure in that I hoped we would have this bridge to sustainability come through philanthropy." But, as more for-profit entities have entered the space – no doubt benefitting from and to some extent relying on the clinical, political and cultural work that MAPS has trailblazed in the field – many former -donors are now asking

**Details on the SPV**

- Target size: $70m.
- The SPV receives 6.1% of North America MDMA revenue for 7 years following initial drug sales.
- 'Reciprocity payment mechanism': after paying back the principal, the SPV returns 15% of the revenue share back to MAPS. After hitting a 3x payback, the SPV returns 50% of the revenue share back to MAPS.
- Vine will not take any carry or fees on the SPV.

themselves "Why should I donate? Let me just invest," explained Doblin.

Doblin's preference for donations over investment is, according to the founder, related to his broader plans to focus on "mass mental health." This might include providing MDMA-AT to places around the world where "there's a lot of trauma," and he worries that having to return money to investors might change decision-making around the loftier goals.
This is somewhat akin to project financing: i.e., investments are structured and appraised on the basis of projected future cash flows, as opposed to the current balance sheet of the project's sponsors. Investors do not gain equity in MAPS PBC, but rather a share of future revenues, as explained above. See McKinsey's New frontiers in pharma R&D investment (PDF) for more on these types of models.

This $70m represents a portion of MAPS' $150m fundraising target for the next three years. MAPS will hope to raise the remainder through non-investment means, such as via philanthropy but also partnerships and joint ventures.

**Recommended Reading**

Lucid News spoke with Doblin shortly after the announcement. Read the interview here, where Doblin shares his thoughts on the new funding model, some further specifics on the mechanisms baked-in to the SPV, the uses of the funds, and more.

## CASE STUDY: PSYMED VENTURES

We spoke to Matias Serebrinsky, one of the three founding partners of PsyMed Ventures. PsyMed began as a syndicate investing in psychedelics companies, and recently announced the launch of a $25m fund to support companies operating in psychedelic medicine, precision psychiatry, and neurotechnology.

Serebrinsky, along with co-founders Dina Burkitbayeva and Greg Kubin, will continue to operate their syndicate—which has around 750 members—alongside the new venture fund. "There are valuable synergies between both," Serebrinsky told Psilocybin Alpha.

Explaining the difference between the two vehicles, Serebrinsky noted:

"We first started the syndicate because it allowed therapists, psychiatrists, practitioners, mental health entrepreneurs, and anyone else that is an accredited investor who wanted to invest in expanding access to psychedelic medicine. We have 750 members, and the syndicate has allowed them to invest starting with $1,000 check sizes. It makes investing way more accessible.

From the fund, we invest in earlier-stage companies (pre-seed to Series A) since it can be difficult to raise large amounts ($250k+) for early-stage businesses through the syndicate. The fund allows for more nimble, faster decisions.

Going forward, we will also invest from the syndicate in follow ons (Series B to pre-IPO) from both the syndicate and our fund."

- Matias Serebrinsky

PsyMed launched its fund in November 2021 and has raised over $8m to date, aiming for a final close of the $25m fund in Q1 2022.

The trio have raised and deployed $6.5m through their syndicate, which has supported the following companies: atai Life Sciences, Beckley Psytech, Bexson Biomedical, Delix Therapeutics, Journey Clinical, Mindstate Design Labs, Reset Pharmaceuticals, Tactogen, Terran Biosciences, and TRIPP.

The fund has made investments in Delix Therapeutics and Freedom Bioscience.

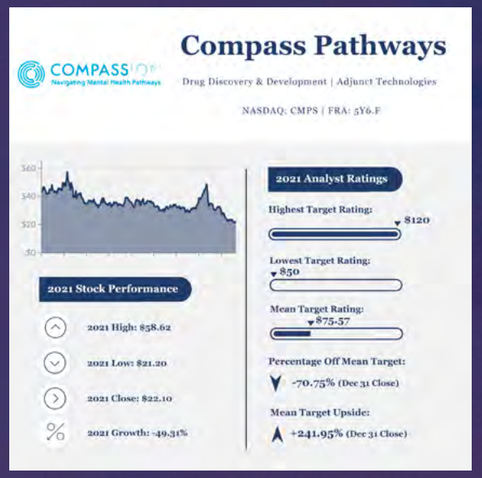
When we asked Serebrinsky about the types of psychedelics companies the trio are most interested in, he explained that, "there are venture-backable opportunities in every part of the ecosystem, it's all about the right team working on the right approach and business model," adding that, "the space is still in its very early stages."

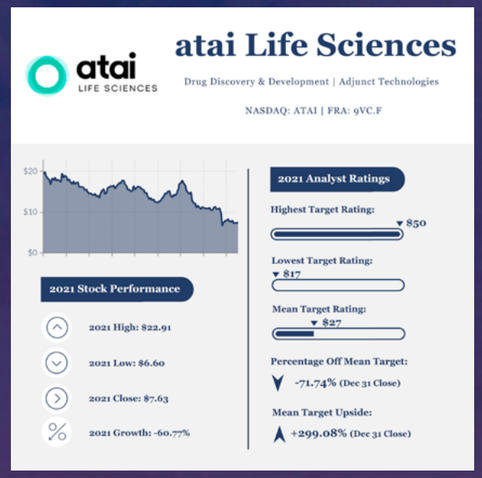
In line with the broader trend identified earlier in this section, PsyMed's focus on drug development companies is set to continue. But, Serebrinsky noted that, "as new psychedelic therapeutics are getting closer to market authorization, we're excited to meet more entrepreneurs working on solutions to reduce friction and improve outcomes."

## 3.9 – OVERVIEW OF ANALYST RATINGS

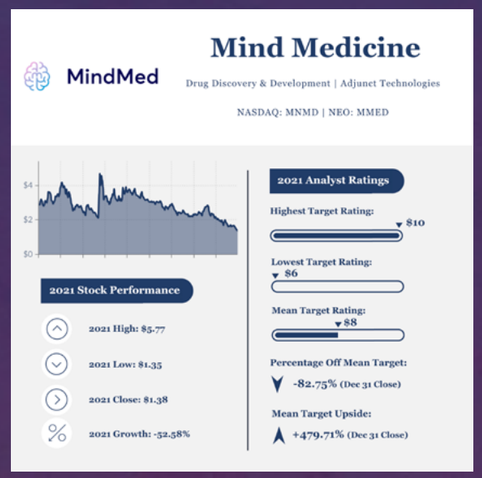
Despite a terrible year in terms of stock price performance across the psychedelics sector, analysts remain bullish on many of the largest psychedelics stocks.

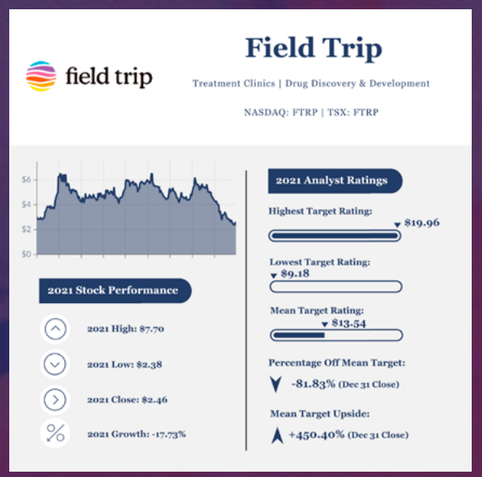
On the next page we present data on 2021 analyst ratings for a number of psychedelics companies and compare them with their stock prices.

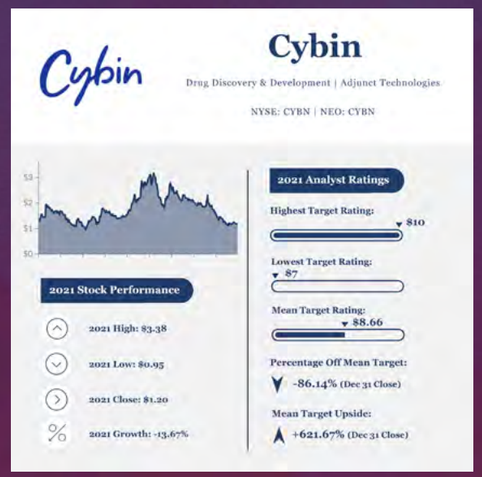

Compass Pathways
COMPASS Pathways
Navigating Mental Health Pathways
Drug Discovery & Development | Adjunct Technologies
NASDAQ: CMPS | FRA: 5Y6.F
$60
$40
$20
$0
2021 Stock Performance
2021 High: $58.62
2021 Low: $21.20
2021 Close: $22.10
2021 Growth: -49.31%
2021 Analyst Ratings
Highest Target Rating:
$120
Lowest Target Rating:
$50
Mean Target Rating:
$75.57
Percentage Off Mean Target:
-70.75% (Dec 31 Close)
Mean Target Upside:
+241.95% (Dec 31 Close)


atai Life Sciences
atai LIFE SCIENCES
Drug Discovery & Development | Adjunct Technologies
NASDAQ: ATAI | FRA: 9VC.F
$20
$10
$0
2021 Stock Performance
2021 High: $22.91
2021 Low: $6.60
2021 Close: $7.63
2021 Growth: -60.77%
2021 Analyst Ratings
Highest Target Rating:
$50
Lowest Target Rating:
$17
Mean Target Rating:
$27
Percentage Off Mean Target:
-71.74% (Dec 31 Close)
Mean Target Upside:
+299.08% (Dec 31 Close)


GH Research
Drug Discovery & Development
NASDAQ: GHRS | FRA: 1KA.F
$30
$20
$10
$0
2021 Stock Performance
2021 High: $30.43
2021 Low: $12.38
2021 Close: $23.33
2021 Growth: +21.19%
2021 Analyst Ratings
Highest Target Rating:
$35
Lowest Target Rating:
$26
Mean Target Rating:
$32
Percentage Off Mean Target:
-27.09% (Dec 31 Close)
Mean Target Upside:
+50.02% (Dec 31 Close)


Mind Medicine
MindMed
Drug Discovery & Development | Adjunct Technologies
NASDAQ: MNMD | NEO: MMED
$4
$2
$0
2021 Stock Performance
2021 High: $5.77
2021 Low: $1.35
2021 Close: $1.38
2021 Growth: -52.58%
2021 Analyst Ratings
Highest Target Rating:
$10
Lowest Target Rating:
$6
Mean Target Rating:
$8
Percentage Off Mean Target:
-82.75% (Dec 31 Close)
Mean Target Upside:
+479.71% (Dec 31 Close)


Field Trip
field trip
Treatment Clinics | Drug Discovery & Development
NASDAQ: FTRP | TSX: FTRP
$6
$4
$2
$0
2021 Stock Performance
2021 High: $7.70
2021 Low: $2.38
2021 Close: $2.46
2021 Growth: -17.73%
2021 Analyst Ratings
Highest Target Rating:
$19.96
Lowest Target Rating:
$9.18
Mean Target Rating:
$13.54
Percentage Off Mean Target:
-81.83% (Dec 31 Close)
Mean Target Upside:
+450.40% (Dec 31 Close)


Cybin
Drug Discovery & Development | Adjunct Technologies
NYSE: CYBN | NEO: CYBN
$3
$2
$1
$0
2021 Stock Performance
2021 High: $3.38
2021 Low: $0.95
2021 Close: $1.20
2021 Growth: -13.67%
2021 Analyst Ratings
Highest Target Rating:
$10
Lowest Target Rating:
$7
Mean Target Rating:
$8.66
Percentage Off Mean Target:
-86.14% (Dec 31 Close)
Mean Target Upside:
+621.67% (Dec 31 Close)

SECTION
**FOUR**

# PSYCHEDELIC PERCEPTIONS IN 2021: POPULAR CULTURE & CONTROVERSY

4

# 4.1 – FOREWORD

In 2021, the psychedelic space was flush with notable, and sometimes controversial events. Burgeoning interest led to the creation and support of research centres, institutes, and conferences all centred around psychedelics. More mainstream media outlets covered psychedelics, TV shows and documentaries featured them, and a great number of celebrities came out of the psychedelics closet.

However, amidst all of the excitement emerged many important, and challenging, ethical considerations that will demand more attention as the space matures.

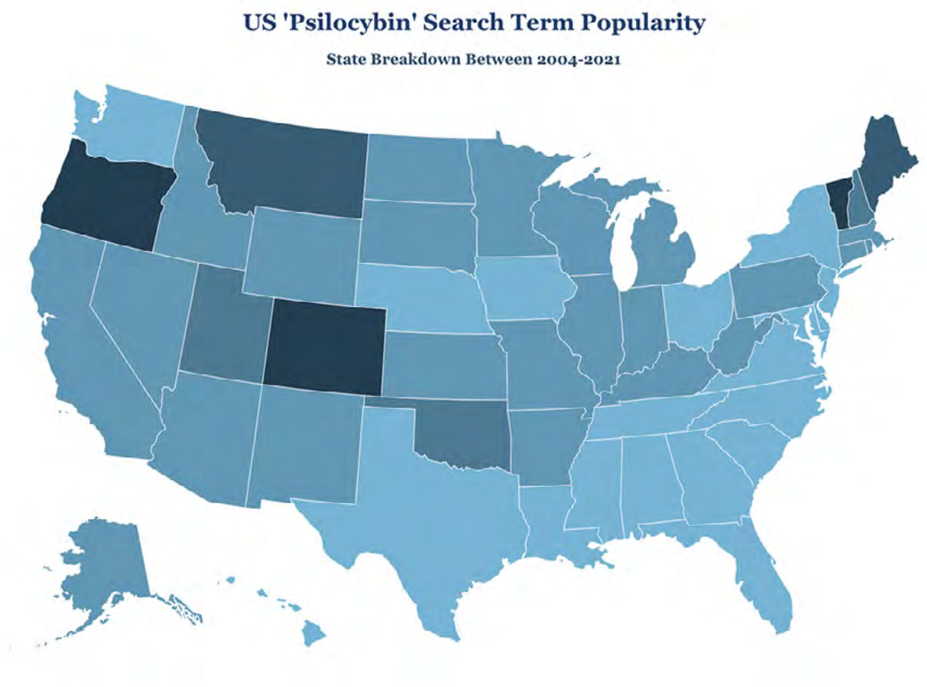
Here, we review a number of pop culture moments that foregrounded psychedelics in 2021, before touching on just a couple of the controversies that developed throughout the year.

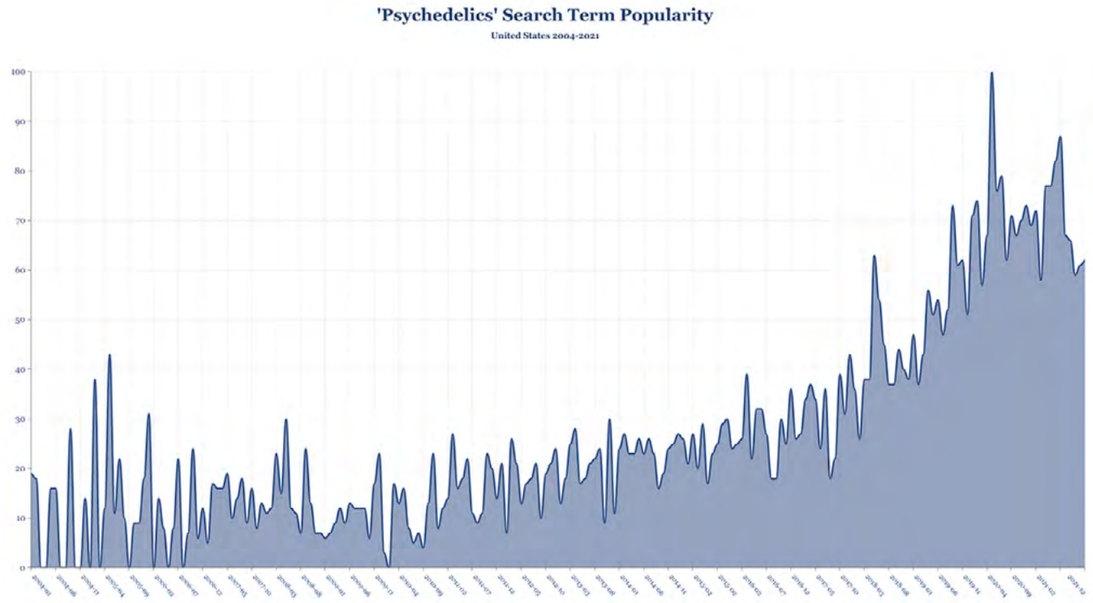
# 4.2 – PSYCHEDELICS IN POPULAR CULTURE

Public interest in psychedelics seemed to continue increasing throughout 2021, with every week bringing a new mainstream media mention or celebrity 'endorsement'.

Using Google search trends as a proxy for public interest, the graph below shows that the last two years have seen significant levels of interest in psychedelics.

The map displayed on the next page, meanwhile, suggests that state-level drug policy reform efforts are driving a significant amount of interest in psychedelics like psilocybin. It's clear that Oregonians are Googling the psychedelic most frequently, no doubt due to the increased attention it's received since Measure 109 passed in November 2020.




## TV, FILM AND CULTURE

Psychedelics also appeared in a number of mainstream TV shows, films, documentaries and cultural arenas in 2021. Below are just a handful of examples..

**Nine Perfect Strangers Drives Interest in Psychedelic Therapies**

Hulu's Nine Perfect Strangers series, which first aired in August 2021, stoked a great deal of interest in psychedelic therapies, but also contributed to the further development of common misconceptions around these practices.

Two articles sought to clarify the portrayals, with Business Insider tackling 12 elements of psychedelics retreats that the show got right and wrong, and Mic publishing a more critical piece in which the title describes the show's portrait of psychedelic wellness retreats as "deranged."

Writing in the LA Times, Qualey (who also authored the Mic piece) is keen to point out that the show's director, Jonathan Levine, is an ardent psychedelic therapy proponent. Levine told Qualey psychedelic therapy "is one of my top five options for the salvation of humanity."

What did you think of Nine Perfect Strangers? Is any publicity [for psychedelic therapy] good publicity?


**Hamilton's Pharmacopeia Returns with Season 3**

The third season of Hamilton Morris' VICE series, Hamilton's Pharmacopeia, aired in January 2021.

The first episode, Synthetic Toad Venom Machine, saw Morris reflect on his earlier reporting regarding an "international toad venom smoking phenomenon" by clarifying the history of 5-MeO-DMT, before urging viewers that wish to experience "The God Molecule" to do so via a synthetic option. Shortly after the episode aired, psychedelics company CaaMTech published research investigating the chemical differences between pure 5-MeO-DMT, its derivatives, and natural Bufo alvarius toad secretions.

The six-part series went on to explore other psychedelics including ibogaine and LSD, with the final episode profiling "a new era of psychedelic research."

**BBC Airs Documentary: The Psychedelic Drug Trial)**

A special hour-long documentary aired on the BBC in May 2021, the culmination of 16 months of filming Imperial College London's escitalopram vs. psilocybin study.

In the film we hear from the likes of Professor David Nutt, Dr Robin Carhart-Harris and Dr Rosalind Watts, as well as participants in the groundbreaking trial.

We discussed the trial itself in our earlier section on Psychedelic Research and Clinical Trials in 2021.

**LSD-Themed Broadway Show Launches: Flying Over Sunset**

A new Broadway musical dramatizes a fictional account of a meeting between Aldous Huxley, Cary Grant and Clare Boothe Luce, all of whom used LSD over the years. The show's website sets the scene:

1950s Hollywood. You are at a beautiful beach house overlooking the Pacific with Cary Grant, Clare Boothe Luce and Aldous Huxley... and they are on an acid trip. Together.

Flying Over Sunset premiered in November, officially opening just over a month later on December 13th.

**Psychedelic City' TV Series and Metaverse Platform Under Development**

A Los Angeles Magazine cover story titled, 'Shrooms! Shamans! Kosher LSD! Why Los Angeles Is Suddenly Tripping Out, is set to be developed as a TV series and metaverse platform, according to The Hollywood Reporter.

The author of the original story, Peter Kiefer, explained: "It's such wonderful fodder for a series and what's more, I think it's an extremely important topic that is only going to become more so in the coming years."

Is this a sign of things to come re: the confluence of psychedelics and other 'edgy' investment and tech categories such as the metaverse, crypto, and VR?


NEWS

'Shrooms! Shamans! Kosher LSD! Why Los Angeles Is Suddenly Tripping Out

COVER STORY: Housewives in the Hills are doing it. Hipsters in Los Feliz, too. L.A. has became ground zero for a new hallucinogen boom, with ayahuas ca ceremonies now as common as barbecues. But is microdosing shrooms really the answer to what ails Angelenos?

By Peter Kiefer - October 21, 2021

**CTV News W5 Investigation 'Harnessing the Power of Psychedelic Drug Therapy'**

An October 2021 W5 investigation shared the stories of Canadians using ketamine and psilocybin as treatments for post-traumatic stress disorder and cancer--related anxiety.

The episode also briefly discusses the status of drug policy in Canada and the need for more well--regulated and accessible psychedelic-assisted psychotherapies.

**CityNews (Canada) 'The Psychedelic Frontier'**

In January 2021, Canadian media outlet CityNews aired The Psychedelic Frontier. The special shared the stories of many Canadians working to deliver or access psychedelic therapies.  The episode follows a Canadian war veteran as he searches for relief from post-traumatic stress disorder (PTSD) and addiction through psychedelic therapy.

CityNews also featured a number of Canadian companies operating in the psychedelic space including Numinus, Braxia, and Red Light Holland.

## ATHLETES IN PSYCHEDELIA

In 2021, a number of prominent athletes expressed their interest in psychedelic therapies. Below are just a few examples....

**UFC Looking at Johns Hopkins Study on Psychedelics As Potential Therapy for Fighters**

ESPN published an article in January of 2021 covering the UFC's growing interest in psychedelics as possible therapies for its athletes. According to the article, the UFC had been in contact with researchers at Johns Hopkins University to discuss the potential psychedelic might have in treating brain injury, addiction, post-traumatic stress disorder (PTSD), and other mental--health challenges.

Jeff Novitzky, the senior president of health and performance of the UFC, described how the company may look to involve both current and retired fighters in psychedelic research. Should these emerging treatments prove to be effective for brain and psychiatric health, UFC president Dana White has said that "we want to be on board and we want to be first."


**Retired NHL Player Daniel Carcillo Heads Up Wesana Health**

Ex-NHL player Daniel Carcillo has emerged as a prominent figure in the psychedelic space. In 2015, Carcillo retired from professional hockey after witnessing and experiencing the enduring health damage caused by concussions. Since then, Carcillo has worked to create a new company, Wesana,  focused on healing brain injuries using psychedelics. The inspiration for Wesana came from the now-CEO's personal healing experience using psychedelics.

In 2021, Wesana, under the leadership of Carcillo, began trading on the Canadian Securities Exchange and has since engaged a number of partners in an effort to develop new treatment options for traumatic brain injuries (TBI).

**Documentary 'Lamar Odom Reborn' Released**

In May 2021, a documentary titled Lamar Odom Reborn was released. The film follows the story of ex-NBA player, Lamar Odom, as he works to overcome his struggles with addiction and depression through "medically-guided alternative treatments." Following a nearly fatal overdose in 2015, Odom's struggles with mental health were propelled into the public spotlight. As the documentary depicts, Odom has since been able to recover and heal with the help of ketamine and ibogaine treatments.

You can also watch a follow-up Q&A on psychedelic medicines with Lamar Odom and others here.

## CELEBRITIES IN PSYCHEDELICS

In 2021, even more celebrities came out of the psychedelic closet, sharing their experiences with a variety of psychedelics via interviews and news pieces.

But, some may argue that the evangelism displayed by at least some of the below celebrities is irresponsible from a harm reduction or environmental point of view.

Take Tyson's comments, for example, in which he sings the praises of 'toad venom': might that encourage folks who hear his comments to seek out toad--derived 5-MeO-DMT, and what might that do for the already-struggling population of Bufo alvarius? We discussed this in a November Bulletin.

Handler's claim that "psilocybin is good for everybody, it puts you in a good mood, keeps you upbeat..." could also be seen as a concerning blanket statement that smoothes out the complexities of the psychedelic experience.

See the spread on this page and the next for more information.

**Joe Rogan Hosts Rick Doblin**

Episode #1661 of The Joe Rogan Experience featured MAPS' Rick Doblin for over 3 hours of discussion...

**Kristen Bell Tried Psilocybin**

After struggling with depression and anxiety for 22 years, Bell says she tried psilocybin.

**Chelsea Handler Says She Microdoses**

On The Tonight Show, Handler said "I take mushrooms almost every day... microdosing mushrooms is a gamechanger."


**Mike Tyson Continues to Discuss 'The Toad'**

Tyson received a great deal of attention for his comments on 'doing the toad' throughout the year.

**Elon Musk Endorses Psychedelics at Code Conference**

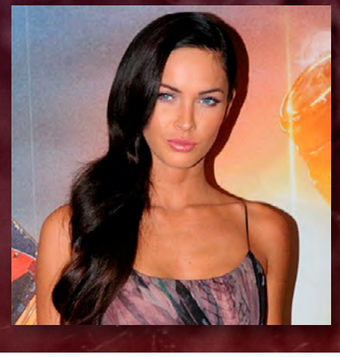
Musk said, "I think generally people should be open to psychedelics..."

**Christina Haack Smoked Toad Venom**

In mid-2021, Haack explained in a lengthy Instagram post that she smoked toad venom which 'reset' her brain.

**Megan Fox Discusses Ayahuasca on Jimmy Kimmel Live**

Fox explained that she 'went to hell for enternity' during her ayahuasca trip.



**Will Smith Discusses Ayahuasca Rituals with GQ**

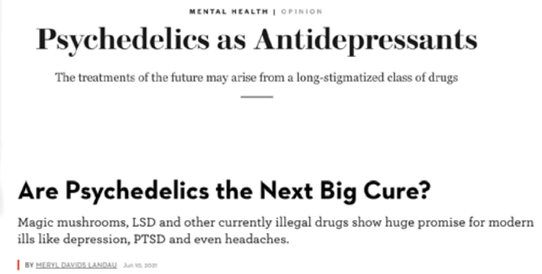
In a Cover Story for GQ, Smith explained that 'more than a dozen ayahusaca rituals' in Peru changed his life.

## SIGNIFICANT NEWS PUBLICATIONS

News outlets from the BBC through to Good Housekeeping covered psychedelics in 2021, with the montage below highlighting just a handful of these headlines.


Advances in psychedelics could change investors' minds

Potential treatments for addiction and mental illnesses are gathering pace


MENTAL HEALTH | OPINION

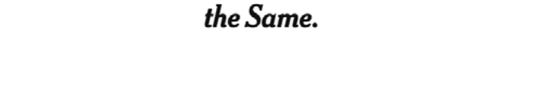
Psychedelics as Antidepressants

The treatments of the future may arise from a long-stigmatized class of drugs


Are Psychedelics the Next Big Cure?

Magic mushrooms, LSD and other currently illegal drugs show huge promise for modern ills like depression, PTSD and even headaches.

BY MERYL DAVIDS LANDAU Jun 10, 2021


*The Psychedelic Revolution Is Coming. Psychiatry May Never Be the Same.*


Business | QuickTake

Why Psychedelics, Big in the 1960s, Are Drawing New Interest Now


DRUGS

The worldview-changing drugs poised to go mainstream

> "I want to be clear that having sex with the client or patient in a psychedelic therapy relationship is always sexual abuse, and that is because of the power dynamic."
>
> - Laura Mae Northrup

# 4.3 – CONTROVERSIES

2021 also foregrounded a number of debates and controversies in the psychedelics space, not least the long overdue discussion around sexual abuse in the context of psychedelic therpay and the salient debate surrounding the role of patents in the space.

Below we touch on these two controversies and debates, but readers should be sure that there are many more.

## SEXUAL ABUSE IN PSYCHEDELIC THERAPY

A collaboration between New York Magazine and Psymposia brings the discussion around (sexual) abuse in the psychedelics space to the foreground via the first season of the Cover Story podcast, titled Power Trip. Across 8 episodes, host iO Tillet Wright and collaborator Lily Kay Ross "uncover the secrets and expose the darkest corners of the psychedelic revolution through a twisted, deeply personal tale at the intersection of mind, body, and control." Learn more, and listen to the series, here.

The podcast series builds on a spate of allegations and testimonies that have emerged in recent months, including that of Will Hall who shared a powerful account of his experience with a number of (formerly-)respected psychedelic therapists and teachers. Hall's account was originally shared in a self-authored article published on Mad in America in September, and is explored in detail in an Inverse article from November.

The discussion was also a recurrent theme at December's Horizons conference in New York. Laura Mae Northrup gave a powerful talk on sexual abuse in psychedelic-assisted therapy, saying what many might hope is obvious: "I want to be clear that having sex with the client or patient in a psychedelic therapy relationship is always sexual abuse, and that is because of the power dynamic."

This healthy and long overdue debate will surely continue into the new year.

## THE PSYCHEDELIC PATENT WARS

The role of intellectual property, and particularly patents, in the psychedelics space continued to be heavily debated in 2021, with some using the phrase 'patent wars' to describe the situation.

**Case Study: Non-Profit Group Challenges COMPASS Pathways Patent**

Much of the criticism has been levied at COMPASS Pathways, which has been awarded patents covering synthetic forms of psilocybin, as well as common elements of a psychedelic-assisted therapy protocol.

In December, COMPASS' "infamous" patent on synthetic psilocybin was challenged by a non-profit group, which argued that COMPASS' Polymorph A is no different to the crystalline forms made over and over again since psilocybin was first synthesized.

The group challenging the patent is Freedom to Operate, a non-profit group dedicated to "protecting psychedelic science and medical development for public benefit," of which Carey Turnbull is at the helm. You can download the post-grant review petition here.

Turnbull footed around half of the bill for the research that underpins the challenge, which took months of work and cost close to a million dollars. The rest came from donors like Bill Linton, Bronner's Soaps, The Steve and Alexandra Cohen Foundation and Evolve Foundation, according to Carey Turnbull.

That expense begins to make sense when you read that researchers involved in the challenge had to scour the world for "high-quality synthetic psilocybin stored in safe conditions," with one such sample being a 1963 bottle of Sandoz psilocybin, obtained via NIDA's Drug Supply Program. Turnbull told Psilocybin Alpha that the sample most extensively used in the research was obtained via Rolan Griffiths' lab at Johns Hopkins University, and was made by Heffter Research Institute founder Dave Nichols.

COMPASS Pathways has 3 months to respond to the post-grant review that this research has informed. Then, the Patent Trial and Appeal Board (PTAB) decides whether a case should proceed to trial. If it does, a lengthy process ensues.

The company responded to the story by stating that they "remain highly confident in the strength of our patents and our polymorph A is the subject of numerous granted patents from several different Patent Offices, confirming that it is novel and inventive."

This isn't the first time the company's patents have been questioned, however. In July 2021, a patent examiner at the UK IP Office issued an opinion on Compass Pathways' UK Polymorph A patent (GB2572023), having received a request for opinion from Kohn & Associates acting on behalf of Freedom to Operate. The examiner found a number of claims to be lacking an "inventive step," a foundational tenet of the patent regime

However, an earlier petition for post-grant review levied at COMPASS was denied in 2020, with the PTAB concluding that the petitioner failed to show that "it is more likely than not" that claims were unpatentable as obvious.

This will certainly be an interesting development to watch, and one that COMPASS is no doubt gearing up to fight. Around the time the news of the challenge broke, COMPASS announced the forthcoming appointment of a new Chief Legal Officer (and, the departure of co-founder Lars Wilde as Chief Business Officer), Matthew Owens. Owens was formerly responsible for legal and IP strategy at Novartis, in his role as Global Head Legal, Digital.

Some of the researchers hired by the non-profit submitted additional findings to an academic crystallography journal, in an article that was accepted later in December.

**Some Recommended Reading**

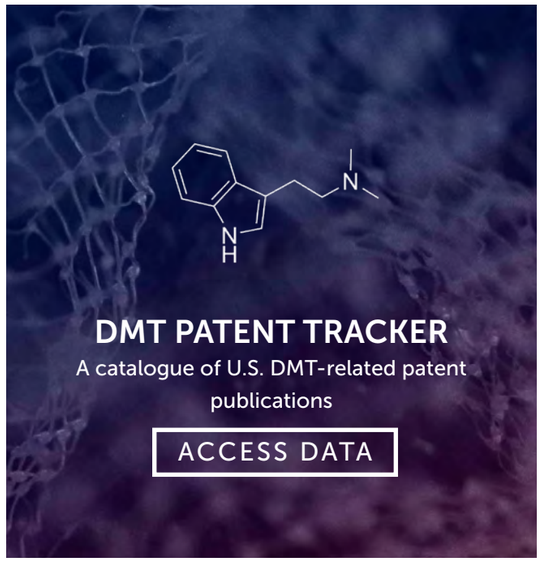
This debate has been charted by Shayla Love's reporting over at Vice, which is recommended reading for those looking to dive deeper into this topic.

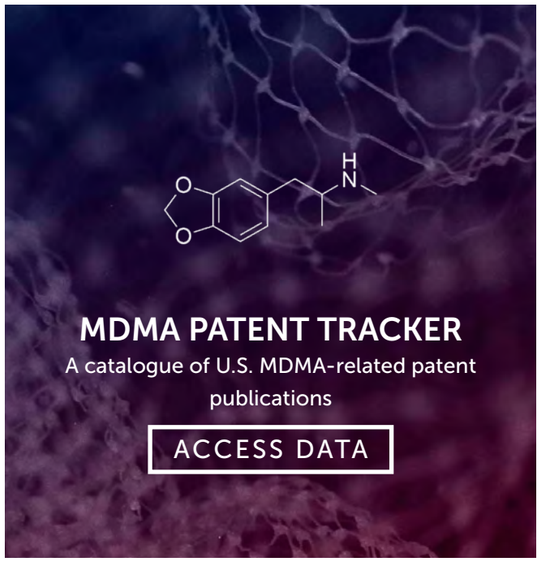
- Can a Company Patent the Basic Components of Psychedelic Therapy? (February '21)
- Investors Are Debating Who Should Own the Future of Psychedelics (March '21)
- The Race to Patent Psychedelics Is Just Getting Started (May '21)
- Is it Possible to Create an Ethical Psychedelics Company? (June '21)
- Psychedelics Patent Claim Raises Questions From Researchers Who Say They Did It First (June '21)
- Can LSD Treat Food Allergies? We Don't Know, But It's Already Been Patented (July '21)
- Psychedelics Are a Billion-Dollar Business, and No One Can Agree Who Should Control It (September '21)
- New Filing Challenges Compass Pathways' Infamous Patent on Synthetic Psilocybin (December '21)

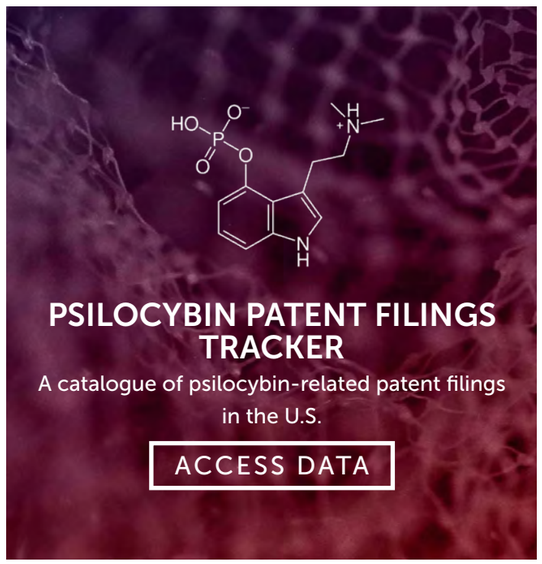
## OUR PATENT TRACKERS

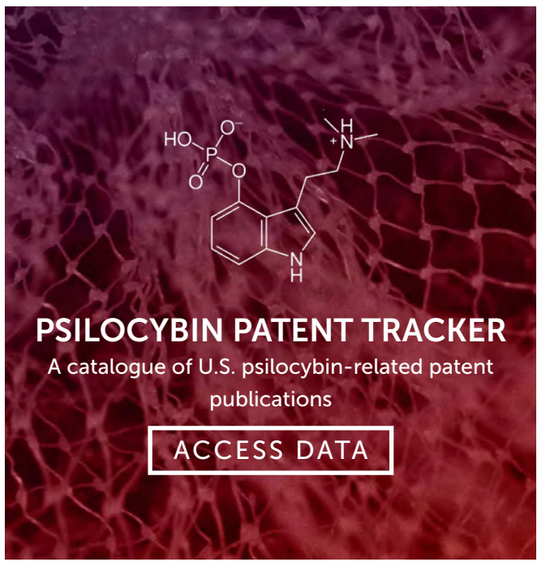
We are pleased to have contributed to greater transparency around psychedelic patents through the provision of our freely-available psychedelic patent trackers which you can access by clicking the embedded boxes below.

Patent trackers are powered by Calyx Law




SECTION
**FIVE**

# LOOKING AHEAD TO A PSYCHEDELIC 2022

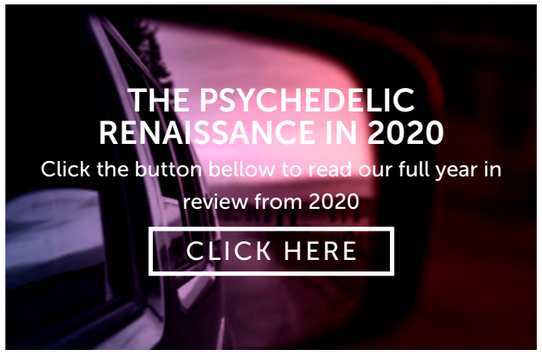
5

# 5.1 – FOREWORD

2022 looks set to be another busy year for the psychedelics space, with a number of late-stage clinical trials commencing or wrapping; important decisions on the table for Oregon's legal supervised psilocybin therapy rollout in 2023; further (psychedelic) drug policy reform efforts set to progress; and much, much more.

Rather than making cold, hard predictions about what's sure to be a very psychedelic 2022, we're going to share some key trends that we'll be keeping an eye on, and covering, in this new year.

**But first, let's take a look back at our 2021 'predictions'...**




# 5.2 – OUR 2021 PREDICTIONS: HOW DID WE DO?

Last year we published a much shorter Year in Review for 2020, which included a Looking Ahead section where we made some broad suggestions of what we might expect to see in 2021. So, how did we do?

**Let's take a look at each broad 'prediction'...**

**2021 Prediction #1**

There are plenty of **catalysts** on the horizon as we enter a new year, including clinical trial readouts from **COMPASS Pathways' Phase 2b** psilocybin-for-depression study and **ATAI Life Sciences' expected IPO**. We should also see **MAPS continue to make progress in their Phase 3** investigations into MDMA-for-PTSD, which appear promising thus far. Should the clinical data from these trials continue to indicate the safety and efficacy of psychedelics such as psilocybin and MDMA, it is likely to continue to propel interest and activity in the broader space.

Well, that was an easy prediction, and one that came true (at least to some extent). As mentioned in our earlier section on Psychedelic Research and Clinical Trials in 2021, data readouts from COMPASS Pathways' Phase 2b and MAPS' Phase 3 study did attract a great deal of mainstream attention. So too did atai Life Sciences' Nasdaq IPO.

However, on the investor side of the equation COMPASS' readout and atai's IPO did little to bolster confidence in the companies' valuations. As aforementioned in this series, both companies' stocks have performed poorly in 2021, reflecting (and perhaps even leading) the broader psychedelics market downtrend: it seems that capital letters are not the only type of capitalisation atai reduced during 2021 (the company name was formerly styled ATAI Life Sciences).

**2021 Prediction #2**

We also expect to see **access to psychedelics**, notably psilocybin, **continue to expand via progressive moves from local governments** (urged by grassroots campaigns) **and national regulatory bodies** such as Health Canada. The combination of bottom-up grassroots advocacy and top-down regulatory amendments may generate a reinforcing cycle that gradually expands access to psychedelics in both a geographical sense, but also in terms of access criteria. **We may even see a national legal framework for psilocybin emerge in Canada next year.** It is likely that **local decriminalisation and legalisation measures in the United States** will follow a similar timeline as marijuana, with **states such as California next in line for such measures**. We anticipate a continuation of the current trend whereby some psychedelics companies publicly state their ambitions to enter these regionally-legalised markets (e.g., Field Trip in the case of Oregon), while others intend to steer clear of entering state markets so long as psychedelics remain federally illegal (e.g., MindMed in the case of Oregon).

You could argue that this was another easy prediction for us to have made back in December 2020. Nonetheless, we are taking this one as a win.

As you can see in our Psychedelics Legalization and Decriminalization Tracker, psychedelic drug policy reform is now prolific in the United States, with a great number of bills emerging in 2021. A prime example being California's SB 519 which, though put on hold, aims to decriminalize a range of psychedelics in the Golden State.

We didn't see the type of national legal framework for psilocybin emerge in Canada that we may have alluded to, but we have seen important reforms to the nationwide Special Access Programme which could afford individuals access to psychedelic-assisted therapies.

And, amid all of these psychedelic drug policy reform developments, many psychedelics companies have attempted to capitalise on the newfound attention and regulatory loosening by press releasing their support for amendments, motions, and movements.

Read our Psychedelic Drug Policy Reform in 2021 section for more on the above topics.

**2021 Prediction #3**

We expect that **mainstream media will increasingly cover developments from the psychedelic space.** This coverage of psychedelics will increasingly contribute to conversations regarding the mental health crisis, which we expect to remain a salient issue given the ongoing impact of COVID-19. Societies across the world have been forced to confront shortcomings in mental health provision, which should catalyse efforts to discover and deliver alternative treatments.

Another easy one, which unsurprisingly came true. As aforementioned, media coverage was stoked by MAPS' Phase 3 results and psychedelic drug policy reform efforts, among other catalysts. See our section on Psychedelic Perceptions in 2021 for more on this topic.

**2021 Prediction #4**

**Technology and digital therapeutics should play an increasing role in the work of psychedelics companies**, from augmenting drug discovery by employing AI, right through to empowering end--users of psychedelic therapies and medicines by providing actionable insights through the use of wearables.

This one certainly rang true. Check out the segment Growth of Digital Therapeutics, Delivery Technologies & Drug Discovery Tech in our earlier section for more on this.

**2021 Prediction #5**

From a financial point of view, we expect **money will continue entering the space in large sums**, with **ATAI's expected IPO representing an important date in the psychedelics financial calendar for 2021**. We may also see **greater M&A activity** in the space next year, and **interest from the more conventional pharma industry** is likely to increase. We also expect some companies in the space to continue seeking out shorter--term revenue streams. Clinics and wellness centres offering ketamine treatment programs are likely to continue to be a dominant trend, along with consumer packaged goods such as nutraceuticals.

A mixed bag, here. While large sums of money have continued to flow into the space, the story on the public markets has been much less rosy: atai's IPO, for example, proved to be a damp squib that failed to lift the psychedelics market.

M&A activity didn't materialise in any substantial way. We will be shamelessly rolling over this prediction into our 2022 batch: more on that below.

**2021 Prediction #6**

We anticipate the **pace of press releases and announcements from psychedelics companies to continue increasing**, particularly in relation to intellectual property (e.g., patent filings) and research and development (including clinical trials). As with any nascent sector, there will also be a great deal of noise that threatens to obscure the underlying value in any given company or project.

Tell us about it! It's been quite the year in terms of the pace of company news and research publications.

Now let's look ahead to 2022...

## 5.3 – TRENDS TO FOLLOW IN 2022

As aforementioned, we're sharing some of the key trends we will be following, and writing about, in 2022. As always, this is by no means exhaustive...

### PSYCHEDELICS R&D MOVES BEYOND MENTAL HEALTH

While mental health conditions like depression and PTSD have represented the beachhead for clinical research into psychedelics, we're now seeing more investigations geared toward treating a broader set of conditions such as neurodegenerative disorders and pain-related indications.

The figure at the bottom of this page (reproduced from our earlier section on Psychedelic Research and Clinical Trials in 2021) visualises a number of these target indications.

Should psychedelics' effects on structural and functional neuroplasticity and inflammation continue to be validated through research, we might expect them to prove efficacious (with or without the 'trip') in the treatment of at least some of the conditions outlined above.

A number of review articles published in 2021 expanded on this potential, including Albert Garcia-Romeu et al.'s exploration of psychedelics as potential novel therapeutics for Alzheimer's disease, and Saeger and Olson's survey of psychedelic-inspired approaches for the treatment of neurodegenerative disorders more broadly.

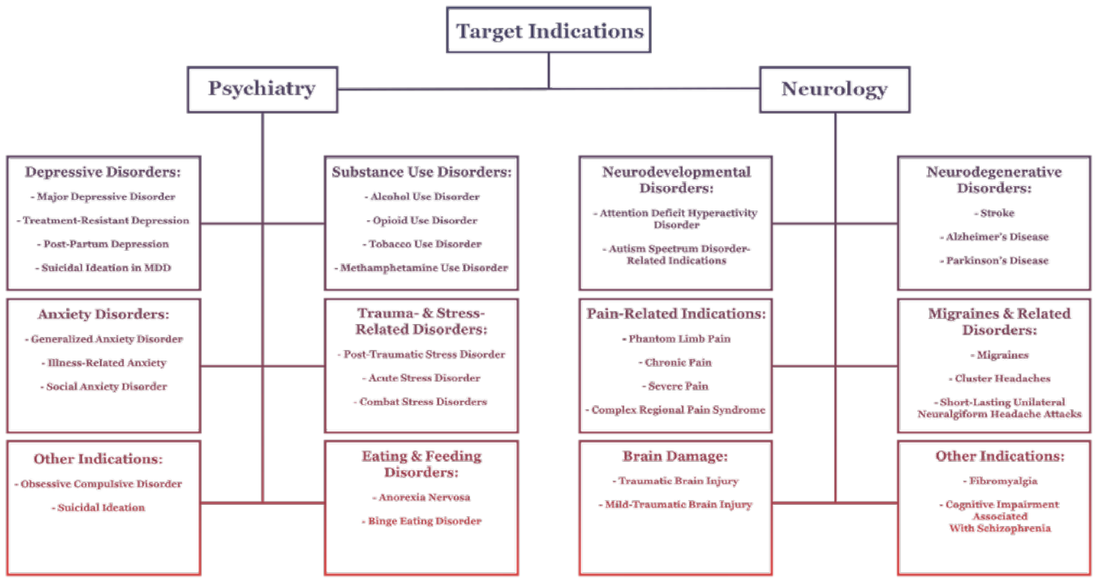
We're already seeing a number of research labs and companies seek to develop psychedelic drugs for the treatment of many of these conditions, and we should expect more of this work to emerge in 2022.

A small portion of this work will enter clinical trials in 2022.

As mentioned earlier in this report: we must be cautious not to overstate the 'promise' of psychedelics to treat such diseases. While psychedelics appear to work in a transdiagnostic manner, much of the research is in early stages, particularly around this broader list of conditions.

This broadening of the research and drug development pipeline to include a whole swathe of new conditions certainly makes it more difficult for investors, analysts, and other observers to make an informed appraisal of any particular drug development programme. Now, not only must interested parties have a grasp of the broader context of neuropsychiatric research and drug development, but also that of fields such as Alzheimer's research, which brings with it a whole new field of debates, varying degrees of (un)certainty in terms of drug targets, and more.

One thing's for certain: it's going to get a lot more difficult to keep tabs on the breadth and variety of the psychedelic drug development pipeline in 2022.



## THE ‘PSYCHEDELIC PATENT WARS’ RAGE ON

**The ‘patent wars’ will be stoked by an acceleration of patent application publications, with potential grants, rejections, and litigation.**

The Intellectual Property (IP) landscape of the psychedelics space is becoming clearer week-by-week as companies announce filings, patent applications publish, and IP offices hand down their verdicts.

As mentioned in the preceding section, the patenting of psychedelics and their related technologies and uses has not been without controversy. At the close of 2021, the non-profit Freedom to Operate filed two petitions for post-grant reviews of COMPASS Pathways’ patents, supported by research conducted by a group of crystallographers. This case alone will be one to watch as we enter 2022, with COMPASS expected to respond in the coming months, and a potential trial thereafter.

It’s unlikely this will be an isolated case, though. Many patent applications will be published in 2022, with the 18 months of secrecy attached to many such filings expiring this year. This means that by the end of 2022, we should have a much clearer picture of the psychedelic intellectual property topography, which may have impacts on drug development pipelines and research activity.

## IS CONSOLIDATION ON THE CARDS?

As aforementioned, we expected some level of consolidation in 2021, but this didn’t play out in any substantial way. At risk of a double fault, we’re rolling this prediction over into 2022.

If the broader economy, biotech sector and public markets continue to flag in 2022, we could see an untenable environment for a number of publicly-traded psychedelics companies. We’re not alone in predicting that there will be a number of companies that fold in 2022: MINDCURE CEO Kelsey Ramsden goes as far to suggest that half of the psychedelics companies with a sub-$300m market cap (a category in which her company sits) will “die” in the coming year.

MAPS’ Rick Doblin, meanwhile, told us that he expects a “major” consolidation of the for-profit psychedelic companies, “with many running out of money or seeing their ideas not borne out once actual research is started.”

But, going bust isn’t the only way that the sector might be reorganised. A less pessimistic prediction is that we will see a greater level of mergers and acquisitions (M&A) in 2022, both from companies outside the psychedelics space, and from within.

Intra-industry acquisitions may be driven by public companies with relatively large sums of cash on hand. As of September 2021, atai had just over $430m cash on hand, while COMPASS and MindMed had around $294m and $146m, respectively.

Indeed, atai was busy in 2021 when it came to launching new programs and making strategic investments, with 6 such deals made. Though, it remains to be seen how substantive each of these are.

We might also expect companies outside the psychedelics space to make acquisitions of psychedelics companies or programs in 2022. Some smaller psychedelics companies may be acquired by larger ones operating in ‘adjacent’ industries, such as cannabis, as was the case with MagicMed Industries which was acquired by Nasdaq-listed CBD biotech Enveric Biosciences in 2021.

Though perhaps more of a stretch, we might even see companies in the broader biotech and pharmaceutical industry acquiring psychedelics companies and programs. After all, Otsuka Pharmaceutical has already invested in and partnered with a handful of companies and drug candidates in the space.

## A CLOSER EYE ON INSURANCE COVERAGE

As MAPS’ MDMA-AT for PTSD nears potential approvals, and COMPASS Pathways enters Phase 3 trials, we will see a greater focus on the cost-effectiveness of psychedelic-assisted therapies and the willingness of insurance companies to cover these novel treatments in 2022.

This is a key priority for MAPS, with Founder Rick Doblin telling Psilocybin Alpha that “a key challenge in 2022 will be the early negotiations with insurance companies for possible coverage of psychedelic-assisted therapies post-approval for prescription use.”

Elliot Marseille, lead author of a 2020 paper that sought to demonstrate the cost-effectiveness of MDMA-AT for the treatment of PTSD, serves as Director of a dedicated initiative housed at UC Berkeley and UCSF. The Global Initiative for Psychedelic Science Economics (GIPSE) is a network of health economists with the shared goal of increasing access to psychedelic therapies by demonstrating (and improving) their cost-effectiveness. The group is working with MAPS as well as the Usona Institute and others.

Insurance coverage will be key to ensuring a scalable and accessible roll-out of psychedelic-assisted therapies. We will be keeping a close eye on this trend, and groups like GIPSE and companies like Enthea, in 2022.


## ALL EYES ON OREGON

The two-year development period for the Oregon Psilocybin Services section ends December 31, 2022. That means that by the end of this year the Oregon Psilocybin Advisory Board must be in a position to implement the regulation of the manufacture, transportation, delivery, sale and purchase of psilocybin products and the provision of psilocybin services in the state. Applications for licences begin January 2, 2023: there’s no wiggle room.

That's a hefty task, and it won't be without debate. Key fault lines include whether microdosing should be included in the provision, to what extent advertising should be permitted, and more. As a recent article on the matter pointed out, the clock is ticking: the Board has until the end of June to send their recommendations to the Oregon Health Authority.

Interested parties should follow these debates closely; we certainly will be.

## OTHER (PSYCHEDELIC) DRUG POLICY REFORM EFFORTS CONTINUE

When we said 'all eyes on Oregon,' we didn't mean to take your attention away from the slew of other (psychedelic) drug policy reform efforts that will develop throughout 2022.

Perhaps most notably is California's SB 519, which would decriminalize a number of psychedelics in the Golden State. The Bill was put on pause in 2021, but is set to be re-introduced this year.

Emerge Law's Sean Clancy is, unsurprisingly, following this trend closely (not least to keep the Psychedelics Legalization and Decriminalization Tracker up-to-date along with the team at Calyx Law). He told us that in 2022 he expects "more local measures and perhaps more ambitious state-wide measures, especially from newer, creative politicians seeking to set themselves apart by following Oregon's bold lead to decriminalize personal possession while regulating specific compounds, such as psilocybin."

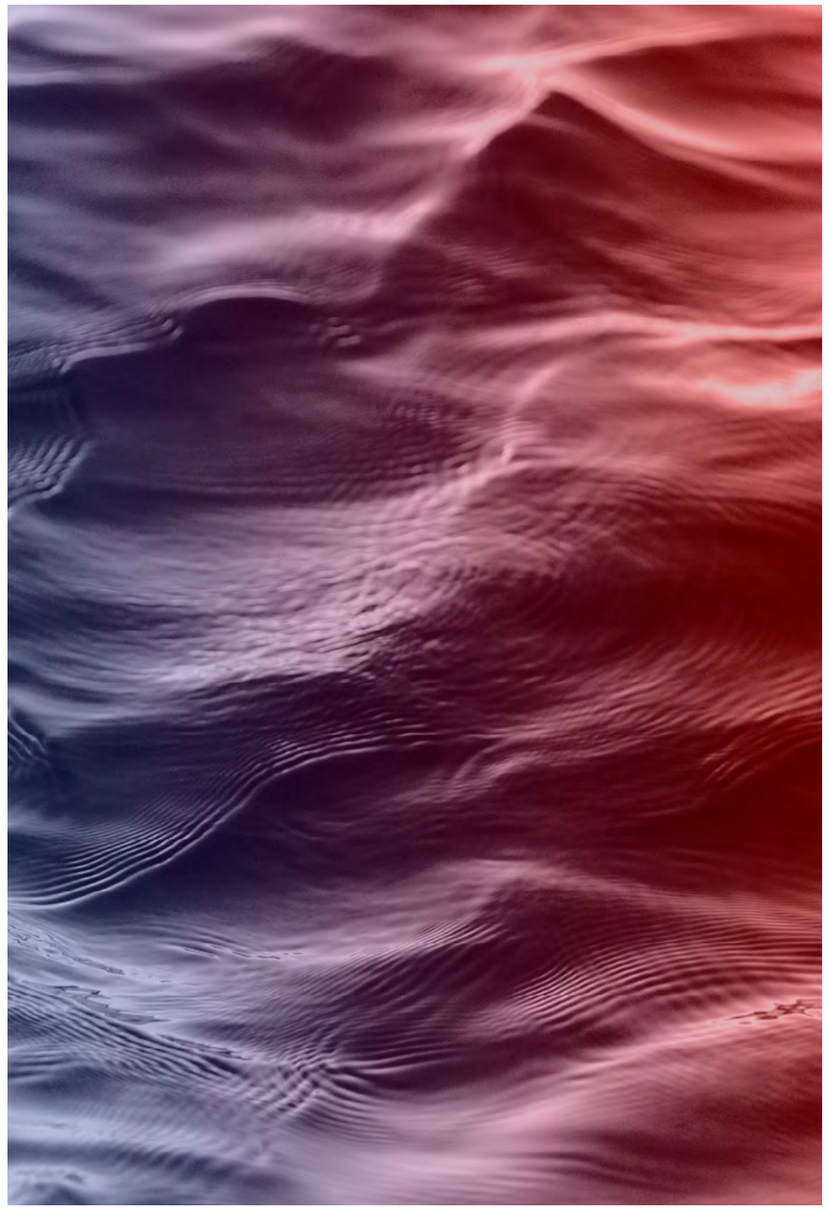
As we expect to see decrim. and legalization initiatives continue apace in 2022, we might also expect to see a greater need for harm reduction efforts. Rick Doblin told us that MAPS' Psychonaut training in psychedelic harm reduction and peer support will launch for the general public in 2022, just one such initiative.

## OTHER TRENDS TO FOLLOW IN 2022

While we couldn't possibly cover every trend that's worth following in 2022, here are several others to keep in mind:

- Psychedelics companies and researchers continue to explore digital therapeutics and innovative tech across the drug development pipeline and patient journey.
- Might we see conventional drug developers expand their pipelines to include psychedelics?
- We'll see plenty of failures in 2022, with a number of preclinical and clinical studies wrapping. Research has shown that Phase II trials have the highest attrition rates out of all clinical stages, and there are plenty of Phase II trials underway in psychedelics.
- The debate around the rigour of trials will continue.

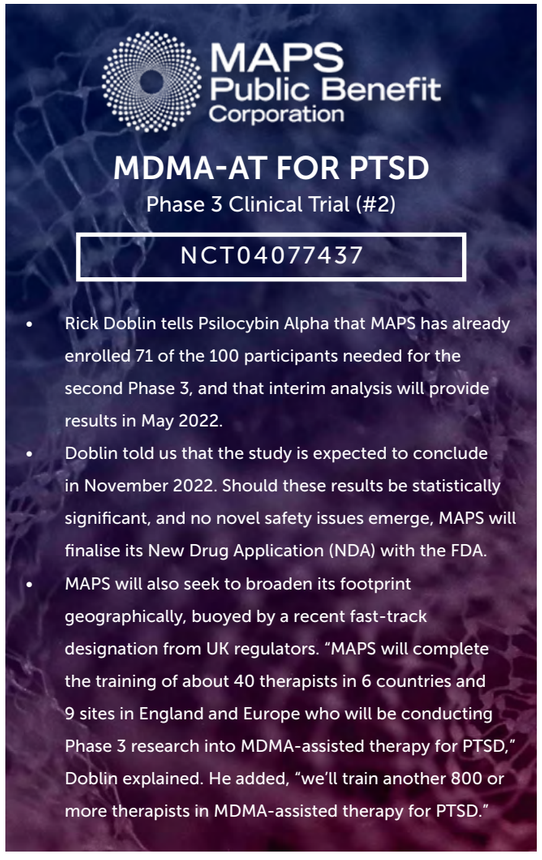
Taken together, many of these trends point toward a changing regulatory, scientific, and financial landscape for psychedelic researchers, practitioners, and (in particular) companies. Pivot or perish will likely be a scenario that a number of these companies face in 2022.



# 5.4 – PSYCHEDELIC CLINICAL TRIAL RESULTS TO WATCH FOR IN 2022

In our Psychedelic Research and Clinical Trials in 2021 section we discussed a handful of publications and readouts that occured over the course of last year. While some of these results, such as MAPS first Phase 3 results, drew a great deal of positive attention to the space, others served to temper expectations somewhat.

Next you will find a sample of clinical trials that, barring any delays, we might expect to see results from over the course of this year.

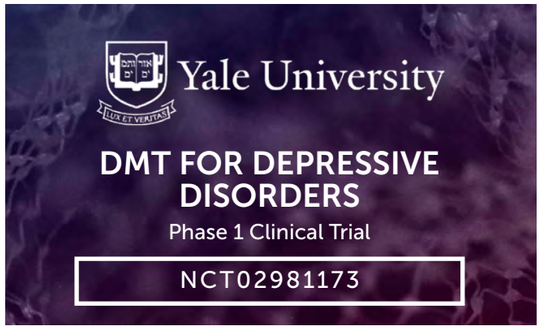



- Rick Doblin tells Psilocybin Alpha that MAPS has already enrolled 71 of the 100 participants needed for the second Phase 3, and that interim analysis will provide results in May 2022.
- Doblin told us that the study is expected to conclude in November 2022. Should these results be statistically significant, and no novel safety issues emerge, MAPS will finalise its New Drug Application (NDA) with the FDA.
- MAPS will also seek to broaden its footprint geographically, buoyed by a recent fast-track designation from UK regulators. "MAPS will complete the training of about 40 therapists in 6 countries and 9 sites in England and Europe who will be conducting Phase 3 research into MDMA-assisted therapy for PTSD," Doblin explained. He added, "we'll train another 800 or more therapists in MDMA-assisted therapy for PTSD."

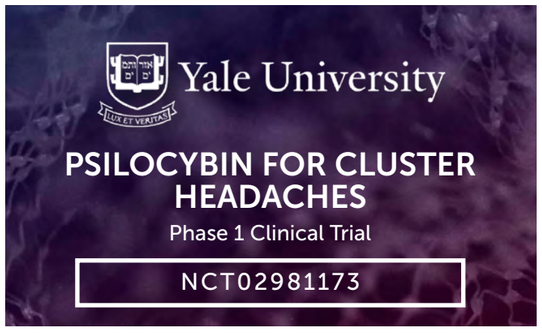












## 5.5 – PSYCHEDELIC CLINICAL TRIALS EXPECTED TO BEGIN IN 2022

In 2021, many companies and academic institutions announced their intent to initiate several new psychedelic clinical trials in the near future. Next, you will find a sample of clinical trials that are expected to begin in 2022.

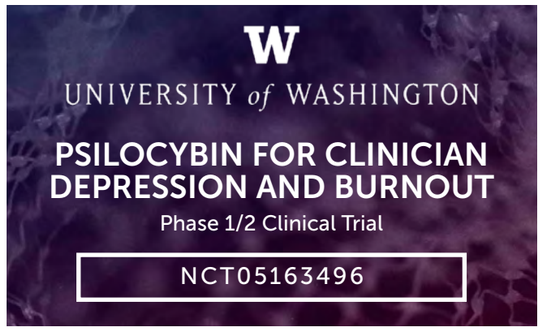
Visit our Psychedelic Drug Development Tracker for more information.


- COMPASS will be the first for-profit company to take a classic psychedelic into a Phase 3 trial this year, following the conclusion of its 2b trial in 2021.

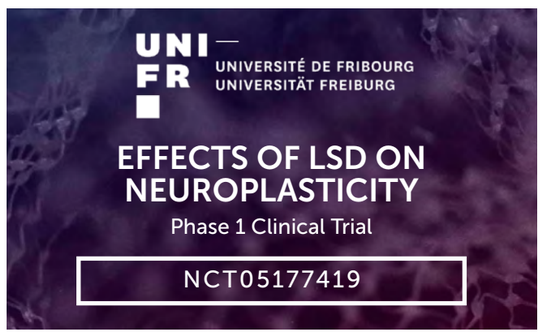


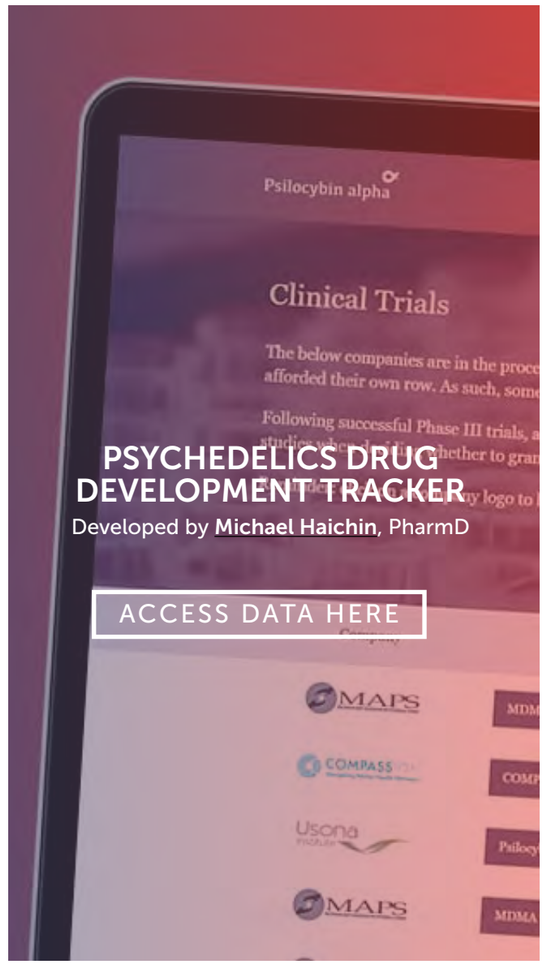










# CLOSING REMARKS

AXIOS VICE BUSINESS INSIDER The New York Times Mother Jones Newsweek

We hope that this report has offered an overview of some of the most salient events and trends in psychedelics last year, from fundamental research and clinical trials through to policy reform and pop culture.

Throughout 2022 we will continue providing news and analysis as well as trackers and resources that allow you to keep tabs on psychedelic patents, policy reform, and more. We are proud that in 2021 these resources were cited in a range of mainstream outlets including Vox, Newsweek, Business Insider, VICE, Wired, Rolling Stone and Mother Jones.

Today, the publication of research, filing of patents and penning of popular media stories covering psychedelics is growing exponentially. So much so, just keeping tabs on this space and identifying reliable sources—or, 'cutting through the noise'—is an endeavour in itself.

That's why we appreciate you, our readers, for your ongoing trust, support and engagement.

**Here's to a very psychedelic 2022!**

**JOSH HARDMAN**
Founder and Editor

Psilocybin alpha

# MEMORABLE QUOTES FROM 2021

"I want to be clear that having sex with the client or patient in a psychedelic therapy relationship is always sexual abuse, and that is because of the power dynamic."

- **Laura Mae Northrup** Speaking at Horizons NYC Business Forum

"I guess people just didn't want to go out and hunt these toads on a large scale, but that changed in the 21st century. Suddenly, there was an enormous explosion in interest in  5-MeO-DMT partially due to various celebrities trying it and talking about their transformative experiences. I think it sort of became what Ayahuasca was, like, maybe 10 or 15 years ago. Where, you know, if you want to show that you're a serious psychedelic person who really cares about this stuff: you need to do Ayahuasca. You have to go to South America and go to a retreat and then you're a real psychedelic person. Well the same thing happened with 5-MeO-DMT: it became a kind of psychedelic status symbol. This is how you show people that you're really into this stuff. That's all fine and good, except it involves the molestation of toads. That also may be okay if one or two people are doing it, but if everybody is doing it the results will absolutely be catastrophic."

- **Hamilton Morris** Speaking at Horizons NYC

"This space could become dominated by companies whose primary obligation is to shareholders. Let's not do that. That's why we're all here."

- **Amy Emerson,** CEO of MAPS Public Benefit Corporation, Speaking at Horizons NYC Business Forum

## "In 2021, we may even have reached a tipping point of acceptability."

- BBC Science Focus Magazine Commenting on 'Psychedelic Therapies'

"I was coming to these ideas right around the same time that the moon landing took place. Then you get some of these astronauts talking about how when they saw the Earth from space, they changed their views. So it's a lot easier and a lot less expensive to give somebody LSD than to shoot them up in space."

- **Rick Doblin** Speaking to GQ

## "Your retreat centre is not a religion."

- **Ismail Ali**, MAPS Policy Director, speaking on the difference between sanctioned religious uses of psychedelics and those retreat centres and other providers that may simply try to invoke such settings.

“The idea behind EmpathBio is that Doblin’s approach, while promising, will only represent MDMA 1.0.”

- **Srini Rao**, CSO at atai Life Sciences

“If MAPS is ‘MDMA 1.0,’ I would say that what atai [and EmpathBio] is working on is ‘MDMA 0.5.”

- **Rick Doblin** Responding to Rao's Comments

“I am very concerned by the patent land grab warming up in the for-profit psychedelic world. Is anyone working on a IP Defense Fund -- or coalition of pro-bono lawyers -- of some type to file USPTO objections/comments, etc. when companies attempt to secure broad patents that could hinder scientific research, reasonable competition (i.e., for "scale" and wide accessibility, we need competition to help drive costs down), and so on? Who are the smartest people thinking about this?”

- **Tim Ferriss**' Tweet on Patent Concerns

“Hence, to your question if I think a monopoly/duopoly is good for innovation/the ecosystem: IF a monopoly/duopoly emerged, it suggests that all the other would-be competitors had failed with their own creative and entrepreneurial endeavours. Then it would be a sign of quality and constitutional reward. In that case, you should not blame them, but blame the rest, who then clearly would have not done a good job. And once more, don’t forget the arbiter is neither me, nor you nor Twitter, but the US legal system and the market - systems that I do have a great deal of trust in.”

- **Christian Angermayer,** Founder and Chairman at atai Life Sciences, Excerpt From An Open Letter Reply to Tim Ferriss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