June 2022

PSYCHEDELIC INDUSTRY MARKET POTENTIAL

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CURRENT LEGAL CLASSIFICATIONS

Legal classification of psychedelics

DRUG	UN STATUS*	US STATUS	CANADA STATUS
Ayahuasca	Uncontrolled	Schedule I/ Exemptions	Schedule III/ Exemptions
Cannabis	Schedule I	Schedule I	Schedule VIII
DMT	Schedule I	Schedule I	Schedule III
Ibogaine	Uncontrolled	Schedule I	Controlled
Ketamine	Uncontrolled	Schedule III	Schedule I
LSD	Schedule I	Schedule I	Schedule III
MDMA	Schedule I	Schedule I	Schedule I
Peyote/ Mescaline	Schedule I/ Exemptions	Schedule I/ Exemptions	Schedule III/ Exemptions
Psilocybin	Schedule I	Schedule I	Schedule III

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

MDMA legalized in Colorado - pending federal descheduling

One example of considerable advancement is that Colorado Governor Jared Polis signed a bill that allows for the legal possession and use of MDMA with a medical prescription. The substance would be used predominantly for PTSD treatments, one of the most prevalent mental health disorders among combat veterans. Colorado's measure will become effective once MDMA is removed from its Schedule I status in the Controlled Substances Act, meaning it would be approved as a prescription drug. Another fact that should also be taken into account is that the bill does not consider MDMA's recreational use.

CANADIAN REGULATIONS

- Health Canada: Controlled Drugs and Substances Act, or CDSA
  - Psilocin and psilocybin are listed under Schedule III of the CDSA, are also restricted drugs under Part J of the Food and Drug Regulations
  - LSD is a Schedule III controlled substance
  - MDMA and ketamine are Schedule I controlled substances
    - A party may seek government approval for an exemption under Section 56(1) of the CDSA to allow for the possession, transport or production of a controlled substance for medical or scientific purposes or if such usage is otherwise in the public interest.
    - Government initiatives such as Safe Supply and the Special Access Program for Drugs
    - Assuming compliance with all relevant laws (Controlled Drugs and Substances Act, Food and Drugs Regulations) and subject to any restrictions placed on the licence by Health Canada, an entity with a **Dealer's Licence** may produce, assemble, sell, provide, transport, send, deliver, import or export a restricted drug (as listed in Part J in the Food and Drugs Regulations, which includes psilocybin and psilocin) (see s. J.01.009(1) of the Food and Drug Regulations). However, a licenced dealer may only import and export controlled substances and restricted drugs in accordance with a permit from Health Canada, which must be obtained for each import or export.
    - Currently, a licenced dealer may only sell psychedelics to an institution for clinical or research purposes. In Canada, an "institution" under Part J of the Food and Drug Regulations is defined as any institution engaged in research on drugs and includes a hospital, a university in Canada or a department or agency of the Government of Canada or of a government of a province or any part of them. Prior to the sale, the research institution must obtain authorization for the sale from Health Canada.
    - Before testing any drug in humans, the product candidate must undergo rigorous preclinical testing. Preclinical studies include laboratory evaluations of drug chemistry, formulation and stability, as well as in vitro and animal studies to assess safety and in some cases to establish the rationale for therapeutic use. If preclinical tests indicate that a substance produces a desired effect and is not toxic, a sponsor may apply to the Health Canada for authorization to conduct a clinical trial.
      - If the clinical studies demonstrate that the potential therapeutic benefits outweigh associated risks, a clinical trial sponsor may file an New Drug Submission, or NDS, with Health Canada.
      - Health Canada must approve an NDS and issue a Notice of Compliance, or NOC, and a Drug Identification Number, or DIN, before a drug may be marketed Canada.
      - Drugs approved for marketing in Canada but remaining on Schedule III of the CDSA will still be subject to the restrictions contained therein. To date, no drugs containing psilocybin or psilocin have been issued a NOC in Canada.

Source: SEC S1 Prospectus Registration Statement

INTERNATIONAL REGULATIONS

- International Conventions Governing Controlled Substances
  - 1961 United Nations, or UN, Single Convention on Narcotic Drugs, or the Single Convention
    - Signatories may not exceed their submitted estimates without furnishing a supplementary estimate to the INCB explaining the need for the adjustment
  - 1971 UN Convention on Psychotropic Substances, or the 1971 Convention
    - Requires that signatories provide the International Narcotics Control Board, or INCB, with **annual statistical reports** of quantities of psychotropic substances manufactured, exported from, or imported to their country
    - Regarding substances in Schedule I of the convention, signatories are required to "prohibit all use except for scientific and very limited medical purposes."
  - 1988 UN Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, or the 1988 Convention
    - All imports and exports of signatory countries — including the lawful import and export of narcotics and psychotropics — must be properly documented and controlled

US REGULATIONS

- Controlled Substances Act (21 U.S.C. § 811), or the CSA, and the Controlled Substances Import and Export Act, or the CSIEA,
  - Psychotropics such as psilocybin, psilocin, DMT and MDMA are regulated as Schedule I controlled substances, and have the strictest controls imposed upon their use for any purpose.
    - Scheduling determinations by the DEA are dependent on FDA approval of a substance or a specific formulation of a substance for medical use and marketing in the United States.
    - Products approved by FDA for medical use and marketing in the United States that contain psilocybin or another such substance would be placed in Schedules II -V , since approval by FDA satisfies the "accepted medical use" requirement.
    - If the DEA does not reschedule psilocybin, LSD, MDMA, DMT and 2C -B as II, III, IV or V, such substances will be subject to individually -allotted manufacturing and procurement quotas
    - In order to obtain DEA registration, facilities will first need to register with the narcotics enforcement department of the state in which they are located. Once a facility receives a **certificate of registration** from the DEA, it is referred to as a registrant. Registrants must have the security, control, recordkeeping, reporting, and inventory mechanisms required by the DEA to prevent loss and diversion of any controlled substances.
    - Several categories of registrations are available, depending on a registrant's principal activity. These categories are: Manufacturing (bulk or dosage form), Distributing, Reverse Distributing (controlled substance waste disposal), Dispensing or Instructing (for medical practitioners, hospitals/clinics, pharmacies and teaching institutions), Research with Schedule I substances, Research with Schedule II through V substances, Narcotic Treatment Program, Importing, Exporting, and Chemical Analysis
    - Our U.S. clients must receive certificates of registration before they may apply to import our products, which must be renewed annually , except for dispensing facility registrations (3 yrs).

IMPORTATION TO THE US

- Only three of the DEA registration categories allow the registrant to apply for authorization to import Schedule I substances: research, import, and chemical analysis. Registrants, such as manufacturers and distributors, without the ability to import must obtain controlled substances from another entity registered under one of the following categories:
  - "Research — Schedule I" registration. The primary activity of this category of registrants is research with Schedule I substances. Coincident activities include: manufacture or import of the "basic class" (i.e., encompassing all the chemical forms) of substance or substances for which registration was issued (provided that such manufacture or import is set forth in the research protocol approved by FDA), and distribution of such class to persons registered or authorized to conduct research with such class of substance or registered or authorized to conduct chemical analysis with controlled substances. We anticipate that the majority of our prospective clients will pursue DEA registration under this category.
  - "Importing" registration. The primary activity of this category of registrants is importation of controlled substances specified on the registration. Coincident activities include distribution of that substance or class for which registration was issued. Importers may not distribute any substance or class for which not they are not registered. Applications for import registrations are subject to a notice and comment period during which bulk manufacturers of the affected basic classes may file written comments or objections to the issuance of the proposed registration.
  - "Chemical Analysis" registration. The primary activity of this category of registrants is analysis of controlled substances. Coincident activities include manufacture and import controlled substances for analytical or instructional activities; distribution of such substances to persons registered or authorized to conduct chemical analysis, instructional activities, or research with such substance; and the conduct of instructional activities with controlled substances.
- In addition to needing a registration for their primary activities, the above registrants must apply for import permits from the DEA to import particular shipments. A separate permit is required for each shipment of a Schedule I substance to be imported.
- U.S. policy favors domestic production of controlled substances. If there are domestic manufacturers of the Schedule I substances, the registrant will have to justify the need for import.
- Registrants are responsible for selecting common or contract carriers that can provide adequate security to guard against in -transit losses.
- The DEA is required to limit imports by registered importers to amounts necessary to provide for the medical, scientific, or other legitimate needs of the United States in the case that competition among domestic manufacturers of the controlled substance is inadequate and will not be rendered adequate by the registration of additional manufacturers. In determining whether domestic competition is adequate, the DEA must consider price rigidity, conditions of supply and demand, and the extent of service and quality competition among the domestic manufacturers.
- In addition to complying with DEA policy regarding importation of Schedule I substances, our clients must also ensure that shipments comply with U.S. Customs and Border Protection, or CBP laws and regulations regarding the importation of merchandise from foreign countries.

CLINICAL TRIALS

- The clinical stage of development involves the administration of the product candidate to healthy volunteers or patients under the supervision of qualified investigators, who generally are physicians not employed by or under the trial sponsor's control, in accordance with good clinical practice, or GCP, requirements, which include the requirements that all research subjects provide their informed consent for their participation in any clinical trial.

- Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Furthermore, each clinical trial must be reviewed and approved by an institutional review board for each institution at which the clinical trial will be conducted to ensure that the risks to individuals participating in the clinical trials are minimized and are reasonable compared to the anticipated benefits.

- Clinical trials to evaluate therapeutic indications to support NDAs for marketing approval are typically conducted in three sequential phases, which may overlap.

    - Phase 1 — Phase 1 clinical trials involve initial introduction of the investigational product into healthy human volunteers or patients with the target disease or condition. These studies are typically designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, excretion, the side effects associated with increasing doses, and, if possible, to gain early evidence of effectiveness.

    - Phase 2 — Phase 2 clinical trials typically involve administration of the investigational product to a limited patient population with a specified disease or condition to evaluate the drug's potential efficacy, to determine the optimal dosages and administration schedule and to identify possible adverse side effects and safety risks. Phase 2 clinical trials are typically controlled and conducted in a limited patient population.

    - Phase 3 — Phase 3 clinical trials typically involve administration of the investigational product to an expanded patient population to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval and physician labeling. In most (though not all) cases, FDA requires two adequate and well controlled Phase 3 clinical trials to support approval of a drug. The Multidisciplinary Association for Psychedelic Studies recently completed Phase 3 trials of a study evaluating MDMA-assisted therapy for severe PTSD.

Source: SEC S1 Prospectus Registration Statement

CLINICAL TRIALS AND CURRENT STUDIES INVOLVING PSYCHOTROPICS

• Current focus is on Depressive Disorders, Anxiety Disorders, Post-Traumatic Stress Disorder, and Addiction

• Potential to enhance functional neuronal connectivity, stimulate neurogenesis, restore brain plasticity, reduce inflammation, and enhance cognition - study published in 2020 by Frontiers in Synaptic Neuroscience in the United Kingdom and reviewed by universities in the United States, Brazil, and Switzerland

• In 2021, scientists at the University of California at Los Angeles made significant discoveries about the interaction of LSD with dopamine that they believe may lead to a better understanding and eventual treatment of schizophrenia and that shows promise in the pursuit of treating physically crippling disorders such as Parkinson's disease.

• So far, only a single psychedelic has been permitted for legal, medical use in the USA: esketamine, a derivative of the previously known anesthetic ketamine, used to treat depression[106]. Psilocybin and MDMA are following suit with promising advances in clinical trials (Table 1):

Table 1. Current clinical trials for each psychedelic.

	Clinical trial status					
Psychedelic drug	Not yet recruiting	Recruiting	Active, not recruiting	Completed	Total	Indications
DMT/ayahuasca	–	4	1	2	7	Healthy, mood, cognitive function, social, empathy, treatment-resistant depression, major depressive disorder, depression, psychedelic experiences
Psilocybin	12	30	11	12	65	Obsessive–compulsive disorder, depression, migraine, Parkinson's disease, anorexia nervosa, bipolar II disorder, autism, fibromyalgia, hyperphagia, trauma, anxiety, treatment-resistant depression, healthy, perception disturbance, visual suppression, psychedelic experiences, opioid use disorder, cancer, body dysmorphic disorders, alcohol use disorder, cocaine-related disorder, cluster headache, Alzheimer disease, nicotine dependence, posttraumatic headache, religious or spiritual problem, grief, distress, pharmacological actions
LSD	1	5	1	1	8	Cluster headache, major depressive disorder, anxiety disorder, brain relaxation, healthy
MDMA	7	8	2	38	55	Psychological effects, social anxiety disorder, healthy, anorexia nervosa restricting type, binge-eating disorder, posttraumatic stress disorder, combat stress disorders, diabetes insipidus, depression, substance-related disorders, amphetamine-related disorders, metabolism, drug addiction, hangover, mechanism of action, social cognition, social anxiety in autistic adults, psychopathology, autism spectrum disorder, abuse liability
Mescaline	–	2	–	–	2	Healthy
Ketamine	50	126	22	419	617	Anesthesia, Parkinson's disease, depression, major depressive disorder, traumatic brain injury, suicidal ideation, anxiety, epilepsy, treatment-resistant depression, acute pain, bipolar I/II disorder, healthy, neuropathic pain, postpartum depression, prenatal depression, opioid use disorder, adolescent suicide, adolescent depression, trauma, chronic pain, cluster headache, postoperative pain, borderline personality disorder, obesity, Rett syndrome, anorexia nervosa, cancer, substance use disorder, social anxiety disorder, obsessive–compulsive disorder, sepsis, posttraumatic stress disorder, multiple sclerosis, alcohol dependence, NMDA receptor function, chronic low back pain, functional neuroimaging, obstructive sleep apnea, schizophrenia, dental anxiety, breast cancer pain

Data obtained from NIH ClinicalTrials.gov. Search conducted: 1 December 2021. 'Healthy' denotes patient trials with no disease indication or outcome but merely the effects of the drug itself.
DMT: N,N-dimethyltryptamine; LSD: Lysergic acid diethylamide; MDMA: 3,4-methylenedioxymethampetamine.

Source: "The Promise of Psychedelic Research"

US RESEARCH CLIENTS PROTOCOL

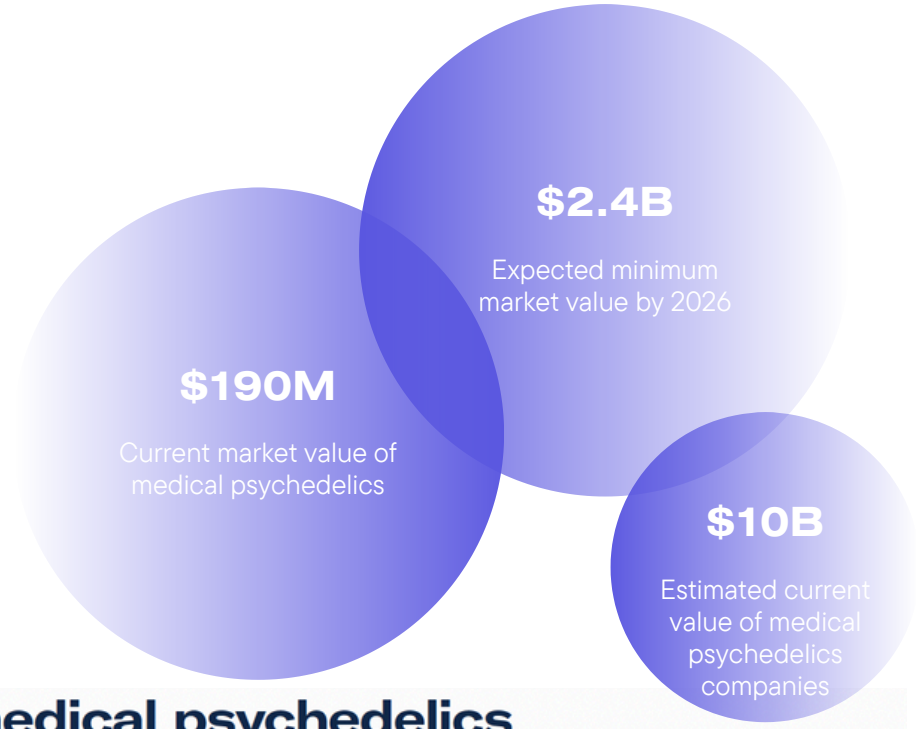
- The research facilities at U.S. academic institutions or companies conducting research that wish to study Schedule I controlled substances must, in addition to meeting the applicable requirements described above, send their research protocol to the DEA.
    - The research protocol must include a statement of the purpose of the research project; the researchers' institutional affiliation and qualifications; the name of the Schedule I substances involved and the amount of each needed; and the source of the Schedule I substances, including whether they will be provided by a domestic or foreign manufacturer; a description of the research to be conducted; a statement of the security provisions for storing and dispensing the substances in a way that prevents diversion; and a statement of the quantity and sources of the substances to be manufactured or imported.
    - All of the foregoing will be submitted by the DEA to the Department of Health and Human Services (HHS) for approval. The research registrant must justify the need for import of the substances, and HHS must approve the importation as part of the research protocol. If the registrant has already submitted an Investigational New Drug, or IND, application to the FDA, proof of such application may be submitted to the DEA in lieu of the foregoing.
    - If a research registrant needs to increase the quantity of a Schedule I substance used for an approved research project, a request must be submitted to the DEA, which will forward the request to FDA for approval. Any change in the research protocol likewise must be submitted to the DEA.
    - In September 2021, the U.S. Office of National Drug Control Policy (ONDCP) issued a legislative proposal to the U.S. Congress to amend the process for obtaining a DEA registration for research with Schedule I substances to align it more closely with Schedule II research registrations. If implemented, the changes may shorten the timeline and simplify the paperwork required for U.S. research facilities to obtain registrations allowing them to access Schedule I substances for scientific purposes. On December 2, 2021, the DEA expressed support for ONDCP's proposal via written testimony submitted to a House Energy and Commerce subcommittee.

- Before testing any drug in humans, the product candidate must undergo rigorous preclinical testing. Preclinical studies include laboratory evaluations of drug chemistry, formulation and stability, as well as in vitro and animal studies to assess safety and in some cases to establish the rationale for therapeutic use. The results of the preclinical studies, together with manufacturing information and analytical data, must be submitted to FDA as part of an IND. An IND is a request for authorization from FDA to administer an investigational product to humans and must become effective before clinical trials may begin.

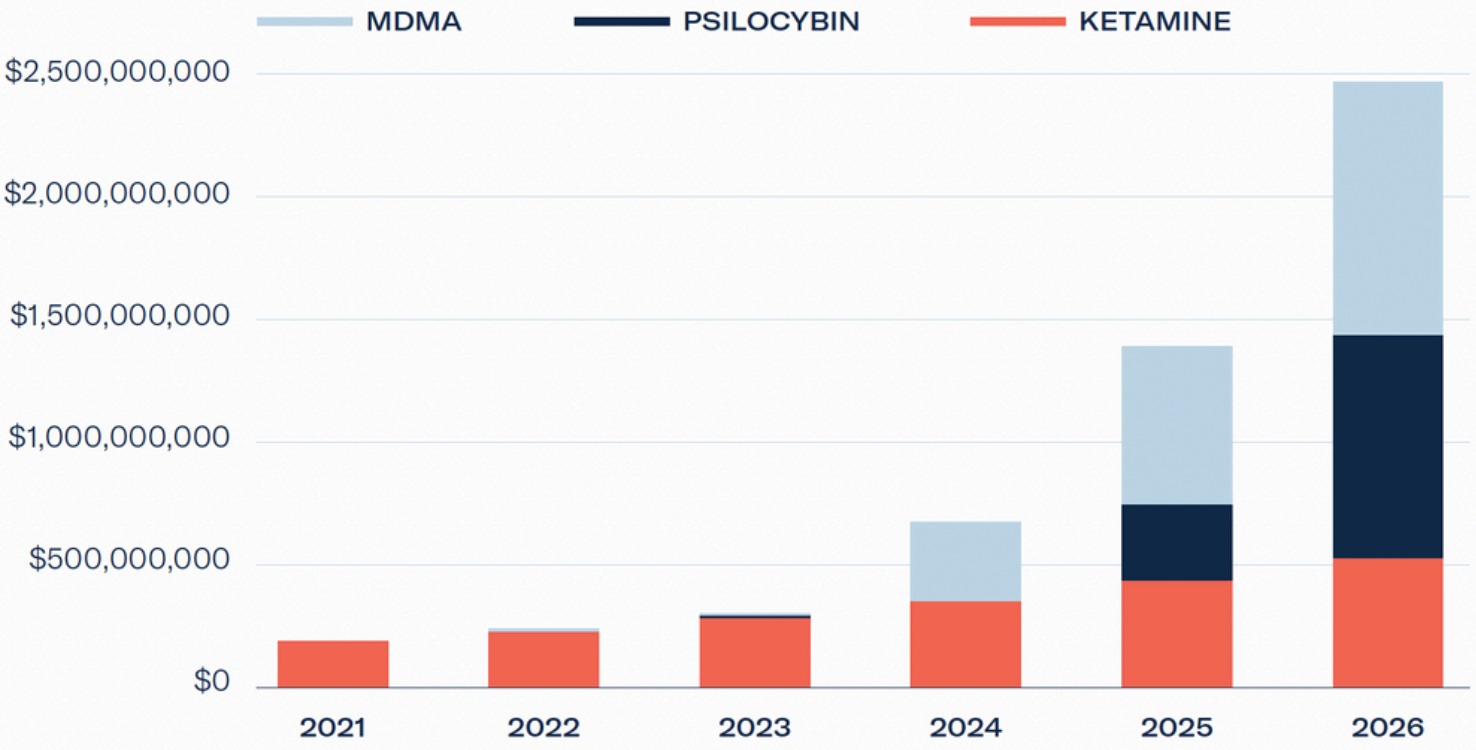
Source: SEC S1 Prospectus Registration Statement

CURRENT STATE OF THE MARKET

According to Our World in Data, the share of the population with mental health and substance use disorders stands at nearly 1 billion people, or 15% of the world population, a proportion that has been stable or rising since 1990. There have been no significant changes in mental health treatments in the last 30 years; up to a third of those suffering from depression do not respond adequately to a course of appropriate antidepressant medication. **The societal burden of depression amounts to more than US$490 billion per year for the US alone**, eclipsing the societal costs of cancer or diabetes.



Projected growth of medical psychedelics market revenues



Source: Blossom

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

LIST OF HEALTH CONDITIONS AND THE PSYCHEDELIC SUBSTANCES WITH THE POTENTIAL TO TREAT THEM:

Source: PSYCH The Psychedelics as Medicine Report 3rd Edition

HEALTH CONDITION	PSYCHEDELIC SUBSTANCE								
	Psilocybin	LSD	MDMA	Ketamine	Ibogaine	Ayahuasca	DMT/5-MeO-DMT	Mescaline/ Peyote	Salvinorin A/Salvia
Depression (MDD) (TRD)	✓	✓	✓	✓		✓	✓	✓	✓
Bipolar disorder				✓					
Suicidal Ideation				✓					
Anxiety	✓	✓	✓	✓				✓	✓
Autism (Social Anxiety)			✓	✓					
PTSD	✓	✓	✓	✓		✓	✓	✓	
Eating Disorders			✓	✓		✓			
Alcohol Use Disorder	✓		✓	✓		✓			
Opioid Use Disorder				✓	✓	✓			
Chronic Pain			✓	✓					
ADHD		✓							
Cluster Headaches	✓	✓							
Stroke							✓		
OCD	✓			✓					
Inflammation		✓		✓				✓	

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

CURRENT OPPORTUNITIES

What and where are the next emerging markets?

Facilitatiors and Training Centers

- Educating therapists

Practice and Treatment Centers

- Direct access to patients as allowed
- Religious access?

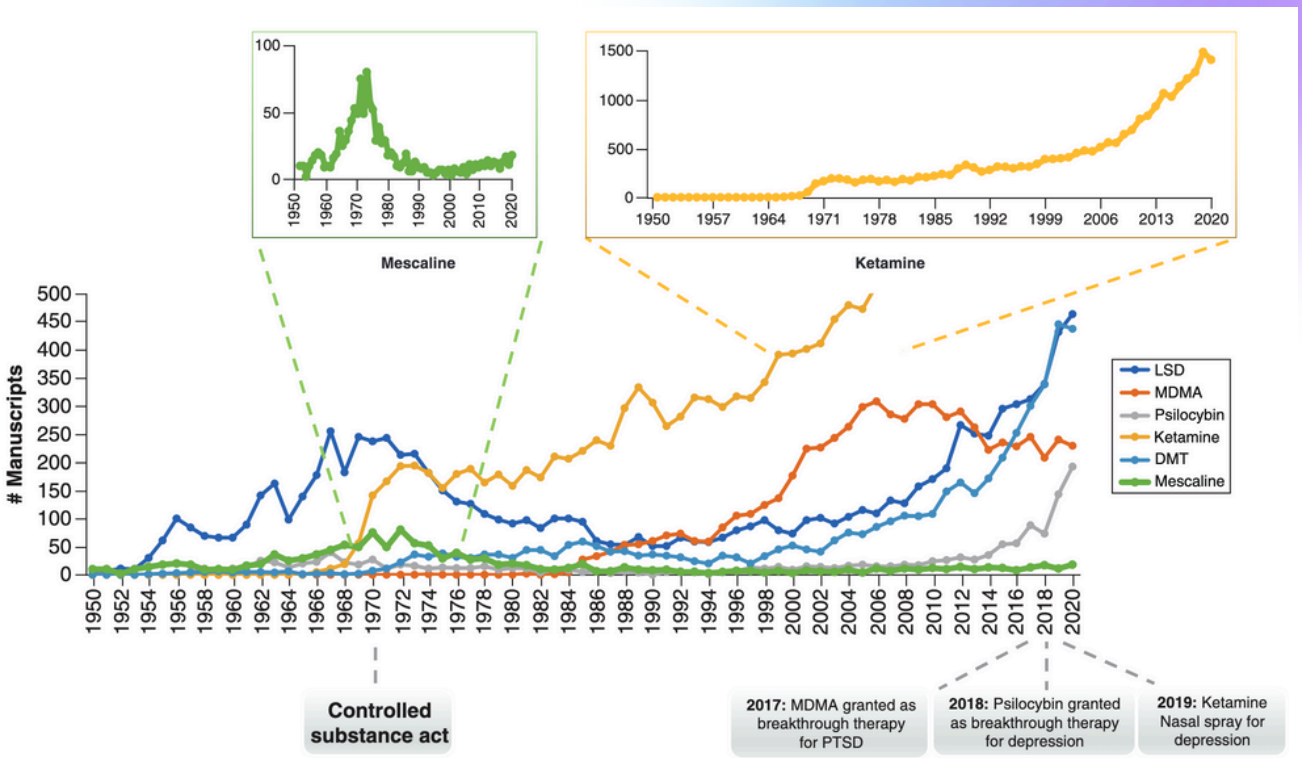


Figure 2. Timeline of research on the different structural motifs of first-generation psychedelics. Notice the distinct high peaks for publications on each psychedelic. The data were obtained from a PubMed search for publications with the search terms 'DMT, *N, N*-dimethyltryptamine, psilocybin, psilocin, 4-phosphoryloxy-*N,N*-dimethyltryptamine, LSD, lysergic acid diethylamide, MDMA, 3,4-methylenedioxymethamphetamine, mescaline, 3,4,5-trimethoxyphenethylamine and ketamine', conducted on 20 November 2021.

Interesting Covid Data

A survey in the Netherlands (n=377) found that regular participants in ayahuasca ceremonies showed better general well-being, fewer lifestyle-related diseases, more physical activity, and a more balanced diet than Dutch normative data. Ceremony attendees also used less alcohol throughout the COVID-19 pandemic, but they did use more illegal drugs than the general population.

CURRENT PSYCHEDELIC NEWS - Emerge Law

Decriminalization, Legalization, & State Efforts

- Maryland Bill To Fund Psychedelics Research And Access For Veterans Takes Effect Without Governor's Signature
- Michigan Activists Give Up 2022 Push For Psychedelics Legalization Ballot Initiative, Shifting Focus To 2024
- Oregon Officials' Rejection Of Rules For Spiritual And Religious Psilocybin Use Called Into Question

Research, Science & Therapy

- Tripping over the potential of psychedelics for autism
- The 18 clinical trials that could make or break the future of the $100 billion psychedelics industry

Business

- 'We spark curiosity': how the psychedelics industry is taking on Davos
- Why this startup is encouraging employees to microdose psychedelics at work
  - MUD\WTR does not include psychedelics in the mushroom coffee it sells—yet. If the legal landscape changes, founder and CEO Shane Heath says that would definitely be something he would explore. But MUD\WTR does support employees who want to microdose magic mushrooms at work.
- Psychedelics Co. Silo Wellness To Acquire Dyscovry Science, Seeking To Leverage Its Govt. Partnerships

World

- British Columbia to Decriminalize Possession of Most Drugs
  - Under the new regulations going into effect on January 31 of next year, those caught with under 2.5 grams of illicit drugs, including heroin and fentanyl, will not face jail time within the Canadian province of 5 million people. Furthermore, police will not seize the drugs, but rather will provide information about accessing addiction and health services.

Culture

- What happens when you combine psychedelics with cybernetics?
- What Do Zoomers Like? Pot or Shrooms, Not Booze
  - Of people aged 18 to 24, 69% prefer marijuana to alcohol
  - More than 10% of Gen Z adults report having used psilocybin in the past six months, versus 3.4% for the general population. Its survey, of 5,000 people, followed Gen Z'ers aged 21 to 23.
- Psychedelic Businesses Offer Guided Trips to Soothe Your Mind
  - Retreat Centers in other countries like Jamaica

Socio-psychedelic imaginaries: envisioning and building legal psychedelic worlds in the United States

In this sociology-based paper, the concept of American socio-psychedelics imaginaries is introduced, i.e., collective visions articulated and enacted to reintegrate psychedelics legally and responsibly into society. These imaginaries diverge and converge around several politics: politics of access, politics of responsibility, politics of naming, politics of assimilation and social change, and politics of epistemic credibility.

TRANSPERSONAL TREATMENTS
Pillars of psychedelic therapy:

Pillars of psychedelic therapy:

- Doing your own work
  - Integrate your own plant medicine relationship
  - Learn your own nervous system first
  - Breathwork practice – can be interesting framework for psychedelic work in non-ordanary state that can act as a similar style of catharsis
  - Transferrance/countertransferrance sensitivity
  - Somatic experience training, kokomi training, personal integration modalities process
- How can you help them?
  - Create the container for inner healing wisdom
- Above ground using ketamine or cannabis assisted therapy
- Someone below ground who can do deep trauma work
  - Start with the basics

- Coaching is all you can do without a masters, under ground or Indigenous stewards
- Masters degree is necessary or PhD or psychD
- In Oregon you may just need HS degree plus a certification
- Psychotherapy for serious trauma patients with intention and specific training
- Titrated approach to slowly work up into safety after establishment
- "Are you at a place in your life right now where you can tolerate things getting worse before they get better?" Can I tolerate this now? Is this the right time for this treatment to reshape your world? Where are you at in life?
- Strong network for integration – friends, family, support, career, relationships
- Non-specific amplifiers of the current mental state – safety is key.
- Explore worst-case scenarios and provide psychoeducation in preparation – importance of informed consent leading up to the treatment
- drugsdata.org and dancesafe test kits
- psychedelics.support to act as an integration work coach – sheri gedasi, navigating psychedelics

- Above-ground psychedelics-assisted psychotherapists
  - Get educated on substances, process, preparation, harm reduction, and integration to support these big experiences as a safety net with trauma-focused training as well
- Clinical drug research in addition to a holistic psychedelic ecosystem
- provide integration support
- ketamine-assisted psychotherapy is very accessible
- Journeyclinical decentralizes ketamine treatment for therapists by referral after they have received the prescription
- Licensed therapists in decriminalized areas – first check licensing boards
  - May give up license or take on risk of losing license
  - Hosting ceremonies – questionable in decriminalized areas for state/fed
- Oregon legalized adult-use service centers will only require a HS diploma plus additional training that was approved by Oregon health association in order to be a facilitator
- ok with certainty and the unknown
- Peer support groups? How do we make these experiences accessible?
- Provide training for people to get the basics and hold a safe educational space
- We're building the psychedelic assisted therapy scaffolding – how do we also build safety a net as well? Additional support from the traditional or new state-run training

"The promise of psychedelic research" notes

- A prominent contemporary researcher, DavidNichols, has defined psychedelics as “powerful psychoactive substances that alter perception and mood and affect numerous cognitive processes”[5]. Within the last decade, David Olson and colleagues established the new term ‘psychoplastogen’ to include psychedelics that can “re-grow atrophied neurons and heal the brain”, rather than simply treating disease symptoms.
- A collaborative approach across disciplines has already begun between medicinal chemists, biologists, neuroscientists and clinicians, to bring the first-generation psychedelics to the market
- Psychedelics have been further divided into two subcategories: hallucinogens (e.g., psilocybin, LSD) and entactogens (e.g., MDMA) due to their subjective effects[48]. Nevertheless, all would still be considered ‘psychoplastogens’ due to their neuronal functional and structural attributes, addressed later in the neural plasticity section of this review. While not necessarily a classic psychedelic, ketamine is considered a ‘dissociative anesthetic’. It is now referred to in the literature as an antidepressant[55].
- The first generation of US FDA-approved psychedelics are considered the classic psychedelics – namely psilocybin, MDMA and LSD; they have existed for centuries, if not millennia, and are schedule I controlled substances in theUSA. Numerous actively recruiting and completed clinical trials illustrate their therapeutic benefits (Table 1).
- The second generation of psychedelics builds upon existing research to create tailor-made molecules. These drug are likely to lag at least 2–3 years behind the first generation. A primary goal within the second generation is to develop drugs with shorter-lasting effects that are derivatives of the classic first generation.
- Activation of the 5-HT2Areceptor is considered to be the key to the effects of psychedelic drugs in humans. Cryo-EM is a newer technology that allows scientists to visualize massive complexes without crystallization. For example, scientists revealed the first 3D structure of LSD actively bound to a 5-HT2A receptor using cryo-EM[81].
- Ketamine, which remains the most well-studied dissociative drug amidst the class of psychedelic studies currently ongoing, can promote both structural and functional plasticity in thePFC, and this has been hypothesized as contributing to its fast-acting therapeutic effect. It is well documented that the NMDA receptor plays a central role in synaptic plasticity via long-term potentiation of hippocampal neurons which subsequently induces phosphorylation of the transcription factor CREB[91,92]. Both ketamine and the classic serotonergic psychedelics increase the sprouting of neurites from neuronal cell bodies (neuritogenesis) and generatedendritic spines in neurons (spinogenesis)in vitroandin vivo[84]. Additionally, these structural developments complement increased synapse number and function (synaptogenesis)[84]. The two key receptors and subsequentcell signaling pathways identified thus far are: the tyrosine kinase family B (TrKB) receptors and the 5-HT2A receptors; and finally, activation of the mTOR cell signaling pathway[84,93].
- TrKB receptor activation plays an essential role in mechanisms of neural structural plasticity, specifically the synthesis of proteins essential for synaptogenesis to occur. BDNF has a high affinity for TrKB and sets off a series of signaling pathways, including mTOR-mediated neural structural plasticity via this direct relationship[93]; therefore, the role of BDNF in both neuritogenesis and spinogenesis has been well established[94]. Psychedelics have been shown to elevate levels of glutamate in addition to BDNF in the PFC, while activating some genes associated with plasticity[93]. Also, other 5-HT signaling drug classes (e.g., SSRIs) without the hallucinogenic effect of psychedelics were previously shown to activate neurogenesis via the well-known BDNF/TrKB-mediated path[72,95].
- The pathological hallmark of psychiatric conditions like depression is the presence of atrophied neurons in theprefrontal cortex, and psychedelics address this issue by modulating mechanisms related to neural plasticity via 5-HT2A receptor agonism and are fast acting compared with their predecessor, the SSRI.