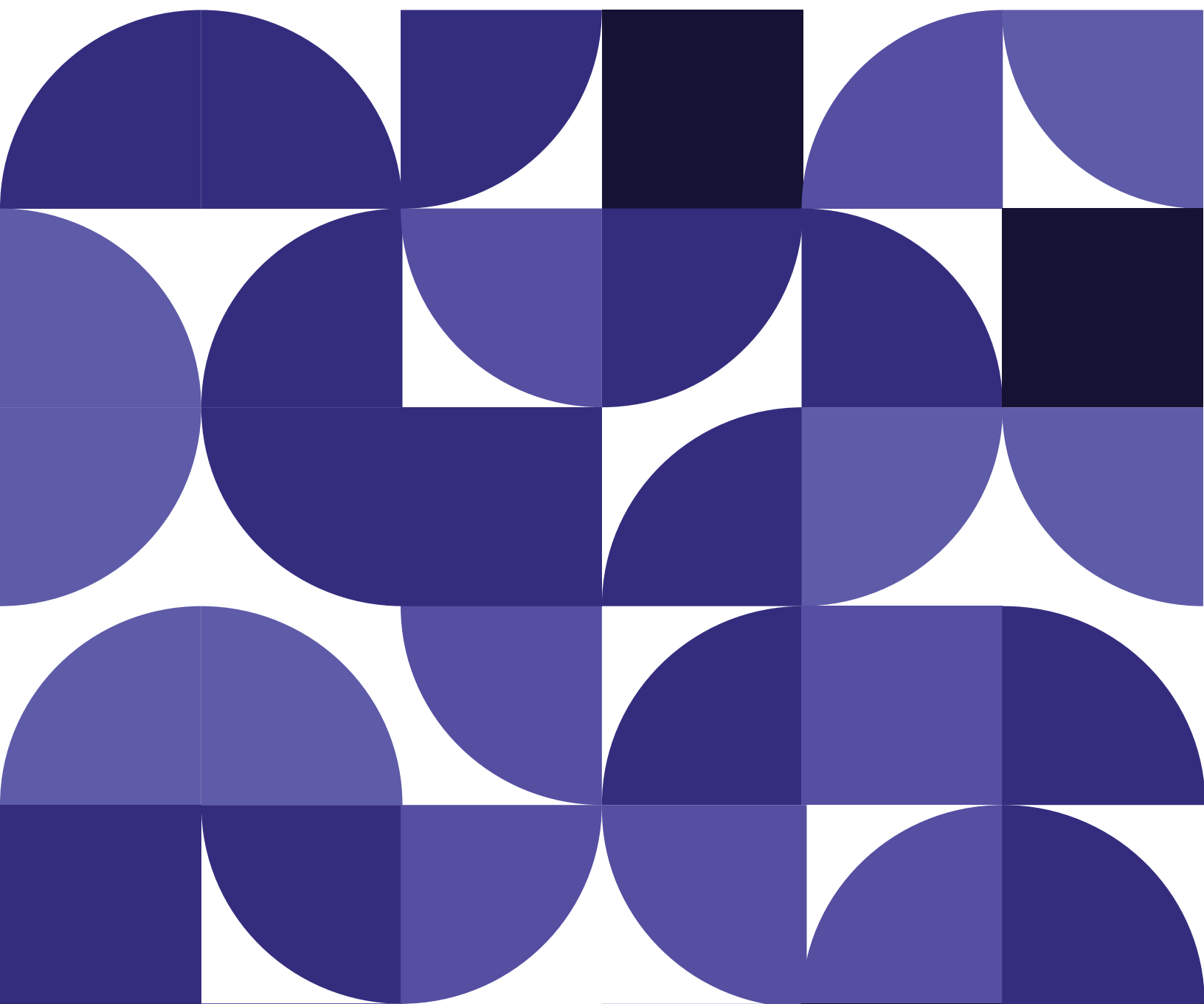


BRAIN FUTURE S

# Psychedelic Medicine

A Review of Clinical Research for a Class of  
Rapidly-Emerging Behavioral Health Interventions



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The opinions and recommendations expressed herein are based on the research of BrainFutures and are intended for informational use only. The content does not constitute medical advice and is subject to change. Before pursuing any course of treatment for a behavioral or medical condition, including the use of psychedelic-assisted therapy, always seek the advice of your physician or other qualified health provider, and review the information together.

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# Executive Summary

**P**sychedelic-assisted therapy (PAT) is rapidly moving towards mainstream clinical applications. A considerable body of research is finding that these compounds, once deemed unfavorable by most of society, are in fact effective at treating serious mental health and substance use disorders (MH/SUDs). Recent well-designed studies at major research universities and research-based organizations are showing compelling results when psychedelic compounds are combined with psychotherapy and administered in a supervised clinical setting. PAT is making a name for itself beyond just study participants and clinicians. Academia, media, industry, legislators, regulators, and the public are all participating in PAT's swift advancement.

With unprecedented interest at hand and a mental health crisis gripping the world, it is imperative to understand the body of evidence that demonstrates the efficacy, effectiveness, and safety of this class of interventions. This report reviews the relevant research to date, focusing on the following set of compounds defined as psychedelics herewithin: psilocybin, ketamine, 3,4-methylenedioxymethamphetamine (MDMA), lysergic acid diethylamide (LSD), N,N-dimethyltryptamine (DMT), ibogaine, and mescaline. Psilocybin, LSD, DMT, and mescaline are often referred to as classic psychedelics due to some shared mechanisms of action. Classic psychedelics primarily exert their effects through specific serotonin pathways in the brain.

What some in the field refer to as non-classic psychedelics, MDMA, ketamine, and ibogaine, are nonetheless considered psychedelics due to their relatively similar experiential effects and potential use for treatment as part of PAT, although their mechanisms of action may differ in some regards from classic psychedelics. Neuroscientific

research has covered extraordinary ground since psychedelic research began, yet more is still to be discovered relative to classic and nonclassic psychedelics' mechanisms of action, overlapping effects on neural networks, and the impact of subjective effects.

## THE RESEARCH

**A** groundswell of research investigating the effects and applications of psychedelics gained momentum in the 1950s. Many studies showed promising results for several compounds' potential as MH/SUD treatments. The Controlled Substance Act of 1970, however, meant that despite early findings, most of these compounds would be classified as Schedule I drugs (assigned to drugs with high potential for abuse and no medical value). As a result, public research money dried up and the field was largely dormant for decades. Due in large part to private philanthropy and persistent researchers, these investigations have accelerated significantly over the past 25 years, and today, a body of clinical outcomes points to effective applications for conditions such as major depressive disorder (MDD), treatment-resistant depression (TRD), post-traumatic stress disorder (PTSD), other anxiety disorders, and substance use disorders (SUD).

Based on recent clinical trials, the Food and Drug Administration (FDA) has granted Breakthrough Therapy designation—a process designed to expedite the development of treatments that hold the potential for substantial improvement compared to available treatments (FDA, 2018)—to three trial sponsors/manufacturers: COMPASS Pathways (psilocybin for TRD), Multidisciplinary Association for Psychedelic Studies (MDMA for PTSD), and Usona Institute (psilocybin for

MDD). This has advanced further research using these psychedelic compounds in combination with psychotherapy to Phase 2 and Phase 3 trials.

Given our global mental health crisis, breakthrough therapies are exactly what is needed. National Institute for Mental Health former director Thomas Insel, MD states:

“Today there are about 30 different antidepressants, 20 different antipsychotic drugs, seven different mood stabilizers used in bipolar disorder, and [six] different classes of drugs for Attention Deficit Hyperactivity Disorder (ADHD). Almost none of these are more effective than the medications we had [three] decades ago, although newer medications have different and, in some cases, better side-effect profiles” (Insel, 2022).

Since the late 50s, more than **36,000** total research papers have been published on psychedelics.

Much of today’s psychedelic research is informed by earlier studies. Since the late 50s, more than 36,000 total research papers have been published on psychedelics, many investigating the mechanisms of action, reporting on observational studies, or offering reviews on specific applications and outcomes. Of these publications seeking to validate or invalidate effective use of said compounds for clinical applications, there have been approximately:

- 491 randomized-controlled trials (RCTs);
- 76 meta-analyses; and
- 1,759 reviews

BrainFutures reviewed the research and selected relevant studies to summarize in our report—the majority of which not only had valid study designs and methodologies, but also worked with human subjects and

investigated the use of these compounds as effective or efficacious treatments in participants with ongoing and hard-to-treat MH/SUDs. In total, BrainFutures outlines and summarizes more than 200 peer-reviewed publications involving psychedelics, including 46 randomized controlled trials (RCTs) and 47 open-label studies with more than 4,000 participants, in addition to eight meta-analyses and 84 reviews. (The eight meta-analyses<sup>1</sup>

THIS REPORT SUMMARIZES

46

RANDOMIZED CONTROLLED TRIALS

47

OPEN LABEL STUDIES

8

META-ANALYSES

84

REVIEWS

=4,650+

STUDY PARTICIPANTS INVOLVED



covered 34 studies and 1,375 subjects, of which 19 studies with 650 participants are in addition to the studies cited directly in this report.)

Across all these studies, the aggregate evidence is positive. While each compound has different specific applications for various conditions, as a set of compounds and potential treatments the clinical evidence for PAT shows noteworthy levels of effectiveness for treating serious MH/SUDs. In fact, compared to treatment as usual (TAU), such as existing psychopharmacology and psychosocial therapies, a growing number of studies of these compounds are demonstrating higher levels of short- and/or long-term effectiveness. These positive outcomes, compared to the lack of consistent effectiveness of many psychotropic drugs and psychosocial treatments are, in part, a main driver in the acceleration of research and investment in the field.

**“Although there is a general public perception that psychedelic drugs are dangerous, from a physiologic standpoint they are in fact one of the safest known classes of [central nervous system] drugs.”**

Additionally, scientific evidence concludes that psychedelics are generally safe from a physiological point of view. In a review written in 2016 by David Nichols, PhD, from University of North Carolina’s Eschelman School of Pharmacy, the author states:

“Although there is a general public perception that psychedelic drugs are dangerous, from a physiologic standpoint they are in fact one of the safest known classes of [central nervous system] drugs. They do not cause addiction, and no overdose deaths have occurred after ingestion of typical doses of LSD, psilocybin, or mescaline” (Nichols, 2016).

With most compounds, and throughout the bulk of the research, a PAT course of treatment includes pre-treatment assessment, the psychotherapeutic component of preparation, the application of the compounds with a several-hour therapeutic and/or supervised observation period, and subsequent therapeutic integration. The intensity of these compounds’ effects requires this suite of comprehensive treatment components, differentiating PAT from standard mental health and substance use interventions—whether they be medication only, therapy only, or a combination of the two.

#### KEY PAT RESEARCH HIGHLIGHTS

The need for mental health and substance use innovations is felt across the field—from providers, to payers, to patients. Approximately 25 million adults in the United States have been on antidepressants for at least two years, a 60 percent increase in less than a decade (Carey & Gebeloff, 2018). Yet for many, these medications have side effects that patients want to avoid. New solutions are urgently needed. Research involving the medicinal use of psychedelics is showing significant promise. Several noteworthy highlights from related studies include the following:

- After two PAT sessions with psilocybin, at least 70 percent of participants with cancer-related psychiatric distress showed clinically significant reductions in symptoms in more than one study (Agin-Liebes et al., 2020; Ross et al., 2021).

- A Phase 2 trial found psilocybin was efficacious in treating MDD, with a clinically significant response in 71 percent of participants and remission from depression in 54 percent at four weeks post treatment (Davis et al., 2021).
- An open-label study using psilocybin to treat MDD in cancer patients demonstrated safety and feasibility, with 50 percent of participants achieving remission in depression symptoms after a single dosing session, which was sustained eight weeks post treatment (Maryland Oncology Hematology, 2021).
- A Phase 2b clinical trial found that a single dose of psilocybin led to statistically significant and clinically relevant reductions in depressive symptoms (COMPASS Pathways, 2021a).
- Intravenous ketamine infusions have demonstrated to be superior to placebo in treating MDD, showing reduced symptoms within 24 to 72 hours (Kraus et al., 2017).
- Ketamine indicated effectiveness for TRD, with response rates over 60 percent within 24 hours, and lasting up to four weeks after end of treatment for a portion of patients (Wan et al., 2015).
- A single infusion of ketamine rapidly reduced symptoms of refractory anxiety within one hour, lasting up to seven days (Glue et al., 2017).
- Two MDMA PAT sessions reduced symptoms of chronic PTSD that were non-responsive to typical psychotherapy or psychopharmacology for up to 74 months (Mithoefer et al., 2013).
- Long-term follow-up (LTFU) outcomes of trials investigating MDMA-assisted therapy for treating PTSD showed that the percentage of participants that no longer qualified for PTSD diagnoses increased from 56 percent to 67 percent between treatment exit and LTFU (Jerome et al., 2020).
- Two to three sessions of MDMA-assisted therapy were found to be more effective at reducing symptoms of PTSD than the current selective serotonin reuptake inhibitors (SSRI) PTSD treatments paroxetine and sertraline (Feduccia et al., 2019).
- The world's first FDA Phase 3 trial using MDMA to treat PTSD found that after three MDMA-assisted therapy sessions, 67 percent of participants no longer qualified for a PTSD diagnosis, and 88 percent experienced a clinically significant reduction in symptoms (Mitchell et al., 2021).

## COST BENEFITS AND INVESTMENTS

**W**hile comprehensive cost analyses have not been completed across all compounds, existing evaluations show significant savings for treatment of mental health conditions. One such study found that if 1,000 people with PTSD were treated with MDMA-assisted therapy in lieu of TAU, the cost savings over a 30-year period would be in excess of \$130 million (Marseille et al., 2022). Another recent report estimates that PAT interventions could save \$270 billion in employer absenteeism/presenteeism costs and healthcare expenses in the U.S. alone (Blossom, 2021).

**Commercial investment in research and development, production, patents, and market development has been greater than \$2 billion.**

With these levels of estimated cost savings and a marked increase in clinical research over the past decade, an impressive amount of investment has poured into this space. This kind of financial activity indicates significant commercial interest and confidence that psychedelic-based treatments will overcome regulatory barriers to find their way into the MH/SUD treatment paradigm.

Philanthropic investment in psychedelic medicine over the past several years has exceeded \$200 million (Psychedelic Science Funders Collaborative, 2021). Simultaneously, commercial investment in research and development, production, patents, and market development has been greater than \$2 billion, with 85 percent of these companies in North America and 15 percent in Europe; currently, 46 psychedelic companies are publicly traded with a combined market cap north of \$6 billion (Blossom, 2021).

### THE TIDE OF PUBLIC OPINION IS TURNING

**I**ncreases in PAT research at academic institutions and companies, widespread media attention, and the decriminalization of psychedelics in many locales, have influenced greater mainstream acceptance of these compounds over the past several years. A recent report highlighted that in a June 2021 survey conducted across five countries, two thirds of Europeans and Americans support legalization of psychedelics for medicinal use (Blossom, 2021). Proprietary research from that report's authors shows that Americans are receptive to PAT, with 71 percent supporting coverage by health insurance. Similarly, if faced with a medical condition for which PAT was shown to be safe and effective, 70 percent would consider it. Additional signs of changing public sentiment are reflected in psychedelic-related decriminalization efforts taking place in cities across the United States—from Oakland, CA to Cambridge, MA. It is not just municipalities taking action; state governments are also engaged. Oregon voted to legalize psilocybin's use with a licensed facilitator in 2020, and other states, including California and Hawaii, are actively exploring loosening legal restrictions on these compounds.

### RECOMMENDATIONS

**T**aking all these inputs together—a large and rapidly growing body of evidence supporting the effectiveness and relative safety of psychedelics as treatments for MH/SUDs, potential cost savings to healthcare payers and the treatment system overall, large and increasing public and private investment in the space, and a changed view on these compounds from notorious to potentially efficacious—it appears, by all measures, that a new era of PAT is close at hand. PAT offers new, 21st century, scientifically-validated applications for serious, treatment-resistant and refractory conditions, as well as potential applications for other MH/SUDs. Based on our research, BrainFutures' recommendations are as follows:

#### **1. Certain PAT interventions with sufficient evidence levels for safety and efficacy should be rapidly adopted once approved by the FDA.**

As a national nonprofit focused on the public good and committed to ways to improve mental health and well-being across all populations, BrainFutures believes a core segment of the rapidly evolving PAT field shows promising efficacy and safety and should be made available as treatments as soon as regulatorily-required studies prove continued safety and efficacy outcomes. Specifically, BrainFutures recommends fast and widespread adoption for PAT therapies, including psilocybin- and MDMA-assisted therapies, upon FDA approval.

BrainFutures also recommends that the U.S. Drug Enforcement Agency (DEA) release safeguards ensuring that the immunity protections of state and federal Right to Try Acts extend to investigational Schedule I substances. In the short-term, this will mean patients with life-threatening or serious conditions will be able to legally access PAT interventions prior to FDA approval.

## **2. Reimbursable and equitable access to approved psychedelic therapies is essential and all payers should adequately cover PAT treatments.**

BrainFutures advocates for all major commercial, government, and self-insured employer payers to make equitable widespread access to ketamine-assisted therapy—and eventually psilocybin- and MDMA-assisted therapies—a reality through adequately covered treatment. This means reimbursement needs to include all related treatment components, including assessment, therapeutic preparation, medication/dosing session (compound, therapy, and observation), and integration therapy.

Ketamine-assisted therapy, along with psilocybin- and MDMA-assisted therapies, are reporting efficacious outcomes for some of the most challenging MH/SUDs, including TRD, PTSD, and addiction (Luoma et al., 2020), as well as positive effects on personality, affect, and well-being (Aday et al., 2020). Findings also show shorter total treatment durations than many current treatment options, which translates to lower health-care-related costs. Research suggests that these treatments can be significantly more effective than current customary treatments including therapy and prescription medications, or in the case of ketamine, can be used as an effective catalyst to TAU, with practitioners reporting that ketamine-assisted therapy accelerates the therapeutic process. This report endorses a future where ketamine and specific Schedule I psychedelics with FDA-approval, along with their assisted therapies, are adequately covered by public and private healthcare payers, making equitable access possible.

## **3. Public research dollars should be invested in advancing the field.**

Findings to date on DMT and ibogaine as potential MH/SUD treatments are favorable, yet these compounds currently have a lower volume and rigor of research. LSD-assisted therapy was well-researched in the mid part of the 20th century and showed promise as a psychiatric intervention, though it too still requires additional studies using modern research standards. To date, mescaline has the smallest body of research but holds some encouraging findings especially related to substance use interventions. All of these compounds, along with more rigorously researched psilocybin, ketamine, and MDMA, are deserving of increased federal, state, as well as private research dollars, to expand their potential therapeutic reach and impact. Since the passing of the Controlled Substance Act in 1970, which controversially categorized most psychedelics as Schedule I substances, the advancement of research has been wholly dependent on private philanthropy and commercial investment. Given the demonstrated outcomes to date, public monies in this field are needed to stem the tide of today's mental health crisis.

# Introduction

In the U.S. during the 1950s and 1960s, psychedelic compounds came into sharper focus for pharmaceutical and academic researchers as well as for many clinicians who had the legal opportunity to work with them in their practices.

By the 60s, these drugs had fully captured the attention and use of party-goers of the cultural revolution. Overuse and perhaps abuse of psychedelics quickly led to more restrictive laws, and ultimately, in tandem with the Nixon administration's War on Drugs, in 1970 most psychedelic compounds were classified as Schedule I substances, considered to have "no currently accepted medical use and a high potential for abuse," according to the Drug Enforcement Agency (DEA). At the time, listing most psychedelics as Schedule I was seen by many researchers to be politically motivated and not evidence-based, as studies prior to 1970 showed medical promise for a number of compounds. Although initial research involving psychedelic compounds was not as rigorous as current scientific investigations, it did include a wide variety of studies that identified mechanisms of action, evaluated tolerability, and investigated clinical applications for treating mental health and substance use disorders (MH/SUDs). Nonetheless, with the DEA's scheduling decision, research funding quickly receded, as did the legal availability of the compounds for further study.

Few studies were conducted for decades, followed by a nascent reemergence in research in the late '80s and into the '90s. Slowly, privately funded and federally-approved research increased, along with the DEA's allowable production of said compounds for scientific purposes. Over the past decade, the number of clinical studies has grown significantly.

Private research funding has resulted in new and promising findings for psychedelic-assisted therapy (PAT), particularly for hard-to-treat conditions such as major depressive disorder (MDD),<sup>2</sup> treatment-resistant depression (TRD),<sup>3</sup> addiction, and post-traumatic stress disorder (PTSD). Finally in

2021, in a sea change from more than a half-century without government funding for therapeutic clinical research on psychedelics (except for U.S. Food and Drug Administration-approved ketamine), the first federal U.S. dollars in 50 years were awarded. Johns Hopkins University's principal investigator Matthew Johnson announced that the university is the lead site for a nearly \$4 million study researching psilocybin-assisted therapy for tobacco addiction funded by the National Institute on Drug Abuse, part of the National Institutes of Health (Johns Hopkins, 2021).

As the field of psychedelic medicine evolves, this BrainFutures report primarily offers an objective review of important PAT clinical outcomes related to specific compounds and conditions. To better understand this research, however, it will help to first put these studies into context. Toward this end, the report begins with brief landscape overviews which include:

- The scale of today's mental health crisis and related costs
- A working definition of psychedelics
- Investments in PAT research and markets
- Safety considerations
- Efforts to ensure PAT quality, access, and affordability
- Public sentiment
- Legislative activity
- The need for proven innovative approaches

A review of the evidence then follows. Each of the primary compounds—psilocybin, ketamine, 3,4-methylenedioxy-methamphetamine (MDMA), lysergic acid diethylamide (LSD), ayahuasca/N-dimethyltryptamine (DMT), ibogaine, and mescaline—has a dedicated section. These sections include a brief overview of the compound along with research highlights, followed by an in-depth review of the most relevant research for safety and tolerability as well as its applications for various conditions.

# Overview of Key Issues

## A MENTAL HEALTH CRISIS EXACERBATED BY A PANDEMIC

**F**rom 2017 to 2019, before the onset of the pandemic, the number of U.S. adults experiencing a mental illness rose by 1.6 million to 45 million, making up 18.6 percent of adult Americans (Reinert, et al., 2019; Mental Health America, n.d.). In 2021, this number jumped by 5 million to nearly 50 million adults, coupled with approximately 1.1 million more people experiencing serious suicidal thoughts compared to two years prior (Reinert, et al., 2021).

Pre COVID-19, the number of Americans aged 12 and older who suffered from a substance use disorder (SUD) was also a worsening public health emergency: the affected population rose from 19.7 million in 2017 (Substance Abuse and Mental Health Services Administration [SAMHSA], 2018) to 20.4 million in 2019 (SAMHSA, 2020). Yet, during the first year of the pandemic, in 2020, this number doubled to 40.3 million<sup>4</sup> (SAMHSA, n.d.).

Relatedly, drug overdose deaths in the U.S. reached 70,630 in 2019, a high number by any account, yet only a slight increase of 400 additional deaths from drug misuse versus 2017 (Centers for Disease Control [CDC], 2021; Hedegaard et al., 2018). In 2020, however, overdose deaths in the U.S. breached 100,000, with more than three-quarters a result of opioid addiction (CDC, 2021b).

In addition to MH/SUDs more broadly, it is also estimated that among U.S. adults, seven percent experience PTSD at some point in their lifetime (National Institute of Mental Health [NIMH], n.d.), with 15 million suffering from the condition in any given year

(U.S. Department of Veterans Affairs, n.d.a). For combat Veterans, these prevalence rates are two to four times higher<sup>5</sup> (Richardson et al., 2010). A large 2020 study found that women with PTSD are seven times more likely to die by suicide than women without the diagnosis, and men with PTSD are four times more likely to take their own life when compared to other men (Fox et al., 2021).

**Decades of data indicate that mental health-related death rates are on the rise, having increased 33% over the past 50 years, while other common chronic medical conditions' death rates are falling.**

Unfortunately, decades of data indicate that mental health-related death rates are on the rise, having increased 33 percent over the past 50 years, while death rates for other common chronic medical conditions are falling (CDC, 2021c). (See Figure 1.)

As former director of the National Institute for Mental Health (NIMH), Thomas Insel, MD states in his book, *Healing: Our Path from Mental Illness to Mental Health* (2022):

*"It's a pretty safe bet in most of medicine that if you treat more people, death and disability drop. But when it comes to mental illness, there are more people getting more treatment than ever, yet death and disability continue to rise."*



**FIRST RESPONDERS ARE OFTEN THE LAST TO GET HELP**

**S**ome of those working the hardest during this pandemic, our first responders, may be among the hardest hit by COVID-19’s impact. In a pre-pandemic 2017 survey, researchers at the University of Phoenix found that upwards of 85 percent of first responders were experiencing behavioral health issues, which were often self-medicated through substance use. At the same time, they were not using support services as 39 percent stated that using such services was stigmatized and would likely result in negative outcomes for their career or job (Nemecek, 2018). With COVID-19’s persistence and polarizing effect, we can only assume that the first responders taking care of our communities are not getting the care they deserve.

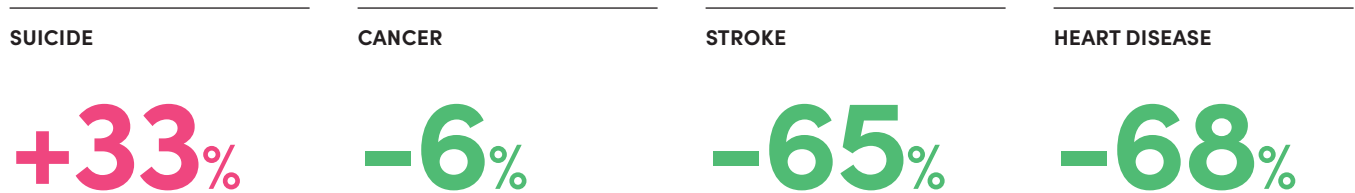
The numbers of people in the U.S. and around the world with MH/SUD issues are both too high and increasing, and related deaths are too severe a price to pay. The pandemic has exacerbated this crisis, and there are strong reasons to believe that our rapidly changing world—with technology, social media, extreme individualism, isolation, rancorous politics, persistent social injustices, addictions of various kinds, civil unrest, environmental degradation, and economic strife—is only fueling the fires of rising mental health conditions.

**MENTAL HEALTH AND ITS IMPACT ON HEALTHCARE COSTS**

**P**romising PAT research is gaining the attention of media, industry, regulators, legislators, and the public. In large part this is because current treatments for MH/SUDs, including pharmacological medications and various forms of therapy, do not fully address today’s mental health emergency. Though prescription drugs and psychosocial treatments are helpful for many people experiencing a wide breadth of issues,

**FIGURE 1. DEATH RATES OF MENTAL HEALTH-RELATED CONDITIONS COMPARED TO COMMON CONDITIONS (1968-2018)**

Mental illness leads other common chronic conditions in all the wrong ways. It surpasses cancer, heart disease, and stroke as the only common chronic condition with climbing deaths over the past **50** years, and is the **#1** cause of disability.



Note: Adapted from Path Forward. (February, 23, 2021). The Path Forward for mental health substance use: Health Equity for all Americans. Slide Deck, page 4.

a large number of individuals have not found effective, long-term relief. Too often their conditions are associated with significant patient suffering, especially for those with treatment-resistant disorders, with prevalence rates continuing to rise (Czeisler et al., 2020).

## Effective treatment of mental health and substance use disorders could significantly reduce skyrocketing overall healthcare costs.

Mental health and substance use diagnoses account for significantly higher medical costs, most of which are not for the direct treatment of the condition. A recent Milliman research report showed that the top 10 percent of high-cost patients account for 70 percent of all medical costs for commercial insurers, with almost 60 percent of this high-cost cohort having a mental health and/or substance use disorder (Davenport et al., 2020). The study further demonstrated that this subgroup of high-cost medical patients with MH/SUDs accounted for 44 percent of all medical spending for the total population. The report indicated that physical (medical/surgical) healthcare costs of those with a mental health condition are approximately 200-600 percent higher than those with no mental health diagnosis. The research concluded that more effective treatment of MH/SUDs could significantly reduce skyrocketing overall healthcare costs. “Appropriate consideration and management of behavioral health conditions that are so prevalent among the population are important parts of a comprehensive strategy to manage total healthcare costs and contribute to positive outcomes for patients,” the report said.

Every year **10 percent** of U.S. adults suffer from MDD at an estimated annual cost to society of approximately **\$326 billion**, a **38 percent** increase from a decade prior.

Additionally, MH/SUDs also have broader (and rising) societal costs. For example, every year 10 percent of U.S. adults suffer from MDD (Hasin et al., 2018) at an estimated annual cost to society of approximately \$326 billion, a 38 percent increase from a decade prior (Greenberg et al., 2021). Direct costs for treating the condition account for just over 11 percent of this total, while the remaining and greatest economic toll comes from expenses associated with comorbidity costs, workplace losses, and suicide-related expenditures (Greenberg et al., 2021). The cost of PTSD and related social anxiety disorders is tallied to be at least \$42.3 billion per year (Greenberg et al., 1999). More effective mental health treatments mean less patient suffering and reined in healthcare costs for all.

### WHAT ARE PSYCHEDELICS?

**P**sychedelics are compounds that affect neurochemistry, causing shifts in experiential perception and mood, often accompanied by vivid mental imagery and altered auditory processing. The term “psychedelic” is credited to psychiatrist Humphry Osmond (1917–2004), and is derived from Greek words meaning “mind manifesting.”

The “original” plant- or fungi-based psychedelics include substances such as psilocybin (psilocybe mushroom), DMT (ayahuasca brew made from rainforest plants),



ibogaine (African iboga bush), and mescaline (cacti including peyote and San Pedro). These compounds have centuries-old or even millenia-old traditional Indigenous histories where they have been (and are) used for healing, religious and sacred ceremonies, and for connecting to nature and community. For clinical research purposes, synthesized versions of these natural substances are often used to control for medical-grade quality and dosing. Today, the list of psychedelics has expanded to, in part, include MDMA, also known as molly or ecstasy, as well as ketamine and LSD. Because these newer compounds do not occur naturally, they must be synthesized in a laboratory.

Psychedelics create temporary shifts in brain activity that can interrupt patterns associated with serious mental health conditions such as depression, anxiety, and PTSD, allowing for changes in brain activity that lead to positive shifts in affect, thoughts, perception, behavior, sense of well-being, purpose, and desire to live.

Psychedelics work by acting at specific neurotransmitter receptors in the brain—typically serotonin receptors, as well as other receptors for neurotransmitters such as norepinephrine, dopamine and glutamate. They create a state of positive disorganized neuroactivity, which has been credited with the perceptual and experiential shifts unique to the psychedelic experience, which, in turn, are germane to the favorable research outcomes (Jarrett, 2019). Psilocybin, LSD, DMT, and mescaline are often called classic psychedelics because all work primarily through affecting specific serotonin receptors, namely they are agonists of the 5-HT<sub>2A</sub> receptor. Compounds often referred to as non-classic psychedelics, including MDMA, ketamine, and ibogaine, each have different mechanisms of action and subjective effects from classic psychedelics. MDMA is a modulator of serotonin reuptake and release from storage vesicles in the presynaptic neuron; ketamine is an antagonist at the NMDA ion channel; and ibogaine has very broad receptor activity.

## A SURGE IN RESEARCH AND INVESTMENT

In recent years, new psychedelic research centers at prestigious institutions—such as at Johns Hopkins University, New York University, Icahn School of Medicine at Mount Sinai, Harvard University, Massachusetts General Hospital, UC Berkeley, University of Wisconsin-Madison, University of Texas, and Imperial College London—were developed to lead academic and scientific investigations of psychedelics and PAT as safe and efficacious behavioral health interventions.

**High-level research activity is validating the powerful case for psychedelics' efficacy at treating challenging mental health conditions when paired with appropriate PAT.**

This high-level research activity is validating psychedelics' efficacy at treating challenging mental health conditions when paired with appropriate PAT psychotherapy protocols that consider set (patient's mindset, beliefs, and expectations) and setting (physical environment of the treatment). PAT protocol components include patient assessment, psychotherapy preparation, the dosing session, and post-dosing integration therapy sessions.

Given the results of recent research, in the past few years, the U.S. Food and Drug Administration (FDA) granted Breakthrough Therapy designation to several sponsors of MDMA and psilocybin clinical trials to “expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)” (Food and Drug

Administration [FDA], 2018). These organizations include Multidisciplinary Association for Psychedelic Studies (MAPS), focused on MDMA for PTSD; COMPASS Pathways, working on psilocybin for TRD; and Usona Institute, advancing research on psilocybin for MDD.

In line with the FDA's Breakthrough Therapy actions, in 2021 the DEA proposed a 50-fold increase in psilocybin production quotas to "provide for the estimated medical, scientific, research, and industrial needs of the United States, for lawful export requirements, and for the establishment and maintenance of reserve stocks" (Drug Enforcement Administration [DEA], 2021).

Through FDA-approved clinical trials conducted by companies, hospital systems, and research universities, psychedelic-assisted therapies are resurging and some studies have shown dramatic results, including alleviating serious conditions that have been non-responsive to traditional therapies. For example, MDMA, a Schedule I drug, has been effective at treating PTSD in multiple trials. Ketamine, an anesthetic for surgical and diagnostic procedures that has held FDA approval since the 1970s, is being used off-label<sup>6</sup> to treat depression, among other conditions. Its derivative, esketamine, a nasal spray used to treat depression, is the first ketamine intervention to receive FDA approval (in 2019) specifically for a psychiatric disorder.

At the same time that clinical studies are showing promise, private investment in formulae and therapeutic approaches has ballooned in anticipation of breakthrough treatments and potential new consumer and healthcare markets. Early indicators of the appetite that investors and patients have for these consciousness-changing therapies can be seen in the off-label use of ketamine as a behavioral health treatment for depression and other mental health disorders, including anxiety and suicidality, and the rise of ketamine clinics popping up across the country (and internationally) to administer the drug for this purpose. From 2015 to 2018, the number of

ketamine clinics in the U.S. grew from 50 to 300, and that count is likely higher today (Bricken, 2020). This is in part a reflection of the limited number of treatments for patients who are treatment-resistant or suicidal and seeking immediate relief. Current treatments including psychotherapy and psychotropic drug prescription can take weeks to months before any symptom relief is achieved, and in many cases symptom relief is not ever reached with treatment as usual (TAU), while intravenous ketamine can bring symptom relief within hours.

**Nearly 50 publicly traded psychedelic companies, at least 100 private companies, and a psychedelics exchange traded fund (ETF): PSY, already exist.**

This kind of promise has venture capital investment in psychedelic companies rapidly accelerating, reaching \$318.2 million in 2020 and 2021 combined, representing 36 deals—up from \$49.5 million of cumulative investments made in the space during the prior five years (Goldhill, 2021). Financial research estimates market growth to reach \$6.9 billion by 2027 (Data Bridge Market Research, 2020). Nearly 50 publicly traded psychedelic companies, at least 100 private companies, and a psychedelics exchange traded fund (ETF): PSY, already exist (Blossom, 2021).

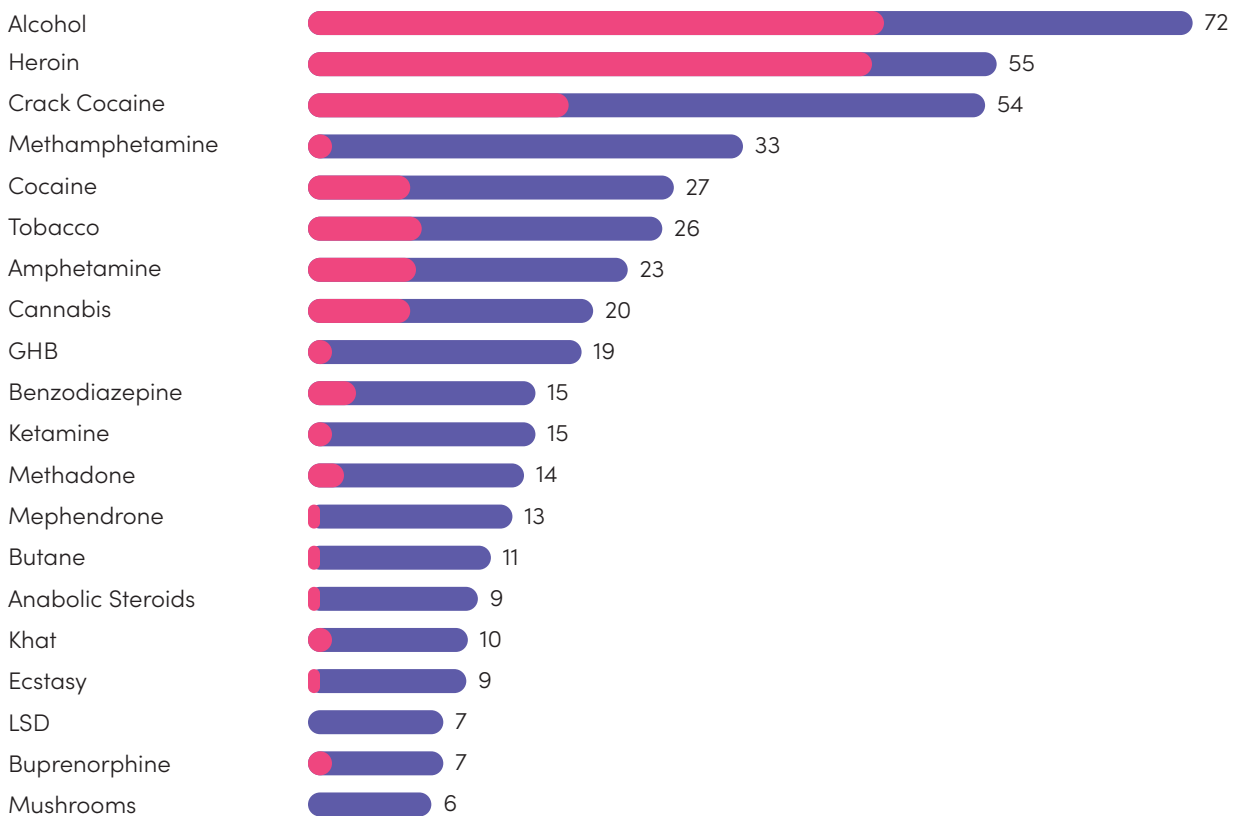
#### SAFETY CONSIDERATIONS: FICTION OR FACT

**W**ith PAT's growing profile in research and the media, a study published in the *Journal of Psychopharmacology* found that most people today consider psilocybin less harmful than alcohol, tobacco, and other drugs, including prescription painkillers, cocaine, and heroin (Roberts et al., 2020). Research supports these perceptions. (See Figure 2.)

Overall safety and tolerability are key considerations and part of the relevant research findings. Generally, mental health PAT contraindications are borderline personality disorders or schizophrenic tendencies (Byock, 2018). Adverse effects of psychedelics are for the most part minimal, transient, and/or mitigated by appropriate clinical protocols, with the greatest risk occurring in unsupervised participation (Johnson et al., 2008). Typical passing

side effects of most psychedelics could include dizziness, headache, nausea/vomiting, fatigue, body pain, irritability, heightened blood pressure and pulse, insomnia, and/or anxiety (COMPASS Pathways, 2021d; Nichols, 2016). Though usually infrequent, more severe potential side effects specific to particular psychedelics are noted in below sections, if applicable, under the compound’s tolerability summary.

**FIGURE 2. HARM SCORES OF DRUGS TO USERS AND OTHERS**



Note. The above graph shows the harms associated with using various drugs for the drug users (purple) and the harm caused to others that is related to drug use (red). Drugs are ranked from most harmful (top) to least harmful (bottom) using a weighted score of the assessment criteria for each drug. Adapted from Nutt, D.J., King, L.A., Phillips, L.D. (October 2010). Drug harms in the UK: a multicriteria decision analysis. *Lancet* 376: 1558-1565. 10.1016/S0140-6736(10)61462-6

In a recent systematic review, certain baseline psychological states and traits showed that “Individuals high in the traits of absorption, openness, and acceptance as well as a state of surrender were more likely to have positive and mystical-type experiences, whereas those low in openness and surrender or in preoccupied, apprehensive, or confused psychological states were more likely to experience acute adverse reactions” (Aday et al., 2021). This review also highlighted potential neurological biomarkers that may predict adverse reactions to psychedelics. However, this requires a brain scan to screen patients, making it a less scalable and less practical approach than a state/trait rating. Additionally, challenging experiences are not necessarily absent of therapeutic value. In fact, clinicians working with PAT note that this is often an opportunity for therapeutic breakthroughs (Dyck & Elcock, 2020). An article overviewing the Aday et al. review states:

“Experiences on psychedelics vary in intensity and tend to comprise three categories: a mystical, insightful or challenging experience. A mystical experience can feel like a spiritual connection to the divine, an insightful experience increases people’s awareness and understanding about themselves, and a challenging experience relates to emotional and physical reactions such as anxiety or increased arousal” (Henderson, 2021).

The key to navigating any of these types of experiences seems to be the support of a skilled facilitator, thus underscoring the importance of supervised sessions (versus recreational use). Practitioner guidelines for PAT safety were produced by Johns Hopkins researchers Matthew Johnson, PhD, William Richards, PhD, and Roland Griffiths, PhD, in their 2008 paper “Human Hallucinogen Research: Guidelines for Safety.” This resource outlines best practices as of the publication date and discusses psychedelic-related safety and tolerability information including:

- Different compounds have slightly different safety considerations, including dosing levels.
- Psychedelics produce low-to-no physiological toxicity, and have not been found to contribute to organ damage or neuropsychological deficits.
- Psychedelics are not considered addictive, as therapeutic use does not lead to compulsive drug seeking (versus opioids).

**All medications come with some risks, and psychedelic medicines are within, and more importantly, often below normal TAU risk ranges.**

In general, perceived risks associated with psychedelics are often influenced by their historical misuse in the ‘60s and ‘70s and consequent stigma, which has persisted for nearly half a century along with their classification as controlled substances. In reality, the risks are lower than many common treatments, including prescription medications for mental health, which often have harrowing side effects. All medications come with some risks, and psychedelic medicines are within, and more importantly, often below normal TAU risk ranges.

#### TREATMENT AS USUAL SAFETY

**P**re-COVID-19, approximately 17 percent of US adults were on one or more psychiatric drugs, with the majority taking antidepressants, followed by anxiety medications, then antipsychotics (Moore & Mattison, 2017). Together, these drugs are the go-to mainstream pharmacopeia of our modern age, and despite more serious risk profiles than most psychedelic compounds, their use as TAU is on the rise. At the onset of the pandemic, in the course of one month, the

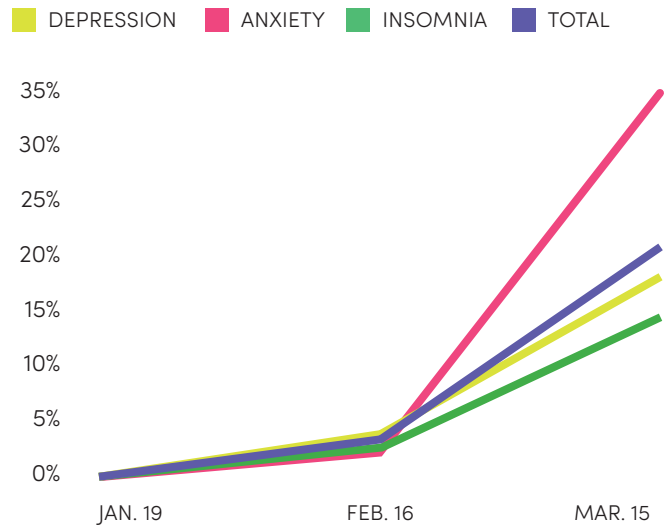
number of new anti-anxiety prescriptions spiked almost 38 percent, according to a report by Express Scripts (2020). (See Figure 3.)

Antidepressants such as selective serotonin reuptake inhibitors (SSRIs), serotonin, norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs), can cause a wide range of side effects including dizziness, fatigue, weight loss/gain, headaches, lack of concentration, vomiting, sexual dysfunction, and heart and circulatory damage, not to mention suicidal thoughts and behaviors, for which they carry a mandatory “black box” warning label (MedlinePlus, 2022a; Fletcher, 2019; MedlinePlus 2022b; University of Illinois, 2021b; Trajcová et al., 2019; Biffi, Scotti, & Corao, 2019; Mayo Clinic, 2022d). This labeling, the most serious type of warning mandated by the FDA, was required after controlled trials found an increased risk of suicidal thoughts and behaviors among children and adolescents taking antidepressants compared to placebo (Spielmans et al., 2020). A multi-year review of adverse effects from the use of typical antidepressants found that close to 6.5 percent of users diagnosed with depression and prescribed medication had serious adverse events including falls, fractures, traffic accidents, upper gastrointestinal bleeds, and other adverse drug reactions. Further, 1.5 percent of first-time users of antidepressants in the study group died (Coupland et al., 2018).

As another example, antipsychotic medications, including those prescribed for TRD and PTSD, are associated with an increased likelihood of sedation, sexual dysfunction, postural hypotension, metabolic syndrome (including obesity and diabetes), cardiac arrhythmia, and sudden cardiac death (Muench & Hamer, 2010); and they nearly double older dementia patients’ chance of death from heart problems, infections, falls, and other ailments, causing the FDA to issue a black box warning (Purse, 2021).

**FIGURE 3. PERCENT CHANGE IN PRESCRIPTIONS FILLED PER WEEK FOR MENTAL HEALTH MEDICATIONS**

BY SELECT WEEKS FROM JANUARY 19, 2020–MARCH 15, 2020



Note. The above graph depicts the increase in prescriptions filled per week for mental health medications in the U.S from January 19th to March 15th 2020. Adapted from Express Scripts. (2020). America’s state of mind - U.S. trends in medication use for depression, anxiety and insomnia. Express Scripts. <https://www.express-scripts.com/corporate/americas-state-of-mind-report>

In addition to various types of psychotherapy, pharmacotherapy TAU for MDD, TRD, and PTSD most often include SSRIs and SNRIs (American Psychiatric Association, 2010; Voineskos, Daskalakis, & Blumberger et al., 2020; U.S. Department of Veterans Affairs, n.d.b; Wang et al., 2016). TAU for MDD also includes mirtazapine, bupropion, and for those still not responding to treatment, monoamine oxidase inhibitors (MAOIs) (American Psychiatric Association, 2010). Treatment-resistant depression pharmacotherapy may also include lithium, triiodothyronine (T3) thyroid hormone medication, as well as second-generation antipsychotics (Voineskos, Daskalakis, & Blumberger et al., 2020).



Additional TAU medications for PTSD are tricyclic antidepressants, MAOIs, anti-anxiety medications (benzodiazepine), atypical antipsychotics, and in some cases the high blood pressure drug prazosin (Mayo Clinic, n.d.; Nobles et al., 2017; Jeong-Ho, 2005). The side effects of SSRIs and SNRIs, as well as of these additional TAU medications for MDD, TRD, and PTSD, are higher<sup>7</sup> than the transdiagnostic safety profile proving out across the most studied PAT compounds and detailed in the research section that follows.

Beyond the side effects of these TAU drugs, access, prescription pathways, and prescription protocols for such pharmacology have their own safety concerns. For example, with few alternatives for care and heightened public need for mental health treatment, close to 80 percent of all antidepressant medications are prescribed by primary care providers with minimal mental health training, not by psychiatrists (Barkil-Oteo, 2013).

**Relative to TAU, PAT would not increase side effect risks, and would likely lower overall risk by providing more treatment options.**

With a rise in MH/SUDs and an increase in prescriptions for related medications absent of best practices, the risks for individuals and the public are increasing. Relative to TAU, PAT would not increase side effect risks, and would likely lower overall risks by providing more treatment options. These new treatments would require a high degree of oversight by licensed mental health professionals and carry a lower risk profile than most of the medications in the current TAU paradigm.

Even so, prudence, and the current regulatory framework of medicine testing and approval, compels researchers and proponents of PAT to proceed carefully and seek both dosage levels and treatment protocols that minimize risks.

## STANDARDS OF PRACTICE, TRAINING, CERTIFICATION, REIMBURSEMENT, AND OVERSIGHT

**I**n support of continued and rigorous clinical research, and to prepare the field for the anticipated growing legal access to PAT interventions, training and education groups that teach and certify qualified psychiatrists, psychologists, and other therapists in PAT are quickly gaining steam in the U.S. and abroad.

Simultaneously, many major PAT players are independently and/or collectively building key pillars to support the emerging field. These include clinical protocols inclusive of dosage and quality parameters, training and certification standards, reimbursement strategies, and third-party administration (TPA) infrastructure to coordinate a provider network upon anticipated FDA approval. Specific examples of these efforts include:

- The Board of Psychedelic Medicine and Therapies (BPMT) aims to nationally certify practitioners for PAT. BPMT plans to certify both licensed and unlicensed providers in distinct tracks for different roles in the conventional healthcare system. Their goal is to create a cross-disciplinary certification process that instills standards for practitioner qualification and consumer protections into the field of practice. BPMT is motivated by the goal of achieving third party reimbursement to enhance access and acceptance of this treatment. BPMT is also pursuing national accreditation to speed this process. This board certification will provide a clear career path for practitioners and enhance professional credibility for this critically important clinical practice.
- The American Psychedelic Practitioners Association (APPA) is an emerging professional association formed to establish standards of care for PAT providers and accreditation for training programs; advocate for safe, effective, and accessible care for all who can benefit from PAT; provide education and mentoring

to its membership; and influence the healthcare system towards the adoption of psychedelic care. APPA is partnering with BPMT to align efforts where appropriate. The practice of ketamine additionally has an established professional association, American Society of Ketamine, Physicians, Psychotherapists & Practitioners (ASKP3).

- Enthea Inc., is a 501c4 non-profit health plan administrator dedicated to psychedelic healthcare. Enthea is developing medical policy for health plan benefit coverage of psychedelic therapies through key stakeholder and subject matter expert collaboration. The organization administers psychedelic healthcare benefits coverage for payers of healthcare benefits and maintains a credentialed PAT provider network to serve health plan members. Enthea is currently working with progressive employers who wish to cover psychedelic healthcare (currently ketamine-assisted therapy) for their employees and family members.
- MAPS, COMPASS Pathways, and Usona Institute—the emerging psychedelic pharmaceutical companies—in addition to California Institute for Integral Studies, Fluence, Synthesis, Sage Institute, Psychedelic Research and Training Institute, and many other for-profit and nonprofit organizations are working on standardizing their own, and in some cases collective, PAT treatment protocols and training best practices.
- Enthea, MAPS, COMPASS Pathways, and Usona Institute are actively exploring reimbursement strategies, including possible use of existing Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes for streamlined billing purposes.

All of these efforts are aimed at ensuring high-quality, industry-wide standards of training and care as well as delivery infrastructures that keep patients safe, distribute up-to-date information to PAT practitioners, and optimize therapeutic outcomes.

### A MATTER OF PUBLIC INTEREST

**W**ith mental health conditions at crisis levels even before the pandemic, people are eager for approaches to care that work. Pivotal publications such as Michael Pollan’s book, *How to Change Your Mind: What the New Science of Psychedelics Teaches Us About Consciousness, Dying, Addiction, Depression, and Transcendence*, and endorsements of psychedelics by thought leaders such as author, podcaster, and entrepreneur Tim Ferriss, have propelled interest in both the clinical and self-development use of these compounds for mental health, well-being, and as part of the human optimization movement. Widespread positive information from these and other sources combined with strong research outcomes from trusted academic establishments have, to a great extent, reframed public opinion about psychedelics—from an anti-drug use perspective to one of responsible use for medicinal/clinical treatment (or for personal development).

**Close to two-thirds of adults in the U.S. would be “open to medical treatment” with psychedelic interventions.**

The amount of public interest in psychedelics should not be underestimated. A 2017 YouGov survey showed that close to two thirds of adults in the U.S. would be “open to medical treatment” with psychedelic interventions if these substances were proven safe (McCarriston, 2017).

Today, with clinical information on PAT safety and efficacy continuing to be reported by news media, and with recent popular books and movies touting the benefits of these compounds at a time when the nation's mental health crisis is desperate for new effective interventions, demand seems to already be outpacing legal access. This popular resurgence of psychedelics has undoubtedly influenced the many PAT decriminalization legislative initiatives seen coast to coast. As human optimization and spirituality interests overlap with urgent mental health and substance use needs, these parallel paths will undoubtedly continue to influence each other.

### DECRIMINALIZATION AND LEGALIZATION TRENDS

**D**ecriminalization is a growing trend that residents of red and blue states alike are approving. Select locales—Denver, Colorado; Santa Cruz and Oakland, California; Detroit and Ann Arbor, Michigan; Washington, D.C.; Northampton, Somerville, and Cambridge, Massachusetts; and Seattle, Washington for example—have voted to decriminalize psilocybin (as well as other psychedelics in some of these cities). Similarly, the entire state of Oregon legalized psilocybin's use through licensed providers, opening doors and reducing legal resistance to its health applications. Connecticut, Hawaii, and Texas are also exploring legislation to study the physical and mental health benefits of psilocybin, and California Senate Bill 519—which proposes the decriminalization of using (not selling) certain psychedelics like psilocybin, MDMA, LSD, and DMT—cleared early hurdles in August 2021 and will be voted on in 2022.

It is also important to note that the ecosystem of psychedelics expands far beyond medical applications. Ceremonial and healing uses of plants and fungi with hallucinogenic properties (and their derivatives) have been practiced by Indigenous communities for thousands of years (Belouin & Henningfield, 2018). Many of these communities around the world and in the U.S. (through

religious freedom exemptions) continue their traditional uses of psychedelics today.

Momentum is also gaining among non-indigenous communities seeking deeper engagement with a sense of spirituality, as well as among many in the human optimization movement. Some of these people report using psychedelics—both ceremonially and personally—to deepen their insights into universal principles of existence and to experience a noetic understanding of interconnectedness with all life. Others use certain psychedelics, including non-hallucinogenic microdoses, to purportedly optimize their own performance and/or stimulate positive shifts in their behaviors or beliefs to increase their capacities to engage in passions and/or professional paths, be those business-based, personal, or transpersonal. A recent report surveying approximately 32,000 people globally (1,850 in the U.S.) indicated that one in four people who reported using psychedelics in the past 12 months microdosed, and 75 percent of this group reported no side effects. Further, close to half of those who microdosed experienced significant enough relief from mental health symptoms that they reduced or stopped taking psychopharmacological medications (Winstock et al., 2021).

Though this BrainFutures' report does not endorse the illegal use of psychedelics, it is important to understand the wave of public engagement that already exists related to these compounds, and the anecdotal reports of benefits that are emerging.

### RECKONING WITH A MENTAL HEALTH TREATMENT AND SUBSTANCE USE CRISIS

**L**ooking back over the past century, medicine, psychiatry, and psychology have made some important advances in the practices of understanding and treating the human psyche and individual behavior toward well-being and societal integration. The mental health field has grown from models centered on



ostracization and institutionalization to offering a plethora of talk and behavioral therapies as well as a wide spectrum of pharmacological medications that help people regulate affect, thoughts, and behavior to live better lives.

The development of antidepressants was a game changer for mental illness. The early 1900s offered essentially no relief for mental health challenges and relied heavily on institutionalization; the mid-1900s were characterized by using opiates and amphetamines to treat mental health issues, followed by electroconvulsive therapy. Antidepressants had their early start in the '50s and '60s, and by the '70s, '80s, and '90s became a hallmark treatment for depression and other disorders—namely with Prozac (fluoxetine) hitting the market in 1988.

Despite these advances, our widespread and persisting mental health challenges require alternative proven approaches. Considering the rising rates of MH/SUDs, the limitations of existing approved medication and therapy at addressing the ongoing crisis, and the disproportionate costs associated with mental health and substance use conditions, PAT is positioned to be the next generation of mental health and substance use interventions.

By just about all accounts, the state of behavioral health in the U.S. today is severe, and current therapies, including all forms of talk therapy as well as antidepressant medications—SSRIs, SNRIs, and tricyclic antidepressants (TCAs)—are unpredictably effective. Some people respond very well, others are engaged in continuously adjusted long-term treatment with limited or little improvement.

In the U.S., an analysis conducted by the New York Times in 2018 shows that almost 25 million adult Americans had been taking antidepressants for at least two years, a 60 percent increase since 2010 (Carey & Gebeloff, 2018). With such high prescription rates, it is important to know how well antidepressants actually work. Earlier research conducted by the NIMH, known

as the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) Study, investigated the effects of depression medication(s), and/or switching medication(s), and/or adding cognitive therapy over time toward symptom remission. The massive, first-of-its-kind study enrolled more than 4,000 individuals and ultimately published results on 2,876 participants (NIMH 2016). In the study, one medication was administered in the first round. Those who did not achieve remission switched and/or increased medication (with some adding therapy) and were evaluated again, up to four times.

**Remission rates in the antidepressant STAR\*D study showed an initial treatment and one switch to another medication were in the 20–30 percent range, while by the time three to four medications were tried, remission dropped to 10–20 percent.**

This was an important protocol, especially because many individuals with TRD or MDD switch medications in search of an effective treatment. The findings indicated that while antidepressants can be an effective treatment for some, particularly in the face of limited options for managing depression, they are no panacea. Remission rates in the antidepressant STAR\*D study showed an initial treatment and one switch to another medication were in the 20–30 percent range, while by the time three to four medications were tried, remission dropped to 10 to 20 percent. A review article of the STAR\*D study noted, “Remission was more likely to occur during the first two treatment levels (20–30 [percent]) than during levels [three] and [four] (10–20 [percent])... Remission

rates in these representative clinics, in general, were lower than expected on the basis of clinical efficacy trials of antidepressants, which typically report remission rates of 35 to 40 [percent]” (Gaynes et al., 2009).

Other research shows similar outcomes. In terms of preventing relapse into chronic depression, taking prescription antidepressant medications is shown to be 27 percent effective compared to placebo (InformedHealth, 2020).

When they work, these medications are incredibly powerful; when they do not work, suffering due to MH/SUDs continues at great personal and financial costs to individuals, healthcare payers, and society. Studies show that the overall effectiveness in all cases of prescription medication or counseling therapy for depression is limited (Hall, 2011). However, combining therapy and medication increases positive outcomes. A review of 52 studies comprising 3,623 patients with either a depressive disorder or anxiety disorder found that, “the effects of combined treatment compared with placebo-only were about twice as large as those of pharmacotherapy compared with placebo-only, underscoring the clinical advantage of combined treatment . . . Monotherapy with psychotropic medication may not constitute optimal care for common mental disorders” (Cuijpers et al., 2014).

## Finding new mental health and substance use treatments is a humanitarian and equity imperative.

Finding new mental health and substance use treatments is a humanitarian and equity imperative. With the long tail of COVID unequally affecting communities of color, the disproportionate prevalence of mental illness among

those incarcerated (Prins, 2014) and homeless (Torrey, n.d.), and few effective treatments for the military Veterans who have served our country, it is essential to offer better treatment options to all who stand to benefit, including some of the most vulnerable among us.

In summary, psychiatry and psychotherapy do have treatments that work, but our current options for dealing with MH/SUDs are effective for only a subset of those in need and limited in their capacity to produce remission. Existing psychotherapy and psychopharmacology alone will not deliver the urgently needed solutions that are required to respond effectively to the deeply concerning mental health trend we are facing.

The research to date indicates that PAT is a promising new treatment that can help address some of the more stubborn and serious MH/SUDs, while potentially creating cost savings for healthcare payers. Authors in a 2016 *Journal of Psychopharmacology* article summarized the potential of psychedelic medicines by stating:

“The overwhelming morbidity and mortality of treatment-refractory psychiatric conditions [those that fail to respond to typical treatment and remain problematic to treat or cure], ranging from mood disorders to addiction, suggest an ethical and public health imperative to use every avenue possible to pursue novel therapeutic agents. We do our patients a disservice by not understanding and appropriately investigating compounds with potential therapeutic value because of their prior controversial associations and on their capacity for misuse” (Lieberman & Shalev, 2016).

In the pages that follow, we heed this advice, and the primary studies of PAT evidence across compounds are reviewed.

# Psychedelic Medicine Clinical Research Summaries

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The current body of evidence for PAT as an effective treatment for MH/SUDs is promising. This report reviews the most significant research to date on psychedelic compounds specifically as they apply to treating serious conditions. In total, BrainFutures analyzed and reviewed over 200 peer-reviewed publications with psychedelics including eight meta-analyses, 46 randomized control trials (RCTs), 47 open-label studies and 84 reviews.

Each compound section that follows begins with an “at a glance” synopsis that overviews a brief history of the compound and the research as well as topline findings and benefits. This is followed by a summary review of primary studies for each compound organized by related conditions.



# Psilocybin

# Psilocybin / AT A GLANCE

## COMPOUND OVERVIEW

Psilocybin is a naturally-occurring, psychoactive chemical found in “magic mushrooms” which grow predominantly in North, Central, and South America but are found across the world (Guzmán, 2005). It is one of the most promising compounds in today’s PAT research. In 2018 and 2019, the FDA granted psilocybin Breakthrough Therapy designation based on results from TRD and MDD clinical trials, respectively. Several public and private companies are invested in the production of psilocybin for PAT. Some organizations are building the infrastructures that would allow PAT to be delivered through healthcare payer networks in anticipation of potential FDA approval and insurance coverage. In 2020, Ballot Measure 109 was passed in Oregon, making it the first state to approve the adult therapeutic or wellness use of psilocybin.

## IN THIS REVIEW

BrainFutures’ research reviews 39 studies with psilocybin (36 peer-reviewed), including nine RCTs<sup>8</sup> and 16 open-label studies<sup>9</sup> with 667 participants, along with two meta-analyses and six reviews. (The two meta-analyses covered eight studies with 301 participants, including three trials with 144 participants not cited directly in this report.) On the whole, research has found psilocybin to be efficacious and, in some cases effective, at treating depression and/or anxiety. There are currently 15 ongoing or recruiting clinical trials for psilocybin and depression and three for anxiety.

## VOLUME AND TYPE OF RESEARCH

Since 1958, there have been 1,301 published papers that referred to psilocybin research, applications, mechanisms of action, or potential uses. Prior to 1971, eight clinical trials were conducted, primarily experimental trials to evaluate the effects of psilocybin on

people. No clinical trials occurred between 1971 and 1995. In 1996, limited trials resumed, researching the effects of the compound on perception including vision and language. In 2006, the first modern trials reporting a mystical experience occurred, and in 2011, the first trials evaluating the effectiveness of psilocybin at relieving cancer-related anxiety were published. In total, since 1996, 52 RCTs have been conducted, as well as nine meta-analyses. During this same time, psilocybin has been cited in 225 published reviews covering a wide range of psychedelic-related topics. This overall surge in research can be seen in Figure 4.

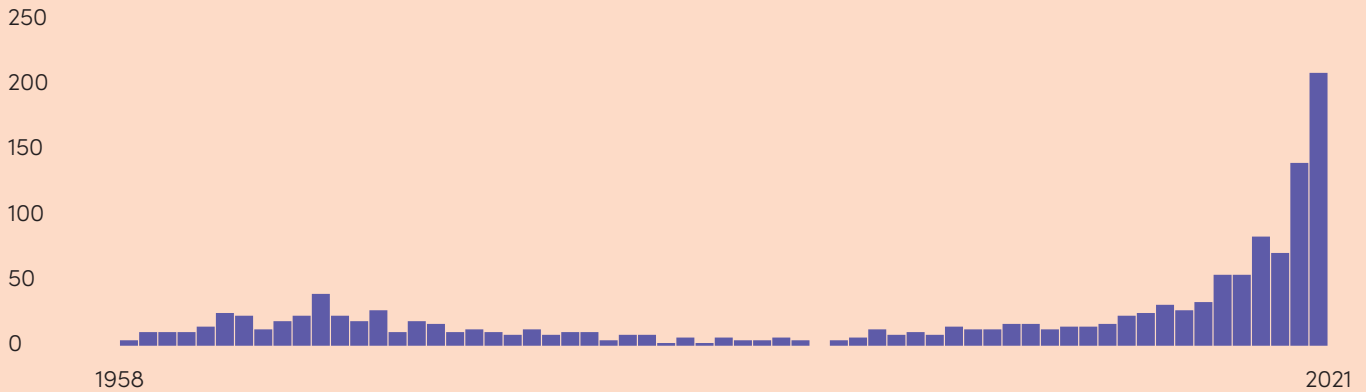
In addition to research on TRD and MDD, ongoing studies are exploring psilocybin as a treatment for a number of other conditions. The clinicaltrials.gov database shows these conditions include headaches (migraine, concussion, chronic cluster, and short-lasting unilateral neuralgiform headache attacks), methamphetamine use disorder, chronic pain, demoralization in patients receiving hospice care, psychological and existential distress in palliative care, mild cognitive impairment, Parkinson’s disease, bipolar II disorder, anorexia nervosa, binge eating disorder, body dysmorphic disorder, fibromyalgia, and more. There is even research underway with healthy adults to investigate the compound’s impact on frontline clinician burnout and professional religious leaders’ nuanced sense of mystical-type experiences, as well as those experiences’ sustained effects on measures of wellbeing.

## AREAS OF RESEARCH SHOWING EFFICACY

- Major Depressive Disorder
- Treatment-Resistant Depression
- Illness-Related Anxiety
- Addiction

**FIGURE 4. PSILOCYBIN RESEARCH ACTIVITY (1958–2021)**

NUMBER OF STUDIES



Note: The above graph represents the increase in publications relating to psilocybin from 1958 to 2021. Adapted from PubMed (2022g). [Data set]. <https://pubmed.ncbi.nlm.nih.gov/?term=psilocybin&filter=years.1958-2021>

**SAMPLE OF RESEARCH FINDINGS**

- Following two doses of psilocybin as part of PAT, at least 70 percent of participants diagnosed with cancer-related psychiatric distress showed a reduction in symptoms in more than one study.
- A Phase 2 trial found psilocybin was efficacious in treating MDD, with a clinically significant response (defined as a 50 percent or more reduction from their baseline GRID-Hamilton Depression Rating Scale) in 71 percent of participants and remission from depression in 54 percent at four weeks post treatment.
- Psilocybin used for tobacco cessation resulted in significant levels of abstinence at six months (80 percent) and 12 months (67 percent).
- The world’s first Phase 2b trial using a single dose of psilocybin to treat depression found statistically significant and clinically relevant reductions in depressive symptom severity.
- Psilocybin is well-tolerated, with transient effects including mild nausea or headache, as well as altered perceptions, including vivid imagery and auditory experiences, that pass following use.

**KEY TAKEAWAY**

**Recent clinical research finds psilocybin, in conjunction with therapy, to be an effective treatment for major depression, TRD, illness-related anxiety and demoralization, and addiction.**

# Psilocybin

**T**he use of mushrooms to alter consciousness, invoke healing, and engage in religious and spiritual ceremonies goes back thousands of years to locations across the globe (Samorini, 1992; Akers, 2011). Their use in pre-Columbian Central American cultures, including the Mayan, Aztec, Olmec and Zapotec, is likely the most well-documented. Aztecs called the psilocybe mushroom *Teonanacatl*, which translates into “the flesh of the gods,” purportedly for its ability to connect users to god-like realms and encounters (Carod-Artal, 2015; Metzner, 2006). These rituals and practices were shut down by Spanish colonization, largely fading into historical narratives.

In our modern era, psilocybe mushrooms came into focus through the work of Maria Sabina, a Catholic-Mexican medicine woman (*curandera*) from Huautla de Jiménez in the Mexican state of Oaxaca, who used the mushrooms in healing rituals (Kabil, 2017). Notably, New York banker Robert Gordon Wasson, an amateur mycologist, made a journey to Huautla de Jiménez to participate in a ceremony with the curandera. He later published his experience in a 1957 *Life* magazine article, “Seeking the Magic Mushroom,” which drew great attention from researchers and psychedelic recreational-use enthusiasts alike.

Subsequent trips by Wasson and his contemporaries led to samples being provided to Swiss chemist Albert Hofmann, who synthesized the compound in 1958 (Pallardy, 2022).<sup>10</sup> Hofmann worked at the pharmaceutical company Sandoz Laboratories that later legally provided psilocybin to interested clinicians and researchers (Geiger, Wurst, & Daniels, 2018).

In 1960, Harvard University clinical psychologist Dr. Timothy Leary. PsyD traveled to Oaxaca to partake in a ritual with Maria Sabina, bringing the psychoactive compound into his college lab to explore using it for expanding consciousness. Leary and Harvard psychology professor Dr. Richard Alpert, PhD (later known as Ram Dass) created the Harvard Psilocybin Projects, which supervised experiments such as the Marsh Chapel Experiment in 1962 (Hiatt, 2016). In this experiment, more popularly known as the Good Friday Experiment, divinity students were given a capsule of either psilocybin or niacin to explore potential effects of the compound on creating a mystical experience (Kime, 2020).

Similar to Leary and Alpert’s interest, a good deal of early research explored psilocybin’s role in creating mystical or consciousness-elevating experiences. These psychedelic effects quickly gained notoriety, leading to widespread use in the hippie counterculture movement of the 1960s. Ultimately, psilocybin was made illegal in 1968 and then classified as Schedule I when the Controlled Substances Act passed in 1970 (Geiger, Wurst, & Daniels, 2018).

As demonstrated in studies overviewed below, the revival in research over recent years has been more clinically rigorous compared to the early experiments. Modern studies focus on both the effects of the experience and the neurological activity of psilocybin as mechanisms for effecting positive changes in treatment-resistant conditions and other MH/SUDs.

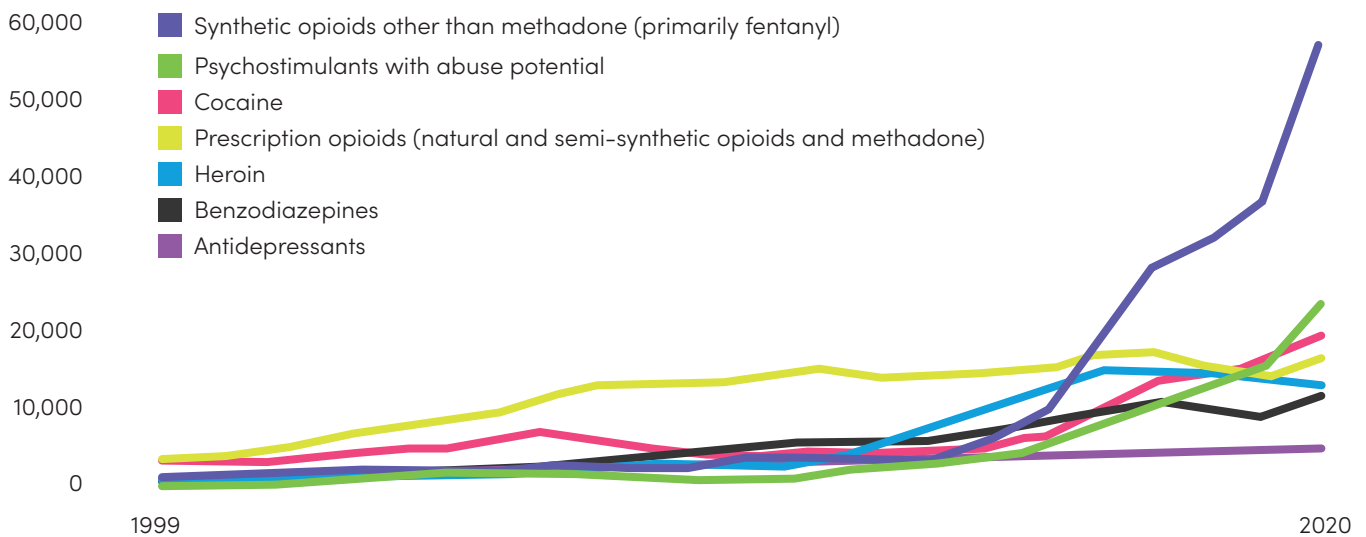
### TOLERABILITY OF PSILOCYBIN TREATMENT

Considering psychedelics’ status as Schedule I substances, the DEA’s most restrictive category, determining whether or not these compounds are safe and tolerable by participants in a therapeutic setting is a key question. Psilocybin’s effects on mood, perception, and cognition begin about 20-40 minutes after ingestion and usually last up to six hours (Daniel & Haberman, 2017). To date, the research shows that besides predictable, transient effects, including occasional mild nausea or headache and altered perception—which could also be called positive dissociative experiences or visions and insights, depending on the frame and vernacular—there are generally few to no adverse effects. Further, no evidence of psychological or physical

dependency is apparent, and in social-recreational use, no increase of criminal activity or serious adverse effects have been found (Johnson et al., 2008). This stands in stark contrast to some widely prescribed drugs, such as opioid painkillers—which are connected to large-scale addiction, death, and illegal activity—as well as traditional mental health treatments, such as SSRIs and SNRIs that are accompanied by significant adverse effects including suicide and unintentional death. (See Figure 5.)

In a recent double-blind, randomized controlled trial, researchers evaluated the safety and feasibility of psilocybin treatment using various dosages (10 mg vs 25 mg) in 89 healthy adults (Rucker et al., 2022). These dosages are consistent with physiologically and pharmacologically

**FIGURE 5. NATIONAL DRUG-INVOLVED OVERDOSE DEATHS: NUMBER AMONG ALL AGES, 1999-2020**



Note: Graph includes deaths with underlying causes of unintentional drug poisoning, suicide intent, homicide intent, or drug poisoning of undetermined intent, as coded in the International Classification of Diseases, 10th Revision. Data source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Deaths 1999-2020 on CDC WONDER Online Database, released 12/2021. Graph adapted from <https://nida.nih.gov/drug-topics/trends-statistics/overdose-death-rates>



well-tolerated doses, and are also consistent with typical treatment doses in studies to date (Brown et al., 2017). Researchers found few adverse effects, most being related to the psilocybin experience, such as altered perception and mood changes. All effects were mild, transient, and diminished rapidly post treatment. This study established that psilocybin could be well tolerated as a treatment medication.

**Researchers suggest that psilocybin is generally well-tolerated, suitable for treatment applications, and that positive, persisting effects are achieved without adverse effects, even at higher doses.**

A 2018 open-label study exploring the dosage range, tolerability, and outcomes of psilocybin-assisted therapy used progressively higher doses of psilocybin (0.3 mg per kg of body weight; 0.45 mg/kg; 0.6 mg/kg) with 12 participants and found no serious adverse effects (Nicholas et al., 2018). Rather, significant positive subjective effects were reported during the experience and at 30 days post-treatment, including non-clinical subjective experiences such as increases in sense of well-being and life satisfaction. The researchers suggest that psilocybin is generally well-tolerated, suitable for treatment applications, and that positive, persisting effects are achieved without adverse effects, even at higher doses.

These studies and other research have established a high degree of tolerability with few, transient effects in healthy subjects. However, in order to use psilocybin as a treatment for serious mental health issues, such as depression, tolerability in patient populations needed to be established.

In a 2016 open-label feasibility study that investigated psilocybin-assisted therapy for TRD, Robin Carhart-Harris, PhD, Mark Bolstridge, MD, and colleagues (2016) found that the treatment was well-tolerated with no serious adverse effects. Participants reported some transient anxiety during treatment onset as the psilocybin was taking effect, and some experienced transient thought disorder, transient mild nausea, and transient headaches. None of the effects were lasting. According to the study:

*“It is also worth noting that psilocybin has a favourable toxicity profile and is not associated with compulsive drug-seeking behaviours in animals or human beings. The side-effects that we noted were minor, and expected in light of previous studies of psilocybin.”*

Researchers have also found that even outside the clinical setting, psilocybin has few negative personal and social impacts. A 2010 review by Dutch researchers tracked social behaviors connected to the recreational use of psilocybin and found no evidence of physical or psychological dependence, and no evidence of increased criminal activity (van Amsterdam et al., 2011). A dozen reports of severe outcomes analyzed in the review related to recreational use over the span of five decades invariably also involved alcohol or other combinations of substances. Where a few fatalities were connected to psilocybin, the review states, “Fatal intoxications due to exposure to magic mushrooms are rare...and often due to the combination of magic mushrooms with other drugs, mostly alcohol.” According to this research, a human would have to eat 17kg of mushrooms in one sitting to die from overdose. The reviewers conclude that:

*“[T]he use of magic mushrooms rarely (if ever) leads to physical or psychological dependence, that acute and chronic adverse effects are relatively infrequent and generally mild, that public health and public order effects are very limited and that criminality*

related to the use, production and trafficking of magic mushrooms is almost non-existent.”

Though the review included recreational use of psilocybin, which is not the focus of this paper, it is important to learn from related individual and societal safety data. When considered alongside the safety results from clinical studies related to its medicinal application, psilocybin appears to pose nominal safety risks to the patient or to the public.

### PSILOCYBIN FOR TREATING DEPRESSION AND ANXIETY

**A**ccording to the current research, studies have found that psilocybin-assisted therapy is effective for hard-to-treat disorders, such as TRD and MDD, with results that have repeatedly shown to be superior to current treatment modalities, including talk therapies and SSRIs/SNRIs.

In a 2021 randomized-controlled, double-blind trial, 233 participants with TRD took a single dose of psilocybin, as part of PAT, after tapering off all medication. Almost 37 percent showed a significant decrease in symptoms at three weeks with 25 percent continuing to show significant reductions in symptoms at 12 weeks (COMPASS Pathways, 2021b). By comparison, SSRIs and other TAU medications typically require at least four weeks to show initial response (Machado-Vieira, et al., 2010)—defined as a 20 percent decrease in symptoms compared to baseline—and up to 12 weeks for significant response or remission. This extended time lag between beginning treatment and significant response has the added risk of non-compliance due to the onset of side effects before noticeable reductions in symptoms (Maddox, et al., 1994). The researchers in this 2021 psilocybin PAT trial point out that “more than 100 million people worldwide are affected by treatment-resistant depression, and as many as 30 percent of these attempt suicide at least once during their lifetime” (COMPASS

Pathways, 2021b). Within the study cohort, the treatment was well-tolerated by 90 percent of the participants, with most experiencing minor side effects such as headache, fatigue, or nausea. A small percentage experienced serious adverse events related to their depression including suicidal ideation, which is common in people with TRD, and was present in all participants during pre-screening. According to the December 2021 press release from trial sponsor COMPASS Pathways:

“TEAs [treatment-emergent adverse events] of suicidal ideation, suicidal behaviour and intentional self-injury were seen in all groups, as is regularly observed in a TRD population. Two thirds of the patients had previous thoughts of wishing to be dead, as assessed by a suicidality scale completed during patient screening; this included all patients reporting one of these adverse events, so all patients who experienced these events during the trial had said in patient screening that they had had suicidal thoughts prior to the trial. Further detailed case-by-case analysis of safety data found no evidence to suggest, at this time, a causal relationship between these reported adverse events and administration of COMP360 [psilocybin]” (COMPASS Pathways, 2021b).

In another recent study, Carhart-Harris conducted a Phase 2, double-blind, randomized clinical trial with 59 participants diagnosed with moderate to severe depression (Carhart-Harris et al., 2021). Participants received either escitalopram (an SSRI) or two 25 mg doses of psilocybin three weeks apart with psychotherapeutic support. Using the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR16) to measure symptoms of depression, researchers found that 70 percent of the psilocybin group responded to treatment, compared to only 48 percent of the escitalopram group.

**“While SSRIs dampen emotional depth by reducing the responsiveness of the brain’s stress circuitry, helping to take the edge off depressive symptoms, psilocybin seems to liberate thought and feeling.”**

To explain the difference in outcomes, Carhart-Harris authored an article about psychedelics for the treatment of depression and stated:

“[W]hile SSRIs dampen emotional depth by reducing the responsiveness of the brain’s stress circuitry, helping to take the edge off depressive symptoms, psilocybin seems to liberate thought and feeling. It does this by ‘dysregulating’ the most evolutionarily developed aspect of our brain, the neocortex. When this liberation occurs alongside professional psychological support, the most common outcome is a renewed breadth of perspective. Psychedelic therapy seems to catalyse a type of psychological growth that is conducive to mental health, overlapping in many respects with spiritual growth” (Carhart-Harris, 2021).

This phenomenon of liberating thoughts and feelings by “dysregulating” patterned brain activity may contribute to the powerful outcomes for psilocybin-assisted therapy versus TAU with talk therapy and SSRIs. Psilocybin-assisted therapy has been shown to effectively break the pattern of rumination by liberating thoughts, as Carhart-Harris indicated.

Additionally, a 2021 exploratory study by COMPASS Pathways found that psilocybin used as an adjunct to therapy in people already taking SSRI medication for

moderate to severe depression has a positive effect on reducing symptoms (COMPASS Pathways, 2021c). The company intends to further explore these outcomes with additional research.

In an earlier trial, researchers at Imperial College London conducted an open-label study on 20 participants diagnosed with TRD that included a 6-month follow-up evaluation (Watts et al., 2017). Patients reported initially and at follow-up that, following treatment with psilocybin, they had an experiential shift from feeling disconnected from self, others, and the world, to feeling connected to self, others, and the world, and an additional shift from emotional avoidance to greater emotional acceptance. In contrast, participants reported that some TAU medications and talk therapies tended to reinforce ongoing experiences of disconnection and avoidance, which seemed to correlate with TRD.

In a 2016 open-label feasibility study, Robin Carhart-Harris and colleagues at Imperial College London observed significant improvement in both depression and anxiety relative to baseline scores in 12 participants with moderate to severe TRD (Carhart-Harris, Bolstridge et al., 2016). Two-thirds of the participants were in remission after one week, with 42 percent remaining in remission after three months. Also, 58 percent of participants continued to respond to the treatment at three months, meaning they demonstrated a 50 percent or greater reduction in depressive symptoms. In summary, the researchers stated:

“Spontaneous recovery in refractory depression is rare, and many of the patients in the present study reported having depression for much of their adult lives ... The magnitude and persistence of the antidepressant effects observed here are not incongruent with what has been observed previously with psilocybin in chronic psychiatric conditions” (Carhart-Harris, Bolstridge et al., 2016).

## Outcomes remained statistically significant at six months post-treatment.

Further supporting the effectiveness of psilocybin on depression, the team at Imperial conducted a six-month follow up with participants in the aforementioned 2016 study (Carhart-Harris et al., 2018). Based on data (using the QIDS-SR16) assessed from one week to six months post-treatment, researchers noted a significant reduction in symptoms of depression during the first five weeks with none of the participants seeking additional or outside treatments during that time. In addition, outcomes

remained statistically significant at six months post-treatment. The researchers stated that “reductions in depressive symptoms at five weeks were predicted by the quality of the acute psychedelic experience,” supporting earlier research indicating that the novel psychedelic or mystical experience is a key antagonist in alleviating symptoms of depression as noted in the below “Psilocybin, Cancer-Related Anxiety, and the Mystical Experience” section.

Collating prior evidence for psilocybin-assisted therapy interventions for anxiety, depression, and substance use, a 2017 review evaluated the results of seven clinical studies, reporting that the research showed significant reductions in symptoms of anxiety, depression, and substance

### FINDING WORDS WHEN SCIENCE MEETS SPIRITUAL EXPERIENCES

**D**efining the “mystical experience” from a clinical perspective poses language and perception barriers, but to assist in the definition, it is helpful to note that some researchers who investigate psychedelics from both allopathic and anthropological perspectives often use the word “entheogen,” which captures the essences of many of these compounds as taught and experienced by Indigenous and traditional cultures. The etymology of the word entheogen translates to “that which causes God to be within an individual” (Miller, 2013). More specifically, entheogens indicate a belief that there is an innate intelligence in the plants or “medicines” that not only affects healing for many of our modern-named mental health disorders, but also provides a “richer understanding of the world for both individuals and cultures” (Tupper, 2002). While the roots of psychedelic experience are largely found in sacred practices, using the term “mystical experience” both honors their origins and provides for a non-theistic and accessible explanation of the

novel psychedelic experience for our modern more secular society.

“Mystical experiences” describe phenomenologically transcendental qualities that seem to be unique to classic psychedelics like psilocybin and DMT, differing from shifts in consciousness derived from other medications or meditative experiences, for example. This led some key researchers to explore how to define and measure this kind of reported experience, and how such an experience might map onto current Western medicine and neuroscientific perspectives of behavioral health.

Science has developed scales and questionnaires to help participants put common and shared language on these experiences and to help find connections between these intervention effects and their treatment outcomes. Some of these instruments include the Mystical Experience Questionnaire, the Altered States of Consciousness Scale, and the Hood Mysticism Scale.

use, with large effect sizes (Thomas et al., 2017). The researchers concluded, "... psilocybin sessions, supported by several weeks of integrative psychotherapy sessions, may significantly improve symptom scores and help patients achieve response or remission within weeks, which could persist for many months after taking psilocybin."

Other measures related to depression were evaluated in a 2018 analysis of 20 people with TRD who participated in the 2016 Carhart-Harris study (Erritzoe et al., 2018). Researchers found that following the treatment, neuroticism decreased and extraversion increased, based on data measured by three indicators: the Revised NEO Personality Inventory (NEO-PI-R), the subjective psilocybin experience with Altered State of Consciousness scale, and depressive symptoms with QIDS-SR16. Without making formal conclusions, the researchers state:

"Our observation of changes in personality measures [associated with reduced symptoms of treatment-resistant depression] after psilocybin therapy was mostly consistent with reports of personality change in relation to conventional antidepressant treatment, although the pronounced increases in Extraversion and Openness might constitute an effect more specific to psychedelic therapy" (Erritzoe et al., 2018).

Additional investigations on the effects of psilocybin treatment on severe depressive disorders include a randomized clinical trial published in 2021 by Alan Davis, PhD and colleagues where 24 participants aged 21 to 75 received psilocybin-assisted therapy. Treatment was conducted over 18 weeks, with two psilocybin sessions: one at 20 mg/70kg, and a second at 30 mg/70kg. Depression severity and improvements were measured using the GRID-Hamilton Depression Rating Scale and the QIDS-SR16. Statistically significant response to the treatment was reported in 71 percent of participants after four weeks, with 54 percent in remission by this point.

From the findings in this study, which builds upon earlier trials, the researchers conclude that, "psilocybin-assisted therapy [is] efficacious in producing large, rapid, and sustained antidepressant effects in patients with major depressive disorder" (Davis et al., 2021).

Aligning with this conclusion, a meta-analysis by Simon Goldberg, PhD and colleagues (2020) analyzed the effects of psilocybin in combination with behavioral interventions on anxiety and depression across four studies (one uncontrolled; three randomized, placebo-controlled; n=117). The analysis found statistically significant, large effects on anxiety and depression in pre, post, and follow-up data in all studies and designs. In addition, this paper found no serious risks of adverse events.

In a long-term follow-up to the Davis and colleagues 2021 randomized controlled trial (RCT) of 24 patients with MDD, researchers at Johns Hopkins found that the effects of a psilocybin-assisted therapy protocol (with two dosing sessions) persisted for a full year for many of the participants, with 75 percent maintaining response status and 58 percent in full remission by the end of the 12-month follow-up period (Gukasyan et al., 2022). (Of note, one third of the patients began using a daily antidepressant during the follow-up period, which "precludes determination of the effects of psilocybin alone in those patients.") The authors suggested that future research could explore whether the effects of psilocybin-assisted therapy on depression persist even beyond the 12-month period of this trial. Principal investigator Natalie Gukasyan, MD, assistant professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine, underscored that these treatment outcomes are due to the compound in combination with therapy:

"Our findings add to evidence that, under carefully controlled conditions, this is a promising therapeutic approach that can lead to significant and durable



improvements in depression... The results we see are in a research setting and require quite a lot of preparation and structured support from trained clinicians and therapists, and people should not attempt to try it on their own" (Martinez, 2022).

### PSILOCYBIN, CANCER-RELATED ANXIETY, AND THE MYSTICAL EXPERIENCE

Initial groundbreaking psilocybin studies came in the form of psilocybin-assisted therapy to treat anxiety and depression in people with life-threatening or terminal cancer. These earlier studies showed positive results, ultimately leading to research on non-cancer-related depression as outlined above. The earlier studies also explored what researchers noted as a primary, consistent outcome of treatment with psilocybin that has been called, as referred to above, the "mystical experience"—a profound realization experience that previously was not properly quantified in behavioral health paradigms. Researchers have observed a strong relationship between the subjective psychological experience of a participant and the clinical outcomes (Griffiths et al., 2011; Ross et al., 2016). Additional observations of increased desire to live and appreciation for life, sense of well-being, and satisfaction led researchers to consider subjective experiences as critical to the mechanisms of action for psilocybin.

**Survey results showed that participants who received psilocybin also "attributed to the experience sustained positive changes in attitudes and behavior."**

In an early randomized clinical trial by Roland Griffiths, PhD, professor in the Departments of Psychiatry and Neurosciences at the Johns Hopkins University School of Medicine, 30 healthy "hallucinogen-naïve adults"

received either psilocybin (30 mg/70 kg) or methylphenidate hydrochloride (40 mg/70 kg, a stimulant and attention deficit hyperactivity disorder medication) (Griffiths et al., 2006). Participants completed questionnaires about their experiences immediately following the sessions and at two-month follow-up. The data showed that psilocybin produced mystical experiences during the sessions, with 67 percent of the participants rating the experience as "either the single most meaningful experience of his or her life or among the top five most meaningful experiences of his or her life." Additionally, survey results showed that participants who received psilocybin also "attributed to the experience sustained positive changes in attitudes and behavior."

In a pilot study, Charles Grob, MD and colleagues (2011) used a moderate dose of psilocybin (0.2 mg/kg) to treat anxiety related to life-threatening cancer in 12 participants with a diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety. Participants underwent treatment as a six-hour assisted therapy for all sessions, active or placebo. As part of the data collection, the "subjects discussed the subjective aesthetic, cognitive, affective, and psychospiritual experiences they had during the session and completed rating instruments." Follow-up data collected every month for six consecutive months post treatment showed promising results. Using five different measurement tools—Beck Depression Inventory (BDI), Profile of Mood States (POMS), State-Trait Anxiety Inventory (STAI), Brief Psychiatric Rating Scale (BPRS), and 5-Dimension Altered States of Consciousness Profile—the researchers found several improvements with the reduction in BDI Score being significant at the six-month follow-up, indicating improvement in mood and affect, with no notable side effects.

To better understand the "mystical experience," a 2015 meta-analysis investigated the reliability and validity of the Mystical Experience Questionnaire (MEQ30) as a

tool for evaluating the experience of people undergoing psilocybin-assisted therapy or treatment (Barrett et al., 2015). As referenced above, reported mystical experiences have been found by psychedelic researchers as a consistent part of higher-dose psilocybin therapy that correlates strongly to positive outcomes for treatment objectives. The researchers reviewed MEQ30 data from 184 participants across multiple studies who received a moderate to high oral dose of psilocybin (at least 20 mg/70 kg) and found the MEQ30 to be an efficient and effective tool for measuring mystical experiences and predicting treatment efficacy.

**Over 80 percent of participants reported improvements in well-being and life satisfaction.**

In 2016, Griffiths and colleagues conducted a more comprehensive double-blind, crossover, randomized clinical trial using two high-dose (22 mg/70kg or 30 mg/70kg) psilocybin sessions to treat 51 people with life-threatening cancer for depression and/or anxiety (Griffiths et al., 2016). The treatment resulted in significant decreases in depression and anxiety symptoms, as measured by self-report and third-party observers. Moreover, a significant increase in optimism, sense of meaning, and quality of life was observed. More than 80 percent of participants reported improvements in well-being and life satisfaction.

In a pivotal 2016 double-blind, randomized, placebo-controlled, crossover trial, 29 people with clinically significant anxiety or depression as a result of life-threatening cancer were given either psilocybin (0.3 mg/kg) or the active placebo, niacin, in combination with psychotherapy (Ross et al., 2016). Initial results were measured up to seven weeks, at which point the groups crossed

over to receive whichever treatment they had not previously received.

**At a six and a half month follow-up, 60-80 percent of the participants continued to demonstrate enduring and clinically significant reductions in anxiety and depression symptoms, as well as an improved sense of quality of life and attitude towards death.**

According to the researchers, “psilocybin produced immediate, substantial, and sustained improvements in anxiety and depression and led to decreases in cancer-related demoralization and hopelessness, improved spiritual well-being, and increased quality of life.” Furthermore, at a six and a half month follow-up, 60 to 80 percent of the participants continued to demonstrate enduring and clinically significant reductions in anxiety and depression symptoms, as well as an improved sense of quality of life and attitude towards death. It is notable that the researchers state that “the psilocybin-induced mystical experience mediated the therapeutic effect of psilocybin on anxiety and depression” (Ross et al, 2016).

An analysis in 2017 of 13 adults with cancer-related anxiety found that a moderate dose of psilocybin with therapy focused on meaning-making found that the treatment produced experiences of joy, bliss, connectedness, surrender, letting go, and forgiveness, among other affective experiences associated with relief from the illness-related anxiety (Belser et al., 2017).

In 2021, researchers revisited the data from the aforementioned 2016 study by Ross and colleagues to further evaluate and analyze the effects of treatment with measures and language that are more compatible with current clinical parlance. The researchers noted that people with life-threatening cancer frequently suffer from elevated Loss of Meaning (LoM), which is a predictor of desire for hastened death, suicidal ideation (SI), and actual suicide (Ross et al., 2021). Analyzing the data, researchers found that psilocybin-assisted psychotherapy resulted in large reductions in SI and LoM as soon as eight hours post-treatment and continuing for at least six and a half months post-treatment. According to the research in this study, “[c]onverging epidemiologic and clinical trial findings suggests a potential antisuicidal effect of this treatment.” Moreover, the researchers state that psilocybin-assisted psychotherapy’s impact on reducing negative feelings such as hopelessness and demoralization makes it a potential alternative to antidepressants for suicidal patients and that it “... may be an effective antisuicidal intervention following a cancer diagnosis.”

In another study that reviewed follow-up data from an RCT that compared psychotherapy plus single-dose psilocybin or single-dose niacin in cancer patients with anxiety or depression, results confirmed long-term positive benefits of psilocybin-assisted psychotherapy (Agin-Liebman et al., 2020). Fifteen out of 16 participants participated in follow-ups at 3.2 and 4.5 years. Participants indicated reductions in anxiety, depression, hopelessness, demoralization, and death anxiety at both follow-ups. At the 4.5-year mark, 60–80 percent of participants continued to have clinically significant reductions in depression and anxiety (depending on the instrument of measure used), 71 percent said the experience was among the most personally meaningful in their lives, 96 percent rated it among the most spiritually significant experiences of their lives, and 100 percent said the experience had had at least a moderate impact on positive behavior change.

More recently, topline, preliminary results from an open-label trial involving cancer patients with MDD found that more than 50 percent achieved remission of depressive symptoms, sustained up to eight weeks, following a single dose of psilocybin (Maryland Oncology Hematology, 2021). In this study, 30 participants received a single, 25 mg dose of psilocybin. The report noted that almost 25 percent of all cancer patients suffer from depression, most of whom do not receive adequate mental health treatment.

### PSILOCYBIN AS A TREATMENT FOR ADDICTION

**B**eyond the potential for psilocybin-assisted therapy to be a breakthrough, efficacious treatment for serious mental health disorders such as TRD, MDD and anxiety, it has also found applications in treating addictions, namely tobacco dependence and alcoholism. Limited published research is demonstrating positive outcomes, and there is a collection of ongoing or actively recruiting trials focused on psilocybin therapy as a treatment for addiction.

A 2014 open-label study investigated the impact of psilocybin treatment on tobacco cessation in 15 middle-aged individuals who smoked about a pack of cigarettes per day for a mean of 31 years and had a mean of six previous quit attempts (Johnson et al., 2014). Participants were treated with two to three doses of psilocybin ranging between 20 mg/70kg and 30 mg/70 kg along with cognitive behavioral therapy (CBT). At six months, 80 percent of the participants indicated seven-day point prevalence abstinence, meaning they had not used tobacco in the prior seven days. The study explains that this is a significant level of potential efficacy compared to traditional cessation treatments—behavioral and pharmacological—which have success rates of less than 35 percent. Additionally, participants with biomarkers of smoking abstinence at six months also scored higher on the measure that rated psilocybin-occasioned mystical experience following their dosing session and had higher



ratings of personal meaning and spiritual significance of psilocybin sessions (Garcia-Romeu et al., 2015). Similar to the psilocybin therapy depression studies noted earlier, lasting positive treatment outcome effects were significantly correlated with a participant's sense of having a mystical experience during the treatment session.

## Psilocybin-assisted therapy produced higher abstinence rates after six months than with other smoking cessation medications or CBT alone.

In a more recent 2016 follow-up to this study, new data from the earlier study was shared, showing psilocybin-assisted therapy produced higher abstinence rates after six months than with other smoking cessation medications or CBT alone (Johnson et al., 2016). Additionally, at 12 months post intervention, 67 percent of participants were smoking abstinent, and approximately 87 percent of subjects reported the dosing session(s) experienced during the original pilot as among the five most personally meaningful and spiritually significant experiences of their lives. As the study notes, "In controlled studies, the most effective smoking cessation medications typically demonstrate less than 31 percent abstinence at 12 months post-treatment whereas the present study found 60 percent abstinence more than a year after psilocybin administration."

In a qualitative analysis of participant accounts from the above-mentioned Johnson study, findings illustrated the power of the combination of therapy and psilocybin. Relative to the therapy component, the researchers state that "preparatory counseling, strong rapport with the study team, and a sense of momentum once engaged in the study treatment were perceived as vital additional factors in achieving abstinence." Simultaneously, they observe that "participants emphasized that the content of psilocybin experiences overshadowed any short-term withdrawal symptoms," and that "Participants reported gaining vivid insights into self-identity and reasons for smoking from their psilocybin sessions. Experiences of interconnectedness, awe, and curiosity persisted beyond the duration of acute drug effects." (Noorani et al., 2018).

A proof-of-concept study conducted by Michael Bogenschutz, MD and colleagues (2015) investigated the effects of psilocybin treatment on 10 individuals with alcohol dependence and found that one to two supervised sessions in combination with Motivational Enhancement Therapy, as well as preparation and debriefing therapy sessions, increased abstinence compared to pre-psilocybin, therapy-only treatment. Increases in abstinence persisted at 36-week follow up.

In a case study of three alcoholics from the 2015 proof-of-concept study, researchers found that treatment with psilocybin significantly reduced the frequency and amount of alcohol consumption and, according to the findings, also significantly reduced symptoms of anxiety and depression immediately post treatment (Bogenschutz et al., 2018).

## PSILOCYBIN IN THE BRAIN

While the data-driven research outcomes of this novel therapy are exciting, scientists are also seeking to understand how psilocybin works in the brain to occasion these compelling outcomes. One of the popular theories as to the mechanism of action is a down-regulation of the default mode network (DMN). The DMN refers to connectivity between specific parts of the brain that produce and run internal, self-reflective processes. In particular, rumination and self-reflection on negative experiences and emotions such as regret, trauma, and loss, along with other negative self-referential processing, take place in the DMN and have been connected to the onset and perpetuation of depression. Major depressive disorder is characterized by increased rumination or the recurrent, reflective, and uncontrollable focus on the depressed mood and its causes and consequences. Major depressive disorder in middle-aged adults has been repeatedly associated with increased activity within the DMN (Manning & Steffens, 2016). Other studies find that an active DMN is present during drug/alcohol craving and withdrawal (Ekhtiari et al., 2016).

Using functional magnetic resonance imaging (fMRI) technology, researchers have visually analyzed brain activity during the psilocybin experience. One of the key findings they have noticed is that psilocybin down-regulates the DMN while up-regulating and increasing connectivity between all areas of the brain (Carhart-Harris et al., 2017). This brain-wide synergy is not present during normal consciousness, and is hard or perhaps impossible to achieve with talk therapy or SSRIs. Researchers hypothesize that this highly connected brain experience allows for the release and integration of experiences, thoughts, and feelings associated with depression, and perhaps anxiety. The sudden, brain-wide activity and integration of experience could be a partial explanation for how people with TRD or MDD can make such

significant progress in only one or two psilocybin-assisted therapy sessions, while typical treatments fail to make progress (Carhart-Harris, 2021).

This brain-wide connectivity may also occasion what some call the “mystical experience,” which can include positive dissociative experiences, including perceptual changes or synesthesia (experiencing a sense through another, e.g., hearing color), as well as transpersonal and transcendental experiences that seem to inform participants about a greater meaning in life. Researchers such as Griffiths and colleagues (2011) and Stephen Ross, MD and colleagues (2016) have suggested that this personally powerful experience, replete with big picture, mystical experiences and/or insights, contributes to long-lasting positive effects for some following psilocybin-assisted therapy.

In a 2021 paper, researchers conducted pre- and post-treatment fMRI analysis on participants in two different studies examining the efficacy of psilocybin for TRD and MDD: an open label study and a double-blind, randomized controlled trial (Daws et al., 2021). In both studies, researchers found that psilocybin therapy reduced the “modular network” of the brain, meaning the concentration of activity in specific networks, such as the DMN. Previous research has indicated that increases in modular network activity, in particular increases in the DMN, are correlated with depression and its behavioral symptoms such as narrow focus and rumination (Zhou et al., 2020). Conversely, psilocybin therapy appears to increase brain-wide activity, relieving the modular function, and through this, appears to enable a release of depression-related brain activity and a consequent reduction in symptoms of depression. The researchers reported:

“We believe that this ‘liberating’ effect of psilocybin on cortical activity occurs via its direct agonist action on cortical 5-HT<sub>2A</sub> receptors, dysregulating activity in regions rich in their expression. We believe chronic escitalopram administration (an SSRI sold under the names Cipralex and Lexapro) does not have the same effect on brain modularity due to its more generalized action on the serotonin system and likely predominant effect on inhibitory postsynaptic 5-HT<sub>1A</sub> receptors, which are richly expressed in limbic circuitry” (Daws et al., 2021).

## TAU medications often require continuous, long-term use, particularly in the case of TRD and MDD.

While SSRIs have shown to be up to 37 percent effective at treating MDD and SNRIs are up to 55 percent effective (Entsuah, Huang, and Thase, 2001), these TAU medications often require continuous, long-term use, particularly in the case of TRD and MDD (InformedHealth, 2020). Further, medications and dosages may need to be changed or modified to achieve effectiveness, and they typically present negative side effects including sexual dysfunction, weight gain, and sleep disturbance (Ferguson, 2001). By contrast, psilocybin-assisted therapy has shown at least comparable effectiveness when treating MDD patients following initial treatment, with only minor, transient side effects such as headache or nausea (Davis et al., 2021).

A study published in 2017 used pre- and post-treatment fMRI data to hypothesize correlations between changes in brain function and reduction in symptoms of depression following treatment with psilocybin (Carhart-Harris et al., 2017). Clinical outcomes found that depression was reduced for all 19 participants immediately following treatment, at one week post treatment, and persisting through to five-week follow-up. The fMRI data showed reduced cerebral blood flow in the temporal cortex, and

particularly in the amygdala. Reducing amygdala activity is correlated with decreasing symptoms of depression. In addition, researchers found that the DMN showed increases in resting-state functional activity, meaning it was connected to and engaged with more areas of the brain during treatment. This finding correlates with previous research suggesting that greater brain network activity and reduced DMN activity contribute to the alleviation of depressive symptoms. These and other changes in brain function were highly present during and after treatment with psilocybin.

Another randomized, double-blind, placebo-controlled study involved a single session of psilocybin (0.31 mg/kg) during a five-day mindfulness retreat, and used fMRI to measure pre- and post-psilocybin session brain activity (Smigielski et al., 2019). The data showed a reduction in DMN self-referential processing. The level of activity change positively correlated to positive shifts in prosocial behavior at four-month follow-up.

A deeper understanding of the molecular mechanisms underpinning the therapeutic benefits of psychedelic compounds may be useful in expanding their application in psychiatry and for research institutions, legislators, and funding bodies to acknowledge their utility. A recent study by Calvin Ly, PhD and colleagues (2018) elucidated some of these molecular mechanisms, and further research continues. Ly’s team observed that the psychedelic compounds psilocybin, DMT, and DOI (a psychedelic amphetamine) promote structural and functional neural plasticity in vitro (within a living organism) and in vivo (e.g., petri dish, etc.). The main findings included increased formation of neural interconnections, specifically through the processes of neuritogenesis (formation of new neurites that become axons or dendrites of a neuron), spinogenesis (growth of dendritic spines in neuron), and synaptogenesis (development of synaptic connections). It was proposed that these changes are driven by increased release of brain-derived neurotrophic factor (BDNF), a protein that activates mTOR, a key signaling cascade that regulates neuronal plasticity and

which is modulated by standard antidepressant and anti-neurodegenerative drugs. Given the observed effects on neuroplasticity and immunomodulatory (immune system activation/suppression) pathways, it is conceivable that psychedelics could also prove useful in treating diseases in which neurodegeneration is implicated, such as Alzheimer's and Parkinson's disease, in addition to potential treatments for MH/SUD.

As cited in the following paragraphs, to further investigate brain activity during psilocybin treatment and determine potential correlates of effectiveness in terms of clinical symptom reduction, some researchers have used fMRI to measure activity in the amygdala, an area of the brain commonly associated with the fight-or-flight response, heightened negative emotional states, trauma, and fear. To do this, the scientists showed participants pictures of frightening faces and measured their reactions in terms of brain activity. Notable studies found reduced amygdala brain activity post psilocybin treatment, which correlates to reduced rumination, fear, and other emotional states connected to depression and anxiety (Mertens et al., 2020).

In a 2020 open-label study, 19 participants with TRD were given a single dose of 25 mg of psilocybin (Mertens et al., 2020). Pre- and post-session fMRI data showed reduced reactivity to fearful faces, which was associated with decreased levels of rumination at one week. This is consistent with the pathology and abatement of TRD and MDD.

“These results are consistent with the idea that psilocybin therapy revives emotional responsiveness on a neural and psychological level, which may be a key treatment mechanism for psychedelic therapy,” the researchers reported. “Independent whole-brain analyses also revealed a post-treatment increase in functional connectivity between the amygdala and ventromedial prefrontal cortex to occipital-parietal cortices [increased overall brain activity] during face processing.” (Mertens et al., 2020). As indicated above in the 2017 Carhart-Harris research,

increased overall brain activity is hypothesized to be one of the key mechanisms contributing to the therapeutic effects of psilocybin therapy. In this study, researchers found that this increased activity persists post-treatment, which could be a causal indicator of longer outcomes found in psilocybin therapy research.

In an open-label pilot study, 12 people received 25 mg/70 kg of psilocybin and were assessed one day prior to treatment (baseline), and one week and one month post treatment, using a slew of measurement tools as well as fMRI data (Barrett et al., 2020). Measurement tools included the POMS, the STAI, the Positive and Negative Affect Schedule – Form X, the Depression, Anxiety, and Stress Scale, the Dispositional Positive Emotion Scale, Big Five Inventory, and the Tellegen Absorption Scale.

Overall, the researchers found that psilocybin reduced negative affect and increased positive affect. At one week post-treatment, anxiety, tension, depression, and mood disturbance scores were significantly lower, while positive affect scores were significantly higher. Some scores modulated back towards baseline at one month, although anxiety scores remained lower and positive affect scores remained higher at one month.

These outcomes occurred in tandem with decreased modular amygdala activity in the brain. According to the researchers, “These preliminary findings suggest that psilocybin may increase emotional and brain plasticity, and the reported findings support the hypothesis that negative affect may be a therapeutic target for psilocybin.”

In another study, which conducted positron emission tomography neuroimaging pre- and one week post-psilocybin on 10 psychedelic-naïve participants, researchers measured openness and mindfulness using the NEO Personality Inventory, and Mindful Attention Awareness Scale measures (Madsen et al., 2020). They conclude that “psilocybin intake is associated with long-term increases in Openness and—as a novel finding—mindfulness, which may be a key element of psilocybin therapy.”

## PSILOCYBIN RECOMMENDATIONS

Due to psilocybin-assisted therapy's promising research results demonstrating efficacy and durability even with a single dose administration, relative safety, and minimal abuse potential, it may become a first line treatment for MDD, TRD, and anxiety disorders. It is reasonable to imagine that many providers and patients could prefer psilocybin PAT to long-term use of SSRIs/SNRIs, which often a) require experimenting with multiple medications to find net benefit and managing drug interaction considerations, b) carry a host of undesirable immediate and longer-term side effects, and c) ultimately fail to work for millions of patients worldwide with treatment-refractory conditions.

**“Such results are unprecedented in psychiatry.”**

As stated in a 2017 review out of Johns Hopkins University, the current research findings on psilocybin offer “considerable therapeutic promise,” and “such results are unprecedented in psychiatry” (Johnson & Griffiths, 2017).

Considering the findings in the research reviewed above, the safety and efficacy of psilocybin-assisted therapy as a treatment for severe depression, anxiety conditions, and certain addictions shows positive outcomes and promise. In this rigorous body of research, the effectiveness of psilocybin-assisted therapy for refractory mental health conditions in several studies is outpacing medication, therapy, and a combination of the two. Based on the research to date, and pending continued efficacy and safety outcomes in Phase 2 and Phase 3 trials required by the FDA, BrainFutures recognizes psilocybin-assisted therapy as one of the evidence-based PATs that should be made available with adequate reimbursement as rapidly as possible for these hard-to-treat mental health and substance use disorders.



# Ketamine



# Ketamine / AT A GLANCE

## COMPOUND OVERVIEW

Ketamine was introduced to the market in 1970 as an FDA-approved anesthetic after clinical trials that began following its formulation in 1962. Ketamine is typically administered in one of several ways—intramuscular, intravenous, orally/sublingually, subcutaneous, or via nasal spray—all of which have a similar pharmacokinetic action though they may vary in absorption rates and bioavailability. For all methods, ketamine treatment for MH/SUD is generally well-tolerated, with side effects including nausea, vomiting, dizziness, labile increases in heart rate and blood pressure, confusion, and grogginess. Under appropriate clinical supervision these are treatable and often wear off within short periods of time, up to several hours for a minority of patients.

Unlike SSRIs and psychotherapy, which can take weeks to months to produce results, ketamine is faster-acting. Studies have found that the rapid onset of effects of ketamine has been effective for quickly reducing suicidal ideation in people with depression and can relieve symptoms of depression as early as within 24 hours of a single session. Emergency use of ketamine for agitation and sedation is commonplace. While questions of effect durability remain for maintaining long-term remission because of a limited number of longitudinal studies, the evidence is convincing for its effectiveness at acutely treating conditions such as MDD, TRD (including unipolar and bipolar depression), PTSD, and OCD.

## IN THIS REVIEW

BrainFutures' research reviews 47 studies with ketamine, including 14 RCTs and six open-label studies with more than 1,200 participants, along with two meta-analyses and 22 reviews. (The two meta-analyses covered nine trials and 267 participants, of which seven trials with 163 participants are not directly cited

in this review.) As a whole, this literature ultimately provides strong evidence for ketamine as an effective treatment for rapid reduction of TRD, MDD, suicidality, and PTSD, and is showing potential as a treatment for SUD, anxiety, chronic pain management, and other mental health conditions. Ongoing research includes approximately 59 active or recruiting studies on ketamine for depression, 15 for TRD, and seven active or recruiting studies on ketamine for PTSD.

## VOLUME AND TYPE OF RESEARCH

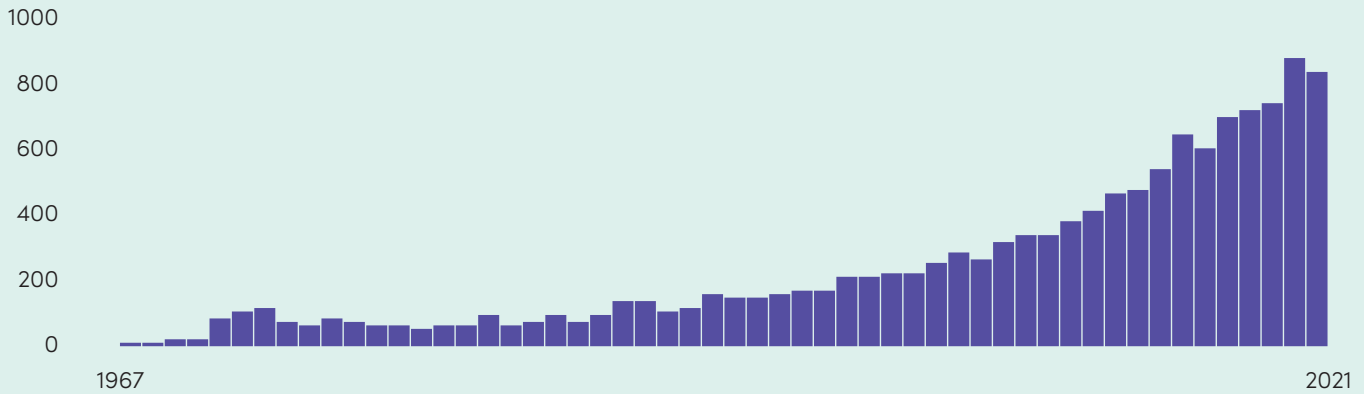
More than 20,000 research papers have been published on ketamine since 1965. The preponderance of research is related to its application as an anesthetic. From the 1970s through 1990s, ketamine usage increased both medically and recreationally. In the late '90s and early 2000s, ketamine began to show evidence as an effective antidepressant. Since 2006, 225 RCTs, 51 meta-analyses, and more than 565 reviews have reported on ketamine's effectiveness at alleviating refractory depression and anxiety, and more recently, suicidality and pain management. (See Figure 6 for ketamine research activity.)

## AREAS OF RESEARCH SHOWING EFFICACY

- Rapid reduction of major depression
- Rapid reduction of TRD
- Rapid reduction of unipolar and bipolar depression
- Rapid reduction of suicidality
- Rapid reduction of PTSD
- SUD treatment
- Pain management
- Anxiety

**FIGURE 6. THERAPEUTIC KETAMINE RESEARCH ACTIVITY (1967–2021)**

NUMBER OF STUDIES



Note: The above graph represents the increase in publications relating to ketamine therapy from 1967 to 2021. Adapted from PubMed (2022c). [Data set]. <https://pubmed.ncbi.nlm.nih.gov/?term=ketamine+therapy>

**SAMPLE OF RESEARCH FINDINGS**

- Intravenous ketamine is superior to placebo in treating MDD, showing reduced symptoms within 24 to 72 hours.
- Ketamine is effective for TRD, with response rates over 60 percent within 24 hours, and lasting up to four weeks post treatment for a portion of patients.
- A single infusion of ketamine rapidly reduces symptoms of PTSD within two hours and lasting up to 24 hours.
- A single infusion of ketamine rapidly reduces symptoms of refractory anxiety within one hour and lasting up to seven days.
- A single infusion of ketamine rapidly reduces suicidal ideation within 40 minutes to 24 hours and lasting up to three days.
- Ketamine-assisted therapy results in higher rates of abstinence in recovery from alcoholism and heroin addiction than traditional treatment methods.
- Ketamine treatment is showing effectiveness at managing chronic pain in conditions such as

fibromyalgia, neuropathy, spinal injury, complex regional pain syndrome (CRPS), and cancer-related neuralgia—reducing the amount of opioids needed for pain management.

**KEY TAKEAWAY**

Over the past two decades there has been a significant increase in research on the effectiveness of ketamine. FDA-approved as an anesthetic since 1970, the use of ketamine off-label as a rapid-acting anti-depressant, anti-anxiety, and anti-suicidal agent has been on a steady growth trend. In addition, ketamine treatments have been shown to be effective at treating PTSD, SUDs, and chronic pain.

# Ketamine

**K**etamine was developed by chemist Calvin Stevens in 1962 for Parke Davis Company (today a subsidiary of Pfizer). Following its FDA approval in 1970, ketamine has grown beyond its original and widespread use as an anesthetic to also be used today off label for analgesic, sedation, and psychiatric purposes (Li and Vlisides, 2016) in a variety of settings, including pediatrics, emergency rooms, and battlefields. Ketamine is included in the World Health Organization List of Essential Medicines (WHO, n.d.).

Uniquely, ketamine is an anesthetic and analgesic that can produce therapeutic dissociative states at certain dosage levels. Though it is considered by some clinicians and researchers to be a nonclassic psychedelic, it is categorized by other clinicians and researchers as psychedelic therapy due to its distinct but nonetheless psychedelic effect.

Ketamine as a possible therapeutic agent in the treatment of mental health was first explored in the 1970s. Though the War on Drugs did not classify ketamine as illegal, as in the case of other psychedelic compounds, research on its use for mental health conditions was still limited until more recently. Ketamine usage, however, did increase both medically and recreationally throughout the 1970s, 80s, and 90s. To address concerns about its growing recreational use, it eventually became a Schedule III federally controlled substance in the U.S. in 1999 (Witt, 2021; Ketamine, n.d.).

In the 1990s and early 2000s, ketamine therapy was successfully tested for depression and addiction using intravenous infusions, and for other early applications including relieving chronic pain and alleviating death anxiety in terminal patients (Li & Vlisides, 2016; Kohtala, 2021). Since then, a significant body of research has established ketamine therapy as a rapid-acting

protocol to address hard-to-treat depression like MDD and TRD (including both unipolar and bipolar), as well as PTSD, OCD, and anxiety. It is also being investigated as an intervention to address addiction.

When using ketamine as a mental health intervention, it can be given alongside therapy, a treatment known as ketamine-assisted therapy (KAT) or ketamine-assisted psychotherapy (KAP), terms that can be used interchangeably. KAT or KAP is the use of ketamine in the context of a psychotherapeutic relationship. (For the purposes of this report, we will use KAT throughout.) What constitutes the best or most appropriate psychotherapy for use with ketamine is still evolving and the subject of some research. Additionally, ketamine for MH/SUD treatment is also given without therapy. Most practitioners who administer the drug without onsite therapy recommend that patients combine the treatment with outside professional therapeutic support before or after administration in order to get the greatest benefit from the treatment.

When ketamine is used as part of a KAT session, lower doses allow conscious communication and are considered psycholytic, whereas higher subanesthetic doses can reduce sensory awareness and can produce out-of-body experiences or modifications in perceptions, considered dissociative or psychedelic. While ketamine can be used at sub-psychedelic doses, down to approximately 0.2 mg/kg, the preponderance of research and benefits have been demonstrated at a higher dose of 0.5 mg/kg ranging up to 2 mg/kg. Ketamine is the only legally prescribable psychedelic medicine with the capacity to induce this spectrum of effects that range from psycholytic to fully psychedelic. As such, it continues to be developed as a support to psychotherapy.

There is an ever-increasing body of neuroscientific investigation and putative explanations of ketamine’s effects. As a Schedule III Drug, with an FDA-approved indication only for anesthesia (with the exception of esketamine), the broad use of ketamine off-label for psychiatric indications has lent itself to an array of commercialization applications and modes of distribution. Like with any psychedelic, quality of care, and ethical use of this powerful medicine are essential and need to always be emphasized.

**DIFFERENT TYPES OF KETAMINE**

**B**efore exploring the research findings, it is important to note that studies have predominantly focused on intravenous (IV) R,S-ketamine (racemic) infusion, but that two mirror component subtypes (enantiomers) of ketamine exist: S-ketamine (esketamine) and R-ketamine (arketamine).

Esketamine received FDA approval in March 2019 for the treatment of TRD, becoming the first mental health application of ketamine to meet FDA requirements for safety and efficacy. It is manufactured by Janssen Pharmaceuticals, Inc., a subsidiary company of Johnson & Johnson, and is available as a prescription medication under the brand name Spravato. Spravato received a follow-on indication for MDD with acute suicidality in 2020.

Though research has shown efficacy for esketamine for TRD and MDD, there have been limited comparisons to the racemic form. Further, the cost of branded Spravato for bi-weekly treatments could run as high as \$6,785/month, far beyond the cost of generic IV racemic treatments, though potentially less expensive at the patient level with insurance coverage (Hamilton, 2019). These cost considerations, as well as the complexity of ordering the drug, processing insurance claims, and complying with the FDA’s Risk Evaluation and Mitigation Strategy

**FIGURE 7. TYPES OF KETAMINE**

**R, S-KETAMINE**

- 50/50 mixture of both R and S enantiomers
- Over 50 years of medical use for anesthesia and pain relief
- Used in most human clinical trials, including as an intervention for various MH/SUDs

**S-KETAMINE (ESKETAMINE)**

- FDA approved for TRD (2019) and for MDD with acute suicidality (2020)
- Recognized for rapid and lasting action in reducing depression and suicidal ideation
- Greater dissociative effects and dopaminergic activity than R-ketamine
- Body removes it more quickly than R-ketamine

**R-KETAMINE (ARKETAMINE)**

- No FDA Approval as an antidepressant yet
- Fewer hallucinogenic and dissociative effects than S-ketamine
- Less dopaminergic activity may translate to lower abuse potential
- Able to stimulate the formation of new neural connections (synaptogenesis)
- May be more potent and longer-lasting, with fewer side effects than S-ketamine
- Almost no controlled human data yet

Note: Figure showing the different types of ketamine. Adapted from Reality Sandwich (2021, March 1). Types of Ketamine: Learn the Differences & Uses for Each. <https://realitysandwich.com/different-types-of-ketamine/>

(REMS) requirements have likely contributed to slower commercial uptake than need may have predicted.

Arketamine is purported to reduce or eliminate hallucinations as a side effect, but human trials are nascent and it has not yet received regulatory approval for any indication (Hashimoto, 2019).

### TOLERABILITY OF KETAMINE TREATMENT

All applications of ketamine at moderate to higher subanesthetic doses typically produce dissociative or psychedelic effects, ranging in expression and intensity depending on individual sensitivity. While terms used to describe ketamine's effects have yet to reach consensus among researchers and clinicians, for the purposes of this report, ketamine effects that are psychomimetic or disassociative in nature with visual/auditory or other perceptual shifts will be called psychedelic. Ketamine does not usually induce psychedelic effects at extremely low doses (<.1 mg/kg), but generally does produce such effects typically starting around .5 mg/kg. Psychedelic dose ranges are still below high-level anesthetic doses. Research has found that doses that produce a psychedelic effect more consistently lead to improved mental health intervention outcomes. The lethal dose of ketamine is approximately 600 mg/kg (Orhurhu, 2021), whereas the typical therapeutic dose is .5 mg/kg, or 1/1,200 of the lethal dose.

Similar to other psychedelics, there are no reported deaths from ketamine therapy and few reported deaths from non-clinical use almost exclusively due to misadventure associated with incapacitation (Lalonde & Wallage 2004). A 2018 systematic review looked at side effects associated with ketamine when used to treat depression (Short et al., 2017). The review included almost 900 patients and showed that:

“Acute and psychotomimetic, cognitive, physiological, and neurological side effects occurred most often immediately following intravenous ketamine administration and resolved within 90 min of treatment; all such effects dissipated within [four hours]. Psychotomimetic side effects most commonly included dissociation, followed by perceptual disturbance, odd or abnormal sensation, derealization, hallucinations, feeling strange or unreal, and depersonalization. Cognitive side effects included poor memory/memory loss, poor concentration, confusion, and cognitive impairment/diminished mental capacity. Physiological effects included acute cardiovascular changes such as increased blood pressure and heart rate, palpitations or arrhythmia, chest pain/tightness/pressure, dizziness upon standing, or decreased blood pressure and/or heart rate. Neurological side effects included headache and dizziness (most common), followed by sedation or drowsiness, faintness/light-headedness, poor coordination/unsteadiness, and tremor/involuntary movements” (Muscat et al., 2021).

A ketamine overdose can produce significant symptoms and side effects, including uncontrolled eye movement, pupil dilation, excessive salivation, hypertension, tachycardia, palpitations, arrhythmias, chest pain, abdominal pain, tenderness, nausea and vomiting, confusion, paranoia, dysphoria, restlessness, confusion, slurred speech, dizziness, ataxia, lockjaw, and muscle stiffness; however, these symptoms typically abate within 15 minutes to several hours without lasting effects (Kowalczyk, et al., 2021). There is no antidote to ketamine poisoning, but usually supervision and symptom treatment are effective at reducing the risk of these side effects. The dosages used in supervised ketamine sessions to treat mental health conditions would not result in overdose or ketamine poisoning.

According to a 2019 analysis, the abuse liability for ketamine appears minimal when administered in a clinical setting. The review analyzed private practice outcome data from 235 patients who received ketamine treatment for mental health conditions ranging from MDD to developmental trauma, PTSD, anxiety, and related disorders, and stated:

“[D]espite the stigma of recreational use and concerns regarding addiction, ketamine used in KAP [ketamine-assisted therapy] practice does not produce any physical dependence. Importantly, we have not had patients seek ketamine outside of our clinical practices or encountered any other indication of addictive behavior” (Dore et al., 2019).

#### KETAMINE AS AN INTERVENTION FOR MAJOR DEPRESSIVE DISORDER

One of the most promising uses of ketamine in the mental health field is to treat MDD. An early controlled study by Dr. Robert M. Berman, MD and colleagues (2000) evaluated ketamine infusions for the treatment of seven individuals with major depression. Researchers reported significant reductions in depressive symptoms within 72 hours of ketamine treatment based on the 25-item Hamilton Rating Scale for Depression (HAM-D). This early study led to later research that confirmed the efficacy of ketamine for rapid reduction of depression symptoms.

A 2014 review and meta-analysis of randomized, double-blind, placebo-controlled trials on the effects of intravenous and nasal ketamine in the treatment of MDD found ketamine to be efficacious in reducing symptoms rapidly with sustained response for up to two weeks following a treatment (McGirr et al., 2014). Researchers reviewed eight RCTs that included 149 participants with MDD and 34 participants with bipolar depression. The researchers found significant clinical remission at one, three, and seven days following a single treatment. Side effects included transient psychotomimetic effects

(delusions and/or delirium), typically reaching peak expression within an hour of the infusion and then returning to baseline.

A 2015 meta-analysis reviewed data from three clinical trials, conducted between 2006 and 2012, that included 205 intravenous ketamine infusions (0.5 mg/kg over 40 minutes) in 97 participants with MDD (Wan et al., 2015). Response to treatment was defined as a greater than 50 percent improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) score. The overall response rate was 67 percent across all participants. Researchers found that the effects of treatment were relatively well-tolerated, with no persistent psychotomimetic or adverse effects or increased substance use among participants.

**“Ketamine constitutes a novel, rapid and efficacious treatment option for patients suffering from treatment resistant depression and exhibits rapid and significant anti-suicidal effects.”**

A 2017 review analyzed 12 trials—a mix of randomized clinical trials and open-label trials—that included 226 participants with MDD who were treated with intravenous or intranasal ketamine (Kraus et al., 2017). Findings indicated significant reduction in symptoms as measured by HAM-D, BDI, and MADRS, and found that ketamine was always superior to placebo. Researchers conclude that with a 61 percent response rate after 24 hours, “ketamine constitutes a novel, rapid and efficacious treatment option for patients suffering from treatment resistant depression and exhibits rapid and significant anti-suicidal effects.”



A randomized controlled trial that treated adolescents aged 13 to 17 years old who have MDD was published in 2021 and found that a single infusion of ketamine significantly reduced symptoms within 24 hours when compared to the control group. Moreover, during the first three days after treatment, 76 percent of the ketamine group continued to experience a reduction in symptoms compared to 35 percent of the active control group (Dwyer et al., 2021).

A 2021 systematic review summarized findings from 83 published reports on human studies investigating the clinical effect of ketamine, S(+)-ketamine (esketamine) or R(-)-ketamine (arketamine) in the treatment of mental health disorders (Walsh et al., 2021). The researchers confirmed that ketamine, in all administrations, produced a rapid antidepressant effect for depression and MDD, and similarly reduced suicidality quickly. As reported in other research, these effects were short-lived, up to four weeks, depending on the number of ketamine sessions and the underlying mental health conditions. (The researchers acknowledged a risk of bias in the reviewed studies, given that some of the reviewed papers lacked a high level of rigor.)

### **KETAMINE FOR TREATMENT-RESISTANT DEPRESSION AND POST-TRAUMATIC STRESS DISORDER**

**A**s indicated in several studies reviewed in the section “Ketamine as an Intervention for Major Depressive Disorder,” evidence has been building that ketamine is effective at providing rapid relief for TRD.

A 2012 open-label study investigated the effects of six ketamine infusions over a 12-day period on 24 people with TRD who had discontinued antidepressant medication (Murrough et al., 2012). The response rate was over 70 percent at treatment completion as measured by the MADRS. Median time to relapse was 18 days after the

last ketamine session. The researchers found that serial ketamine infusions produce a rapid antidepressant effect in TRD patients.

A 2013 open-label study of 14 participants with TRD examined the effects of six serial ketamine infusions (0.5 mg/kg on Mondays, Wednesdays, and Fridays) over a 12-day period (Shiroma et al., 2013). Out of the 12 participants who completed the treatment protocol, 66 percent of participants achieved remission by the end of the treatment with approximately 92 percent responding to the treatment. Five participants maintained response status throughout the four weeks of follow-up, while six participants relapsed within four weeks.

A 2014 review of ketamine research analyzed 24 studies including 416 participants who were treated with ketamine for TRD (Serafini et al., 2014). The researchers noted that up to 20 percent of all people diagnosed with depression are suffering from TRD, and that ketamine may be an efficacious treatment for this form of the illness. They concluded from their review that ketamine does in fact have rapid antidepressant effects for people with TRD, showing positive effects within 24 hours of application. They also noted that ketamine was effective at lowering suicidal ideation for people with TRD. However, they warned that psychotomimetic side effects could complicate the application of ketamine as a treatment for depression.

A multicenter, randomized, placebo-controlled trial investigated the effects of IV esketamine on 30 patients with TRD and found a “rapid and robust” antidepressant effect within two hours with only transient side effects, primarily headache, nausea, and dissociation (Singh et al., 2015).

A 2016 double-blind, randomized, placebo-controlled, dose-frequency study evaluated intravenous ketamine used on 67 TRD patients (including 45 women) (Singh et al., 2016). IV ketamine was administered at 0.5 mg/kg

two or three times per week. Both dosage levels produce rapid-onset and sustained antidepressant effects for a 15-day period.

A 2022 retrospective study analyzed the records from 9,016 patients with depression (across severity levels) who had undergone ketamine intravenous therapy (KIT)—generally consisting of a series of four to eight infusions administered over seven to 28 days—between 2016 and 2020 (McInnes, et al., 2022). Of these, 537 patients had sufficient data for review. This analysis found less robust response and remission rates than reported in the above ketamine studies, with approximately 54 percent of the patients showing a response to ketamine treatment and approximately 29 percent achieving remission as measured 14–31 days after the initial round of ketamine administration. The study also reported that approximately eight percent of patients experienced an increase in depressive symptoms, but given the review’s uncontrolled conditions and no data on patient medication history, psychiatric history, or medical history, the cause is inconclusive. As for durability of effect, the report stated:

“Kaplan–Meier analyses showed that a patient who responds to KIT induction has approximately 80 [percent] probability of sustaining response at [four] weeks and approximately 60 [percent] probability at [eight] weeks, even without maintenance infusions.”

Research has looked at ketamine for treating both TRD and PTSD together and for PTSD alone. In a 2018 open-label study, researchers investigated the efficacy of serial ketamine infusions (0.5 mg/kg six times in 12 days) in 15 patients experiencing TRD and PTSD comorbidly. The researchers found an 80 percent remission rate for PTSD and a 93 percent response rate for TRD. The median relapse times for those in remission with PTSD and TRD were 41 days and 20 days, respectively. These findings indicate ketamine’s effectiveness for rapid reduction of treatment-resistant and comorbid mental health symptoms (Albott et al., 2018).

## A single-dose treatment of ketamine resulted in a rapid reduction of PTSD symptoms.

In a more focused study, a randomized double-blind crossover trial published in 2014 evaluated the efficacy of ketamine infusions for PTSD versus midazolam—a benzodiazepine sold under the brand Versed (Feder et al., 2014). In 41 patients seen between 2005 and 2009 at the Icahn School of Medicine in New York, researchers found that, as a primary outcome measure, those randomly assigned ketamine showed greater reduction of PTSD symptoms than midazolam-administered participants as indicated by the Impact of Event Scale–Revised. A single-dose treatment of ketamine resulted in a rapid reduction of PTSD symptoms that were maintained beyond 24 hours by all participants. The treatment was generally well tolerated with dissociative symptoms typically abating within two hours. Common transient side effects included blurred vision, dry mouth, restlessness, fatigue, nausea, poor coordination, and headache.

Similarly, in a 2021 RCT of individuals with chronic PTSD, 30 participants were randomly assigned to a test group that received intravenous ketamine or a control group that, like the above study, received an IV psychoactive placebo (midazolam) (Feder et al., 2021). The ketamine group showed a significant and rapid reduction in PTSD symptoms compared to the control group, lasting more than two weeks post treatment, with no major side effects.

The above research supporting ketamine for the acute treatment of MDD and TRD shows significant efficacy; and studies have found ketamine to be effective at relieving PTSD, a serious anxiety disorder, both independently and co-occurring with depression. Relapse for depression conditions treated with ketamine, however, tends to be at higher rates and occur sooner for single

administration versus multiple doses (Murrough et al., 2012; McInnes et al., 2022). This suggests that a series of administrations may be required for higher durability of effect. Additionally, variables and unknowns in data collection exist across studies. Most notably, this relates to whether patients received psychotherapeutic support outside of a ketamine treatment protocol. To clarify the efficacy of ketamine treatment as a stand-alone or in combination with therapy, some leading researchers in the KAT field are engaging in more rigorous studies on ketamine and psychotherapy, as has been done with other psychedelics, to determine if the combined treatments found in KAT may have better outcomes and more specific applications than ketamine administration alone.

**MORE ON KETAMINE TREATMENT FOR DEPRESSION AND ANXIETY, AS WELL AS OBSESSIVE COMPULSIVE DISORDER**

**R**esearchers and doctors have noticed that people with less refractory depression experience immediate relief after exposure to ketamine, leading to studies investigating the effectiveness and safety of ketamine as a treatment for a broader population with depression.

**“There is a clear unmet need for rapid-acting and more efficacious treatments.”**

A 2018 study published in the *Journal of Psychiatric Research* found that six serial IV ketamine infusions (0.5 mg/kg) over 12 days increased both response rates and remission rates in 97 patients with unipolar and bipolar depression compared to baseline (Zheng et al., 2018). Additionally, the researchers noted a 68 percent response rate and a 50.5 percent remission rate, and also noted significant decreases in suicidal ideation and anxiety as measured by the Scale for Suicidal Ideations-part 1 and the 14-item Hamilton Anxiety Scale (HAM-A),

respectively. The researchers note that, “approximately one-third of depressed patients are treatment-resistant to currently available antidepressants and there is a significant therapeutic time lag of weeks to months. There is a clear unmet need for rapid-acting and more efficacious treatments.”

A 2019 research review stated that of the approximately 20 percent of the population suffering from depression (pre-COVID), approximately 30 percent of sufferers were treatment-resistant to currently available therapies. Following a review of the research, the researchers indicated that:

“[Ketamine] caused rapid-acting and sustained antidepressant effects in depressed patients, including TRD. In addition, ketamine significantly reduced suicidal thoughts in depressed patients. Furthermore, ketamine showed antidepressant effects in patients with BD [bipolar disorder], PTSD, OCD, GAD [general anxiety disorder], and SAD [seasonal affective disorder]. Thus, the discovery of antidepressant actions of ketamine is the greatest breakthrough in the field of depression in over 60 years” (Zhang & Hashimoto, 2019).

In a 2019 review of KAT for patients with MDD, PTSD, and anxiety disorders (cited earlier in this report), researchers found that ketamine is effective at decreasing depression and other mental health conditions and may be preferable to other medications in terms of side-effect burdens (Dore et al., 2019). In summary, the authors state:

“The side-effect profile is important to highlight, given that the most common reason for discontinuing conventional pharmacological treatment for depression and anxiety is the inability to tolerate side effects such as nausea or sexual dysfunction. Ketamine can be administered frequently when symptoms are acute (up to every 48 hours), or

periodically in a maintenance format, depending on the needs of the patient. Episodic, intermittent use of a medication is, for many patients, preferable to constant exposure, as with daily antidepressants. Intermittent use of medication also decreases the potential for adverse effects.”

To evaluate the efficacy of KAT, researchers used BDI scores for depression and HAM-A for anxiety, finding significant decreases in all scores following ketamine therapy. (See Figure 8.)

A 2020 review that explored the effectiveness of ketamine treatment for depression also noted the high occurrence of depression in the U.S.—roughly one in five people—and the limitations and more serious side effects of available pharmacologic treatments such as SSRIs (Pribish et al., 2020). It also underscored how conventional antidepressants can take weeks before patients see effects.

The researchers explained the promise of ketamine when compared to the limitations of TAU:

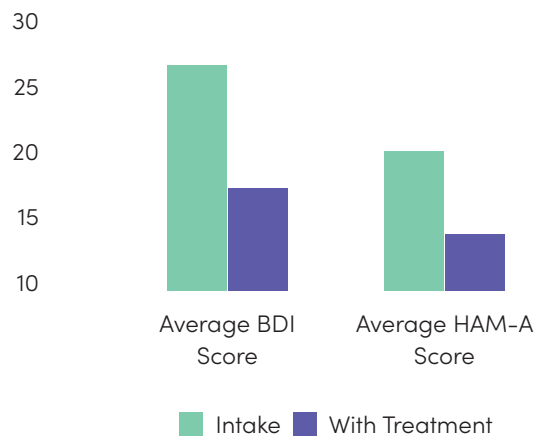
“Depression is thought to be caused by enhanced subcortical and limbic activity, which affects cognition and emotion regulation. Ketamine offers a promising alternative to conventional antidepressants due to its rapid onset and apparent efficacy. More broadly, ketamine appears to have efficacy in treating multiple internalizing disorders including depression, anxiety, and obsessive-compulsive disorder” (Pribish et al., 2020).

The review stated that, according to current research,

“A single subanesthetic dose (0.5 mg/kg) of intravenous (IV) ketamine hydrochloride has been shown to have a rapid antidepressant effect, which begins as early as two hours after ketamine administration, peaks at 24 hours, and lasts for up to 7–14 days. This effect has been noted in both unipolar and bipolar depression, although effect duration may be shorter in patients with bipolar disorder.”

**FIGURE 8. KAT SIGNIFICANTLY DECREASES DEPRESSION AND ANXIETY**

CLINICALLY SIGNIFICANT DECREASE IN BOTH HAM-A AND BDI AFTER TREATMENT (P<0.0001)



Note: The graph above shows average depression (BDI) and anxiety (HAM-A) at baseline (green) and following ketamine treatment (purple). The lower scores indicate reduced symptoms following KAT. Adapted from Dore, J., Turnipseed, B., Dwyer, S., Turnipseed, A., Andries, J., Ascani, G., ... Wolfson, P. (2019). Ketamine Assisted Psychotherapy (KAP): Patient Demographics, Clinical Data and Outcomes in Three Large Practices Administering Ketamine with Psychotherapy. *Journal of Psychoactive Drugs*, 189-198. <https://doi.org/10.1080/02791072.2019.1587556>

A 2017 open-label study evaluated the effect of ketamine on 12 patients with refractory generalized anxiety disorder and/or social anxiety disorder and found that a single dose relieved anxiety within one hour of treatment and lasted up to seven days (Glue et al., 2017).

A 2007 open-label study offered ketamine-enhanced therapy to terminally ill patients to enable a “death rehearsal” and reduce end-of-life anxiety (Kolp et al., 2007). The researchers hypothesized that the dissociative/psychedelic effects of intramuscular ketamine would lead to patients experiencing a simulated near-death experience, and perhaps relieve some of the grief response associated with terminal illness. The study design and numbers of participants were extremely limited, but some of the case studies with individuals who participated showed promise for this type of therapy. These outcomes may have inspired some of the more recent studies with ketamine and the previously mentioned psilocybin, as well as with other compounds that have been found to be effective at relieving depression and anxiety related to life-threatening cancer and other illnesses.

A 2013 randomized controlled trial investigated the efficacy of ketamine for treating obsessive-compulsive disorder (OCD) (Rodriguez et al., 2013). The researchers noted that serotonin reuptake inhibitors (SRIs) typically used to treat OCD take at least two to three months before producing clinically meaningful improvements. During the trial they found that the participants who received an infusion of ketamine showed significant improvement in obsessions within minutes, as measured by the OCD visual analog scale (OCD-VAS) and the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Researchers also found that the rapid reduction in symptoms following one ketamine infusion lasted up to a week for people with OCD.

The Zach Walsh, PhD and colleagues 2021 review mentioned earlier also found ketamine to be effective at relieving symptoms of social anxiety disorder, generalized

anxiety disorder (GAD), and PTSD, in some cases versus placebo, depending on the research reviewed. Again, these outcomes were short-lived, lasting up to two weeks after cessation of treatment.

## KETAMINE AND SUICIDE PREVENTION

**A**s indicated above, an interesting and perhaps powerful treatment opportunity given ketamine’s ability to rapidly abate symptoms is in suicide prevention.

**Even a single dose of ketamine alleviates suicidal ideation almost immediately.**

Several studies have found that even a single dose of ketamine alleviates suicidal ideation almost immediately, which could save lives considering the typical time lag before results are seen with other medications or talk therapy.

In a 2014 randomized controlled trial, 54 patients with TRD and explicit suicidal ideation were treated with either ketamine or midazolam (Price et al., 2014). Using the Beck Scale for Suicidal Ideation (BSS), MADRS suicide item, and Quick Inventory of Depressive Symptoms (QIDS) suicide item, the study found that explicit suicidal ideation was significantly reduced at 24 hours in the ketamine cohort but not in the midazolam group.

In a double-blinded, randomized, placebo-controlled study of 10 U.S. members of the military who were suicidal, a single, subanesthetic dose (0.2 mg/kg) significantly decreased suicidality and hopelessness within 40 minutes in the ketamine cohort while there was no change in the control group that received saline IV (Burger et al., 2016).



In a similar randomized controlled trial, 42 patients with newly diagnosed cancer suffering from overall depression and suicidal ideation were treated with ketamine or midazolam (Fan et al., 2017). As measured by the BSS and the suicidal part of the MADRS on days one and three, suicidal ideation decreased significantly in the ketamine group compared to control. In addition, overall depression symptoms decreased in the ketamine group.

The 2017 Kraus et al. review referenced above also concluded that “existing evidence suggests that ketamine may act as a potent and rapid antidepressant with anti-suicidal action in acute suicidal crises, as well as treatment in highly resistant forms of depression.”

**“IV ketamine may have increased utility in specialized populations, such as the military, cancer patients, and patients with Alzheimer's disease.”**

A 2020 review cited earlier also points out the anti-suicidal outcomes of IV ketamine therapy by stating, “IV ketamine may have increased utility in specialized populations, such as the military, cancer patients, and patients with Alzheimer's disease. In active duty military populations, long-term psychiatric admission for suicidality may create unique problems including separating the patient from his or her support network and leading to administrative obstacles in returning to duty” (Pribish et al., 2020).

In 2020, Spravato (esketamine) received FDA approval for the treatment of adults with MDD with acute suicidal ideation or behavior who presented in an emergency room or inpatient clinic. Across two Phase 3 clinical trials involving 456 participants, researchers at Janssen Pharmaceuticals found significant improvements

in depression scores at four and 24 hours, and up to 25 days later. The study also showed improvements on suicidal ideation, which was a consistent symptom across all participants. In both trials, participants were randomly assigned to esketamine (84 mg) or placebo nasal spray twice weekly for four weeks in addition to comprehensive medical care, including antidepressant therapy, taking benzodiazepines, or other medical treatments as necessary (Canuso et al., 2021).

In a 2021 review discussed earlier, data analysis also looked at six systematic reviews specific to ketamine outcomes on suicidal ideation (which included several meta-analyses). The review concluded that data provided “support for robust, rapid and transient ...anti-suicidal effects of ketamine” (Walsh et al., 2021).

A 2022 retrospective study, also reported on earlier, showed that 73 percent of 356 patients with baseline suicidal ideation experienced a reduction in this symptom after ketamine treatment of four to eight infusions over one to four weeks (McInnes et al., 2022). Of the almost 400 patients, 43 percent no longer exhibited any suicidal ideations. A small percentage (six percent) reported an increase in suicidal ideation, yet due to the open-label study not being able to collect patient medication history, psychiatric history, or medical history, the cause for this is inconclusive.

**“Despite advances in psychiatric treatments and psychosocial interventions that reduce repeat suicide attempts, there remain few evidence-based interventions that rapidly reduce suicide risk.”**



Currently, several ongoing studies are researching the efficacy of ketamine on suicide prevention in both adults and adolescents. The NIMH is supporting this effort. In their “News and Events” updates they make a strong statement about the need for effective treatments, and list proposed or ongoing studies aimed at combatting suicide. They state:

“Suicide rates have been steadily rising in the U.S. for the past two decades. While recent progress has been made in bending the curve in this trajectory, much work remains to be done to save lives. ... Research shows that up to 80 percent of people who die by suicide visit health care settings in the year before their death, and about a fifth of people who die by suicide are seen in a health care setting within the week of their death. Despite advances in psychiatric treatments and psychosocial interventions that reduce repeat suicide attempts, there remain few evidence-based interventions that rapidly reduce suicide risk within healthcare settings. The lack of such interventions often means that people at high risk for suicide must be treated in resource-intensive health care settings, such as the emergency department or inpatient settings. Identifying and developing rapid-acting treatments can reduce or eliminate the need for hospitalization and help “jumpstart” the recovery trajectory.

NIMH is supporting eight new research projects that focus on testing the safety, efficacy, and feasibility of ketamine and esketamine (medications known to rapidly reduce depressive symptoms in hours or days) or transcranial magnetic stimulation (which uses magnets to activate specific parts of the brain), to rapidly reduce suicidal thoughts and behaviors in youth and adults” (NIMH, 2021).

## KETAMINE FOR TREATING ALCOHOLISM AND SUBSTANCE USE DISORDERS

**K**etamine also shows promise in treating SUD. A 1997 review stated that the psychedelic experience from ketamine treatment contributed to the effectiveness in ketamine-assisted psychotherapy for alcoholism (Krupitsky & Grinenko, 1997). In this clinical trial of 211 alcoholic patients, researchers found that 66 percent of 111 participants experienced total abstinence after one year following ketamine treatment, compared to 24 percent of patients in the conventional treatment group. Additionally, the researchers further reported that participants demonstrated positive transformation in the areas of self concept and emotions, as well as life values and sense of purpose. These psychological changes were “shown to favor a sober lifestyle,” according to the researchers’ findings.

In a 2002 double-blind randomized control study, researchers looked at the effects of ketamine psychotherapy on detoxified heroin addicts (Krupitsky et al., 2002). Seventy participants were randomly assigned to a lower dose (0.2 mg/kg) or a higher dose (2.0 mg/kg) of ketamine. The higher dose group experienced hallucinogenic/psychedelic effects, whereas the lower dose group experienced “sub-psychedelic” effects. Researchers found that the higher dose of ketamine resulted in higher rates of abstinence at two-year follow-up, as well as fewer cravings and increases in positive mental attitudes. The researchers attributed the more successful outcomes in the higher dose, in part, to the psychedelic experience.

A 2021 review reported on earlier also concluded that ketamine is effective for treating SUD, resulting in higher abstinence rates compared to TAU for alcohol, cocaine, and opioid abuse (Walsh et al., 2021).

## KETAMINE SHOWS PROMISE AS A PAIN RELIEVER

**A**lthough pain conditions are not mental health conditions per se, studies suggest that those suffering from chronic pain are four times more likely to have depression or anxiety than those who are pain-free (Kleiber, Jain, & Trivedi, 2005). Finding effective solutions to address pain, especially if they avoid the prescription of opiates, can go a long way toward improving today's mental health and substance use challenges. Some of the studies that have shown ketamine to be useful in managing pain are highlighted below.

A 2004 qualitative and quantitative systematic review looked at 37 RCTs involving 1,336 patients who received ketamine when added to opioid analgesia in order to reduce the amount of opioids needed (Subramanian, Subramanian, & Steinbrook, 2004). The review concluded that "small dose ketamine has been shown to be a useful and safe additive to standard practice opioid analgesia in 54 [percent] of studies." This offers promising findings because when patients receive large doses of opioids and/or receive opioids for an extended duration, tolerance can result. Ketamine as a possible agent to reduce prescribed opioid use could potentially help with post-operative pain, and the less opioids patients are prescribed, the lower the likelihood of abuse. A 2005 systematic review of ketamine to help treat post-operative pain also looked at 37 trials (Bell et al., 2005). It found that "In the first 24 [hours] after surgery, ketamine reduces morphine requirements. Ketamine also reduces PONV [post-operative nausea and vomiting]. Adverse effects are mild or absent."

A 2004 study analyzed the case notes of 33 patients diagnosed with pain in the arms and legs as a result of an injury known as complex regional pain syndrome (CRPS) and treated by subanesthetic intravenous ketamine (Correll et al., 2004). Most received one treatment, one-third of participants received two treatments, and two patients received three treatments. Findings

showed that after the first dose of ketamine, 76 percent of patients reported complete pain relief, with 54 percent remaining pain free for more than three months. For the 12 patients that were administered a second dose, all reported complete pain relief, with 58 percent remaining pain free for more than a year. Feeling inebriated was the most common side effect, followed by reports of light-headedness, dizziness, and nausea. Four patients showed alterations in liver function profiles which resolved with termination of treatment.

An open-label study conducted the following year with 40 patients experiencing the same CRPS diagnosis showed similar promising results (Goldberg et al., 2005). Participants received a 10-day outpatient infusion of ketamine, starting at 40 mg and ending at 80 mg by the last day of treatment. Patients reported "a significant reduction in pain intensity... with a significant reduction in the percentage of patients experiencing pain by Day 10 as well as a reduction in the level of their 'worst' pain... Moreover, there was a significant improvement in the ability to initiate movement by the 10th day."

A 2009 double-blind controlled study of 19 CRPS patients (10 placebo and nine active treatment) showed that IV ketamine infusions produced statistically significant reductions in pain parameters, while the placebo group showed no treatment effect (Schwartzman et al., 2009). According to the study, "All subjects were infused intravenously with normal saline with or without ketamine for [four hours] (25 ml/h) daily for 10 days. The maximum ketamine infusion rate was 0.35 mg/kg/h, not to exceed 25 mg/h over a [four hour] period." Reported improvements across test parameters up to four weeks post treatment ranged from greater than 50 percent (n=1), to 20–30 percent improvement (n=4), to 10–20 percent improvement (n=3) and less than 10 percent improvement (n=1), with an average decrease in reported pain of 27 percent from baseline.

A 2010 review analyzed trials published after 2008 using ketamine to treat non-cancer pain through long-term intravenous infusions (Noppers et al., 2010). The review concluded, “There is now evidence from a limited number of studies that pain relief lasting for months is observed after long-term intravenous ketamine infusion, suggesting a modulatory effect of ketamine in the process of chronic pain.”

A 2012 retrospective analysis evaluated the effect of ketamine infusions in relieving patients who suffer from chronic pain (Patil & Anitescu, 2012). A total of 49 inpatient and 369 outpatient ketamine infusions over a five-year period from 2004 to 2009 were analyzed. Pain was measured using a visual analog scale pre- and post-procedure. Overall, ketamine infusions resulted in pain relief lasting up to three weeks with few adverse effects for the majority of patients.

In another review, researchers found that ketamine can be an effective treatment for chronic pain with few side effects at sub-anesthetic doses. Subsequently, using ketamine to treat pain can reduce the number of opioid doses typically required to manage pain (Kronenberg,

2002). A 2021 review supported these findings, including ketamine as a treatment for cancer-related neuropathic pain, and indicated that ketamine may counteract opioid-induced hyperalgesia—pain that occurs from long-term opioid use (Culp et al., 2021; Lee et al., 2011).

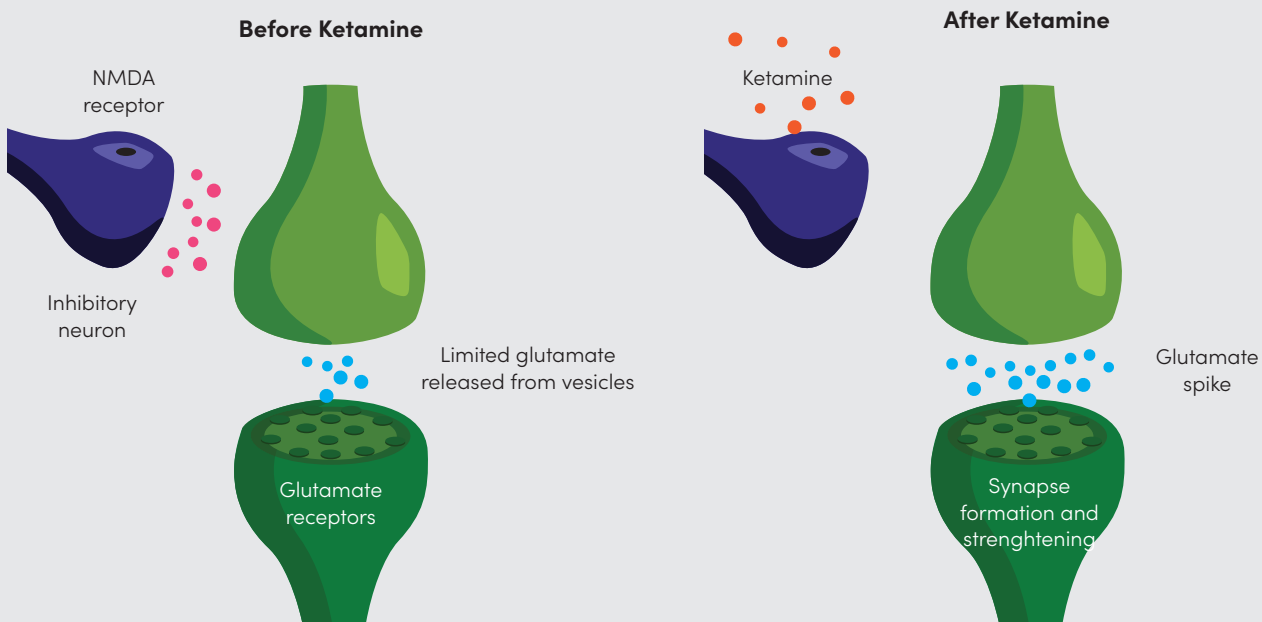
In June 2018, a joint effort between the American Society of Regional Anesthesia and Pain Medicine and the American Academy of Pain Medicine published guidelines for the use of ketamine as a treatment for chronic pain (Cohen et al., 2018). The guidelines indicate ketamine for opioid-dependent or opioid-tolerant patients with acute chronic pain, patients undergoing painful surgery, and sleep apnea, among other conditions. Practitioners are currently using ketamine to manage chronic pain in conditions such as fibromyalgia, neuropathy, spinal injury, CRPS, stroke or heart attack, and cancer. An in-progress randomized-controlled trial is researching the potential role of ketamine as opioid-replacement therapy, the results of which are expected in 2023 (Tompkins, 2021).

## KETAMINE IN THE BRAIN

Researchers speculate that depression is a result of a neuronal dysfunction or deficiency, largely brought about by chronic stress of various sorts. They find that ketamine infusions rapidly restore neural activity to regulated mood states, thereby producing a rapid-onset antidepressant effect. In the simplest sense, depression destabilizes specific synaptic brain activity; treatment with ketamine rapidly restores this brain activity, quickly and temporarily alleviating symptoms of depression for up to four weeks, depending on the treatment and the participant.

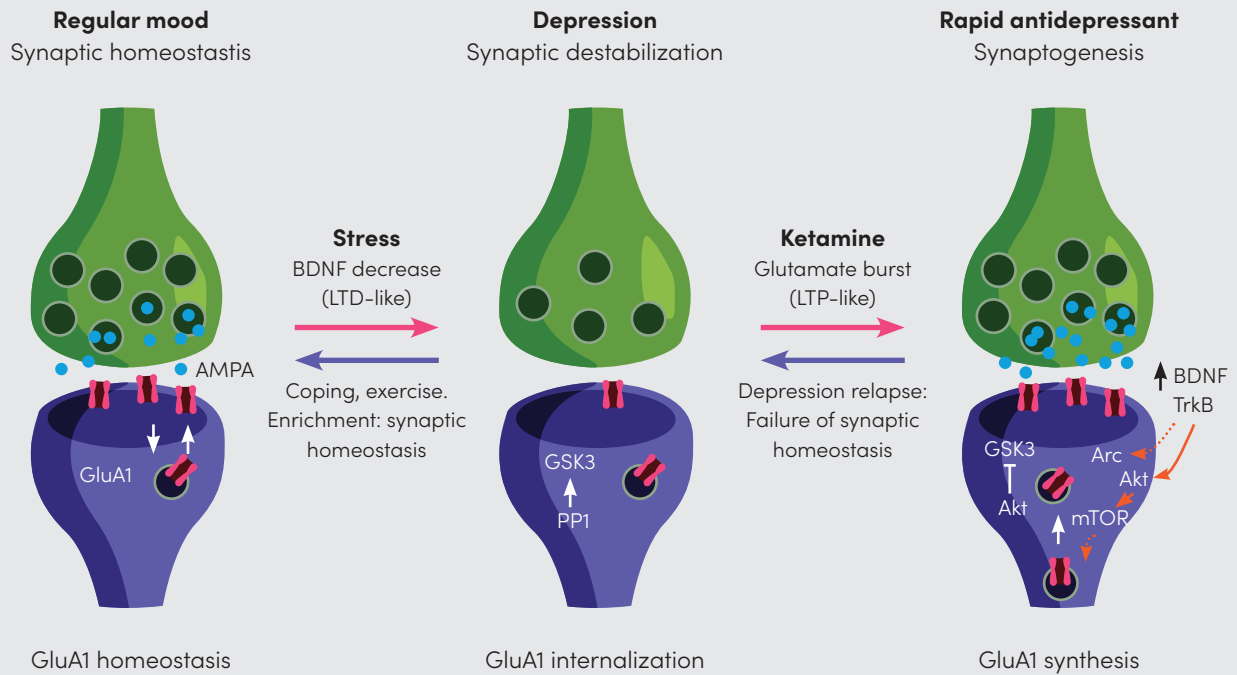
Figure 9 below illustrates how ketamine works in the brain by blocking NMDA receptors. This stimulates a release of the neurotransmitter glutamate, which causes synapses to form and fire, and strengthens neuronal activity. In turn, this action increases effective brain function and may account, in-part, for ketamine’s ability to help alleviate refractory mental health issues such as TRD and PTSD (Torrice, 2020). Figure 10 on the next page shows the same process in more detail, identifying relationships between specific neurotransmitters.

**FIGURE 9. HOW KETAMINE RESTORES HEALTHY SYNAPTIC ACTIVITY**



Note: Possible mechanism of action for ketamine’s effect on the brain. Ketamine (orange) can be seen to block NMDA receptors on the inhibitory neuron (purple). This leads to a spike in glutamate release (blue) from the presynaptic neuron. This leads to activation of AMPA receptors on the postsynaptic neuron which ultimately triggers synaptogenesis, strengthening the connection between neurons. Image adapted with permission from Chemical & Engineering News (© 2020 American Chemical Society). A version of this image appeared in the article “Ketamine is revolutionizing antidepressant research, but we still don’t know how it works” originally posted Jan. 15, 2020, and found in the Jan. 20, 2020, issue (Vol 98, issue 3) authored by Michael Torrice. <https://cen.acs.org/biological-chemistry/neuroscience/Ketamine-revolutionizing-antidepressant-research-still/98/i3>

**FIGURE 10. KETAMINE-ASSISTED THERAPY AND SYNAPTOGENESIS**



The image above shows how ketamine restores brain synapses back to normal levels in people with depression. Adapted from Duman, R., & Aghajanian, G. (2012). Synaptic Dysfunction in Depression: Potential Therapeutic Targets. *Science*, 68-72. <https://doi.org/10.1126/science.1222939>

In more technical parlance, ketamine has been shown to bind to and block NMDA receptors (Figure 10). In doing so, ketamine increases the level of glutamate at synapses (the space where neurons meet). This spike in glutamate leads to the activation of other glutamate receptors, known as AMPA receptors, which are integral to synaptic plasticity. Plasticity refers to the process of strengthening the connection between neurons and is an integral part of the neurochemical foundations of learning and memory.

Thus, the initial ketamine-induced blockade of NMDA receptors coupled with increasing levels of glutamate and AMPA receptor activation leads to the release of other molecules which promote synaptogenesis—the formation of new synapses. By creating new synapses and strengthening existing connections between neurons, ketamine has the ability to positively affect mood, thought patterns, and cognition (Meisner, 2019). Ultimately, this action increases brain function overall and may account, in-part, for ketamine’s ability to help alleviate the symptoms of refractory mental health issues such as TRD and PTSD (Torrice, 2020).

## KETAMINE RECOMMENDATIONS

The research findings above confirm that ketamine is effective at rapidly reducing symptoms of MDD, TRD, and suicidality. Furthermore, ketamine may be an effective treatment for substance use disorders and, even at lower doses, alleviate chronic pain. Based on the evidence, BrainFutures supports recommendations for ketamine or ketamine-assisted therapy for treatment of such conditions. Research points to medication with multiple psychotropic compounds plus psychosocial therapies being more effective. As such, BrainFutures acknowledges that many patients are likely to benefit from psychotherapy accompanying ketamine treatments. Providers should make on-site psychotherapy or referrals available to these patients so treatment can most reliably translate into improvements in mental health.

KAT insurance coverage at adequate rates should be prioritized by payers, especially in light of the 2008 Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act, which prevents health plans that provide mental health and/or substance use disorder benefits from imposing greater limitations on those benefits than on medical/surgical benefits (U.S. Centers for Medicare & Medicaid Services, n.d).



# MDMA

## MDMA / AT A GLANCE

### COMPOUND OVERVIEW

MDMA (3,4-methylenedioxymethamphetamine) was first synthesized in 1912 during an effort to develop drugs for wound management. It was found much later to produce euphoric and empathetic states, which led to increases in recreational use, particularly in the 1980s. The first U.S. government-approved MDMA psychological research study was conducted on healthy adults between 1993–1995 and led by Charles Grob, MD (Grob et al., 1995; Miller, 2017). More recent trials are revealing that MDMA can have a powerful effect on alleviating symptoms of PTSD. In August 2017, the FDA granted Breakthrough Therapy designation to MAPS for MDMA-assisted psychotherapy for PTSD, paving the way for a potential expedited approval process pending results of ongoing Phase 3 trials.

### IN THIS REVIEW

BrainFutures' research reviews 39 studies with MDMA (38 peer-reviewed), including nine RCTs and six open-label studies<sup>11</sup> covering 301 participants, along with two meta-analyses and 14 reviews. (The two meta-analyses covered six trials with 103 participants, all of which are cited directly in this review.) Together, these studies have shown efficacy in MDMA's ability to alleviate PTSD in combination with psychotherapy. Currently, there is one active or recruiting study on MDMA for depression and six active or recruiting studies on MDMA for PTSD.

### VOLUME AND TYPE OF RESEARCH

Since 1985, there have been more than 5,000 published reports or papers on MDMA (see Figure 11), most of which addressed the use/abuse of the substance and investigated mechanisms of action or potential risks. Also since that time, more than 230 papers on MDMA as a support for psychotherapy have

been published, including 27 RCTs, six meta-analyses, and more than 60 reviews. The preponderance of evidence is showing that MDMA in combination with therapy is an efficacious treatment for PTSD.

### AREAS OF RESEARCH SHOWING EFFICACY

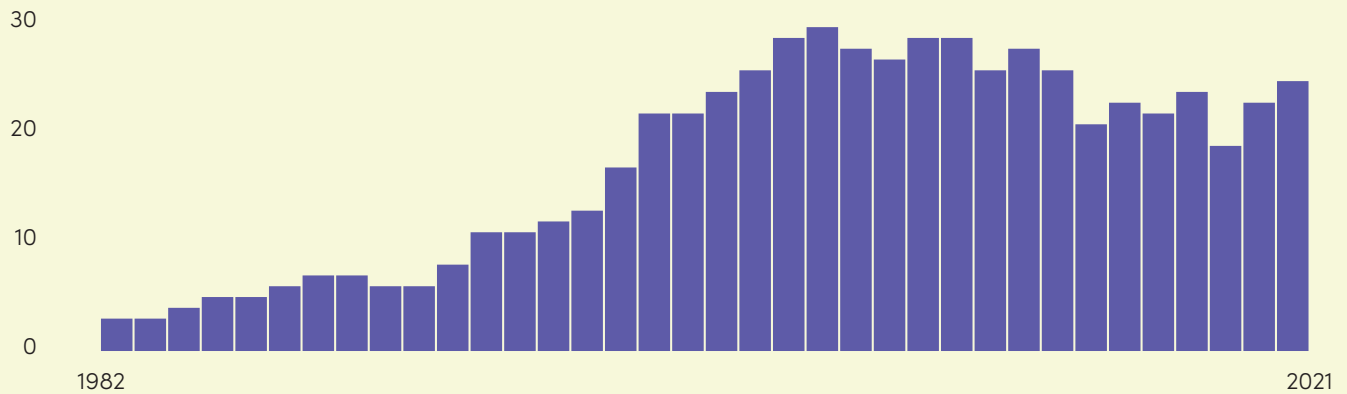
- PTSD
- Anxiety
- Depression

### SAMPLE OF RESEARCH FINDINGS

- PAT reduced symptoms of chronic PTSD that were non-responsive to typical psychotherapy or psychopharmacology, with reduced symptoms lasting for up to 74 months.
- Long-term follow-up (LTFU) outcomes of trials investigating MDMA-assisted therapy for treating PTSD showed that the percentage of participants that no longer qualified for PTSD diagnoses increased from 56 percent to 67 percent between treatment exit and LTFU.
- Two to three sessions of MDMA-assisted therapy were found to be more effective at reducing symptoms of PTSD than the current SSRI PTSD treatments paroxetine and sertraline.
- The results from the world's first Phase 3 trial using MDMA found that after three MDMA-assisted therapy sessions, 67 percent of participants no longer qualify for a PTSD diagnosis and 88 percent experienced a clinically significant reduction in symptoms.
- Economic analysis projects that MDMA-assisted therapy for PTSD can generate significant health-care cost savings compared to TAU.

**FIGURE 11. MDMA RESEARCH ACTIVITY (1982–2021)**

NUMBER OF STUDIES



Note. The above graph represents the increase in publications relating to MDMA from 1982 to 2021. Adapted from PubMed (2022e). [Data set]. <https://pubmed.ncbi.nlm.nih.gov/?term=mdma>

**KEY TAKEAWAY**

Given the data to date, MDMA-assisted therapy is an effective and efficacious intervention for PTSD. Current research results are showing that MDMA-based PAT typically leads to more effective and lasting outcomes than TAU for this condition.

# MDMA

**M**DMA (3,4-methylenedioxymethamphetamine) was synthesized in 1912 by German chemist Dr Anton Köllisch at Merck & Company as a candidate or intermediate compound in their efforts to develop a drug that would stop bleeding (Freudenmann, Öxler, & Bernschneider-Reif, 2006). While it never resulted in this application, MDMA was found to be a psychoactive compound that floods the brain with serotonin, as well as dopamine and norepinephrine (Gough et al., 1991).

Thought to be more gentle than classic psychedelics, the compound does not cause hallucinogenic-type effects, but it is reported to engender increases in sensations, feelings of euphoria, empathy, personal insight, self-acceptance, openness, warmth and understanding towards others, as well as reduced feelings of fear and anxiety (Miller, 2017). Based on some of these effects, it is often referred to as an entactogen or empathogen.

MDMA avoided being classified as a Schedule I drug until the mid 1980s (National Institute on Drug Abuse, 2017). This advanced its use by psychiatrists and psychotherapists in the 1970s and 1980s to help promote therapeutic engagement. As one article explained, “Because of its benign, feeling-enhancing, and nonhallucinatory properties, MDMA was used by a few dozen psychotherapists in the United States between 1977 and 1985, when it was still legal” (Passie, 2018). A survey of U.S. and Swiss psychiatrists and clinical psychologists who used MDMA with patients was conducted by Deborah Harlow, MA with the following results:

“Respondents reported on over 6,000 sessions with over 1,800 patients. The use of MDMA in patients suffering from depression, terminal illness,

post-traumatic stress syndrome and various phobias was particularly recommended. The use of MDMA in the treatment of cocaine addiction seemed promising though the success of MDMA in the treatment of alcoholism was reported to be less dramatic. The use of MDMA in marital therapy was also reported to be very effective. There was strong support for using MDMA in the training of psychotherapists” (Harlow, D. 1990).

The genesis of this interest among mental health clinicians can be attributed to biochemist Alexander Shulgin, PhD who, along with David Nichols, PhD, published the first paper on the effects of MDMA in humans (Sessa, Higbed, & Nutt, 2019; Shulgin & Nichols, 1978). In 1976, Shulgin also introduced MDMA to psychologist Leo Zeff, PhD who reportedly administered MDMA to at least four thousand people (Passie, 2018).

In 1984, Zeff worked with Joseph Downing, MD to conduct the first psychophysiological study of MDMA in humans (Passie, 2018). This safety study with 32 individuals was largely done in secret, albeit legally, as the FDA did not yet need to approve clinical studies with MDMA (Miller, 2017). It was initiated in an effort to gather data to support an appeal of the anticipated DEA classification of the drug, and the results (noted in the “Tolerability of MDMA Treatment” section below) validated the compound’s safety in clinical use.

Another early clinical MDMA-assisted therapy study that took place in the 1980s was by George Greer, MD (Greer & Tolbert, 1986). Dr. Greer had been offering MDMA-assisted therapy sessions and was a member of Association for the Responsible Use of Psychedelic Agents (ARUPA), along with Rick Doblin, PhD, Stan

Grof, MD, Rick Strassman, MD, and other key players in psychedelic research at that time. Hearing that scheduling of MDMA by the DEA was imminent, Greer published a study that summarized specific findings from his practice over a period of five years.

The then-novel study not only explored the potential benefits of MDMA-assisted therapy but also carefully looked at the side effects during and post-treatment. This study laid the foundations for further investigations, including study design, dosage, quality of therapeutic environment, and other aspects of treatment.

In general, psychotherapeutic use produced limited research in the 1970s and 1980s, with much of the psychotherapeutic efforts and activities chronicled in the article, “The early use of MDMA (‘Ecstasy’) in psychotherapy (1977–1985)” (Passie, 2018). MDMA’s street form, known as ecstasy or molly, found its way into the drug culture of the 1980s with a reputation for offering a long-lasting euphoric high. Due to this increased non-clinical use and related safety concerns, MDMA did in fact become a Schedule I substance in 1986.

It was not until 1992 that the FDA cleared Dr. Charles Grob, MD to conduct human studies (State News Service, 1992), followed by another FDA-approved study some years later by MAPS.

MAPS and its founder, Rick Doblin, played a key role in advancing research and the potential use of MDMA for MH/SUD treatment throughout the 1980s, 1990s, and early 2000s. Today the organization is poised to be the first to potentially garner FDA approval for MDMA with PAT to treat PTSD.

### TOLERABILITY OF MDMA TREATMENT

**M**DMMA is reported to evoke less-intense and better-tolerated states than LSD with a shorter duration of acute effects, while promoting empathetic and euphoric feelings (Sessa et al., 2019).

Effects generally begin after 30 to 40 minutes and can last up to six hours. In the first psychophysiological safety study of MDMA in humans noted above, the study reported:

“There were moderate, consistent biochemical, cardiovascular and neurobehavioral changes within normal limits that peaked between one and two hours following ingestion, returning to predrug levels within 24 hours. This experimental situation produced no observed or reported psychological or physiological damage, either during the 24-hour study period or during the three-month follow-up period. While the subjects are not typical of the general population, the findings support the general impression among knowledgeable professionals that MDMA is reasonably safe, produces positive mood changes in users, does not cause negative problems (if used sparingly and episodically) and is without evidence of abuse” (Downing, 1986).

Scientists have investigated potential brain neurotoxicity caused by MDMA (Reneman et al., 2001; Sarkar & Schumed, 2010). Early and ongoing studies primarily evaluated the effects of heavy and long-term recreational MDMA use on the brain and found that over time, MDMA has the potential to create neurotoxicity by depleting serotonin and causing lasting neurotransmitter changes (Kish et al., 2000). However, evidence of neurotoxicity is predominantly present in long-term, high-dose recreational use, and high-dose animal/primate studies. Some researchers have also pointed out that there is reason to question the usefulness of primate studies as analogs for potential harm in humans due to the differing pharmacokinetics between species (Grob, 2000).

A significant basis for concern of neurotoxicity from MDMA came from a series of studies conducted between 1998 and 2003 by George Ricaurte, MD, PhD and colleagues, who purportedly received \$14.6 million in federal funding during this time to study the risks

of MDMA—a controversial amount given the absence of federal funding to explore psychedelics’ potential therapeutic value (MAPS, n.d.b). A 2002 study led by Ricaurte and published in *Science* reported neurotoxicity in primates from MDMA use (Ricaurte, et al. 2002). It was later retracted after a review of the methods revealed that the researchers had given the animals methamphetamine and not MDMA (Pincock, 2003). This led to reactions from key researchers and practitioners in the PAT field, including Rick Doblin of MAPS and Phil Wolfson, MD, of The Center for Transformational Psychotherapy, who challenged the findings and suggested that the 2002 study, and potentially other studies involving Ricaurte (e.g. Bolla et al., 1998; Hatzidimitriou et al., 1999), may have been biased toward finding neurotoxicity from MDMA (Miller, 2017; Mithoefer et al., 2003; Ricaurte et al., 2003; Philipkoski, 2003).

In a response to the retracted study, MAPS said:

“Ricaurte et al. now report that they administered methamphetamine, and not MDMA, to all but one animal, reportedly because the two drugs were misidentified...Despite this mishap and the continued failure to find dopamine toxicity in non-human primates, the authors continue to hypothesize that an unspecified dose regimen of MDMA could be neurotoxic to dopaminergic cells” (MAPS, n.d.a).

Research on animals suggests that a lethal dose of MDMA would be around 45 mg/kg; but even at 9 mg/kg, users have experienced serious enough physiological effects, such as brain hyperthermia, to result in death (Kiyatkin, et al., 2014). As with other compounds, these severe warnings apply exclusively to unsupervised, recreational overuse, often in combination with other substances. In rave dance settings, for example, a popular environment for recreational use of MDMA, malignant hyperthermia can be tied to exertion, and hyponatraemia can be caused by overhydration (Miller 2017; Salathe et al., 2018).

Though a review of scientific literature looking at MDMA fatalities identified 51 deaths by overdose and another 36 from accidents, suicide, or unknown cause, these were from nonclinical use (Kalant, 2001). A 2019 review of MDMA-assisted therapy puts these numbers into perspective.

“[R]ecreational ecstasy use frequently involves impure samples of MDMA, taking multiple other drugs and often paying little attention to the physiological aspects of the drug experience... One study demonstrated that after removing confounding factors of concomitant drugs, there were only three deaths per year attributed solely to MDMA. Further studies that control for confounding factors show no evidence of neurotoxicity with MDMA when used in isolation and no lasting neurocognitive impairments. ... Over 1,600 doses of clinical MDMA have been administered in research settings in recent years, with only one report of a drug-related self-limiting serious adverse event and no deaths” (Sessa et al., 2019).

Clinical MDMA-assisted therapy uses moderate to high doses, usually starting with an initial dose between 75 mg and 125 mg, followed by an optional second dose 1.5-2.5 hours later at half that of the first. This puts a treatment session administration at a maximum of 187.5 mg per session, typically with a repeated protocol in two to three sessions over several weeks (Mithoefer et al., 2019). By contrast, non-clinical/recreational doses are typically much greater, up to 500 mg and higher, and pills may be tainted with other drugs (Morefield et al., 2011); MDMA-assisted therapy dose ranges are also far below toxic dosage levels or levels detected in death from overdose. Additionally, MDMA-PAT dosage levels are far below the acute levels administered in animal/primate studies exploring MDMA’s harm potential.



## MDMA-ASSISTED THERAPY AND PTSD

**A**n expanding body of evidence is showing that MDMA-assisted therapy is efficacious in the treatment of PTSD. A study published in 2008 based on research conducted between 2000–2002 sought to investigate the physiological and psychological safety of MDMA when used in low doses to treat PTSD in women who had been sexually assaulted (Bousso et al., 2008). According to the researchers, while “this study was originally planned to include 29 subjects, political pressures led to the closing of the study before it could be finished, at which time only six subjects had been treated.” The authors presented the following findings: “...low doses of MDMA administered as an adjunct to psychotherapy were found to be safe for the six subjects with chronic PTSD treated in this clinical trial and there were promising signs of efficacy and reduced PTSD symptomatology.”

In 2010, a more rigorous randomized controlled trial of MDMA for PTSD was published involving 20 participants with chronic PTSD who were non-responsive to typical psychotherapy or psychopharmacological medications (Mithoefer et al., 2010). Twelve participants received MDMA while eight received an inactive placebo. All participants received pre-treatment and follow-up psychotherapy in addition to the active treatment 8-hour assisted psychotherapy session. Based on measurements using the Clinician-Administered PTSD Scale (CAPS) at baseline, four days after each session, and at two months post-treatment, the active group showed a significant decrease in PTSD symptoms versus placebo, with no serious adverse effects. The authors concluded that, “MDMA-assisted psychotherapy can be administered to posttraumatic stress disorder patients without evidence of harm, and it may be useful in patients refractory to other treatments.” (Refractory, as mentioned above, means non-responsive to typical treatments.)

In 2013, researchers reported on long-term follow-up outcomes from the 2010 trial and found that 88 percent of the participants maintained clinically significant symptom relief based on outcome measures collected 17 to 74 months after the last MDMA session (Mithoefer et al., 2013). The researchers report, “It was promising that we found the majority of these subjects with previously severe PTSD who were unresponsive to existing treatments had symptomatic relief provided by MDMA-assisted psychotherapy that persisted over time, with no subjects reporting harm from participation in the study.”

By this time, enough safety and efficacy data had been published to support more research and different study designs in order to validate or invalidate early findings.

A double-blind, randomized, placebo-controlled trial published in 2013 investigated the effects of either 25 mg or 125 mg of MDMA as an adjunct to psychotherapy in 12 people with treatment-resistant PTSD (Oehen et al., 2013). Three MDMA sessions were interspersed with weekly psychotherapy sessions, and outcomes were recorded at baseline, two months, and one year. Researchers found the MDMA sessions to be safe, with no serious adverse effects. They did not see statistically significant reductions in CAPS scores, while there were clinically and statistically significant reductions in symptoms based on self-reported Posttraumatic Diagnostic Scale (PDS) scores. Interestingly, researchers found that CAPS scores did improve by the one-year follow-up.

Based on the success of key studies, MAPS has published a lengthy treatment protocol for MDMA-assisted therapy, including need-to-know information for therapists around preparation, the dosing session, follow-up care, and more (Mithoefer, 2013).

**Researchers working with MAPS have found that 67 percent of the group who received MDMA, compared to 32 percent of the group who received placebo, no longer qualified for a PTSD diagnosis after three treatment sessions.**

In August 2017, the FDA granted Breakthrough Therapy designation to MDMA as a PAT compound for PTSD, paving the way for Phase 3, multi-site trials conducted by MAPS that are awaiting completion. Breakthrough Therapy designation was granted due to the positive results from previous trials, as well as the lack of other viable treatments for refractory PTSD. The only two pharmacological treatments currently approved for refractory PTSD are the SSRIs sertraline hydrochloride (Zoloft) and paroxetine hydrochloride (Paxil). However, research has found that trauma-focused psychotherapy is more effective than current medications at treating PTSD (Lee et al., 2016). Proponents of MDMA-assisted therapy for PTSD contend that this protocol is more effective than all other current treatments. Noteworthily, in the first of their Phase 3 trials, researchers working with MAPS have found that 67 percent of the group who received MDMA, compared to 32 percent of the group who received placebo, no longer qualified for a PTSD diagnosis after three treatment sessions and 88 percent experienced a clinically significant reduction in symptoms (Mitchell et al., 2021).

A 2018 paper reviewed the clinical evidence to date and suggested that the same increases in neurotransmitter activity that increased concern for toxicity may in fact be part of the MDMA's mechanism in alleviating PTSD (Feduccia & Mithoefer, 2018). From the paper,

“... this review has provided evidence that the beneficial synergistic effects of MDMA with psychotherapy are attributed, at least in part, to the complex neuropharmacological profile of this entactogen creating a neural setting primed to facilitate new learning and extinguish fear related to traumatic memories. With actions on numerous neurotransmitter and neural pathways, MDMA can theoretically manipulate modulators of emotional learning and memory during psychotherapy in key brain regions, including the amygdala, hippocampus, and prefrontal cortex.”

A 2018 randomized controlled trial compared 100 mg and 125 mg active doses with a low dose (40 mg) of MDMA for people with chronic PTSD (Ot'alora et al., 2018). Although MDMA reduced CAPS scores across all three groups, the largest reductions were associated with a dose of 125 mg. Improvements in CAPS scores were maintained over a 12-month follow-up period. The researchers concluded, “Our findings support previous investigations of MDMA-assisted psychotherapy as an innovative, efficacious treatment for posttraumatic stress disorder” (Ot'alora et al., 2018).

A 2018 randomized, double-blind, dose-response, Phase 2 trial examined the impact of MDMA-assisted psychotherapy on Veterans and first responders with treatment-resistant PTSD (Mithoefer et al., 2018). Twenty-six participants with a CAPS score above 50 for at least six months received either 30 mg (control), 75 mg, or 125 mg MDMA as part of an eight-hour psychotherapy session. CAPS scores were taken at baseline, one month, and one year. The 75 mg and 125 mg groups saw significant decreases in scores (decreases in symptoms/improvement in condition) with large effect sizes at one month and again at one year. The study stated, “Active doses (75 mg and 125 mg) of MDMA with adjunctive psychotherapy in a controlled setting were effective and well tolerated in reducing PTSD symptoms in Veterans and first responders.”

**“MDMA-assisted psychotherapy was superior in Phase [2] trials in terms of safety and efficacy compared to sertraline hydrochloride and paroxetine hydrochloride, the two approved SSRIs for the treatment of PTSD.”**

A 2019 review presented findings and evidence “showing that MDMA-assisted psychotherapy was superior in Phase [2] trials in terms of safety and efficacy compared to sertraline hydrochloride and paroxetine hydrochloride, the two approved SSRIs for the treatment of PTSD” (Feduccia et al., 2019). The Feduccia study references a review of six prior randomized, double-blind, controlled clinical trials including 103 participants conducted from 2004 and 2017, that states, “MDMA-assisted psychotherapy was efficacious and well tolerated in a large sample of adults with PTSD” (Mithoefer et al., 2019). These earlier studies supported expansion into Phase 3 trials and led to FDA granting a Breakthrough Therapy designation for this “promising treatment.”

The review further explained that the successful Phase 2 trials included participants suffering from treatment-resistant PTSD for an average of 17.9 years, and that the treatment in the studies included “three preparatory psychotherapy sessions, followed by two to three blind-ed, eight-hour experimental psychotherapy sessions with MDMA (75–125 mg) or comparator/placebo (0–40 mg MDMA), and three 90-min non-drug integrative psychotherapy visits following each experimental session” (Mithoefer et al., 2019). The success of these trials cleared the way for Phase 3 trials and set the groundwork for MDMA-assisted therapy protocols and best practices.

Similar research in a 2020 study evaluated the long-term follow-up (LTFU) outcomes of MDMA-assisted psychotherapy for treatment of PTSD from the six trials mentioned above and found that, “PTSD symptoms were reduced one to two months after MDMA-assisted psychotherapy, and symptom improvement continued at least 12 months post-treatment” (Jerome et al., 2020). Additionally, these durability of effect outcomes showed that the percentage of participants that no longer qualified for PTSD diagnoses increased from 56 percent to 67 percent between treatment exit and LTFU, a compelling result by any measure.

A 2020 meta-analysis reviewed four randomized controlled trials treating PTSD with MDMA-assisted therapy (Illingworth et al., 2020). Based on CAPS scores, 75 mg and 125 mg doses showed significant decreases in PTSD symptoms, leading researchers to conclude there exists “...potential therapeutic benefit with minimal physical and neurocognitive risk for the use of MDMA-assisted psychotherapy in TR-PTSD [treatment-resistant PTSD] ...”

In couple partnerships where one person has significant PTSD, cognitive-behavioral conjoint therapy (CBCT), where both partners participate in the therapy, can be more effective than individual therapy. A recent open-label trial explored MDMA-assisted CBCT with six couples in various stages of relationship satisfaction where one person was diagnosed with PTSD (Monson et al., 2020). Fifteen CBCT sessions over seven weeks included two MDMA sessions where both partners participated. The study found significant improvement in PTSD symptoms as tracked by clinician-assessed, patient-rated, and partner-rated measures. Further, they noted improvements in relational happiness and individually reported improvements in depression, sleep, emotion regulation, and trauma-related beliefs.

A 2021 randomized, double-blind, placebo-controlled trial investigated the effects of MDMA-assisted therapy on 90 participants with severe PTSD, some of whom had comorbidities including dissociation, depression, a history of alcohol and substance use disorders, and childhood trauma (Mitchell et al., 2021). PTSD symptoms were measured at baseline and at two months after the last session using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Participants were continuously monitored for adverse events and suicidality. MDMA-assisted therapy showed significant reductions in PTSD symptoms with a large effect size compared to placebo. The researchers summarize,

“These data indicate that, compared with manualized therapy with inactive placebo, MDMA-assisted therapy is highly efficacious in individuals with severe PTSD, and treatment is safe and well-tolerated, even in those with comorbidities. We conclude that MDMA-assisted therapy represents a potential breakthrough treatment that merits expedited clinical evaluation.”

Therapists and clinicians are aware that sleep disorders frequently accompany PTSD. Participants in randomized controlled trials that measured the effectiveness of MDMA-assisted therapy on PTSD were also tracked for improvements in sleep. Researchers found that, compared to baseline, study participants had improved sleep after two months, and that it further improved by 12-month follow-up. They state that “[d]ata from these randomized controlled double-blind studies provide evidence for the beneficial effects of MDMA-assisted psychotherapy in treating SDs [sleep disorders] in individuals with PTSD” (Ponte et al., 2021).

A big question for the adoption of a new treatment by healthcare payers is relative cost and improvements compared to current, usual, and customary treatment. Analysis has shown that MDMA for PTSD could provide significant savings.

### MDMA SHOWN TO MITIGATE THE COST OF PTSD

**A** 2020 study evaluated the cost-effectiveness of MDMA-assisted therapy for PTSD based on the protocols used in six double-blind Phase 2 studies. It was found, on average, that MDMA-assisted therapy consisted of a mean of two and a half 90-minute prep sessions, two eight-hour MDMA sessions, and a mean of three and a half post-treatment integration sessions. The study calculated net outcomes over 30 years and included medical costs, mortality, and quality-adjusted life-years (QALY, a generic measure of disease burden used to assess the economic value of medical interventions: one QALY = one year of perfect health).

**“For 1,000 individuals with PTSD, MDMA-assisted therapy would generate savings of \$103.2 million.”**

The analysis found that for 1,000 individuals with PTSD, MDMA-assisted therapy would generate savings of \$103.2 million and gain 5,553 QALYs compared to TAU (Marseille et al., 2020). A follow-up analysis published in February 2022 based on Phase 3 study protocols showed QALYs at 4,856 and saving estimates at \$132.9 million (Marseille et al., 2022).

## MDMA FOR OTHER ANXIETY DISORDERS AND DEPRESSION

One of the early studies on MDMA in humans included 29 participants with various levels of psychological distress or mental disorders (Greer & Tolbert, 1986). Participant subjective reports were analyzed and follow-ups took place between two months and two years after the treatment. Of the participants, eight had Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnoses—including depressive disorders (four), anxiety disorder (one), and personality disorders (three). Following MDMA treatment, all eight reported “significant relief from their problems” with two reporting lasting remission. The study’s overall findings were generally positive with a majority of the 29 participants noting positive changes in mood (18), attitude (23), beliefs about self/others/world (16), relationships (28), occupation (16), and life goals (15). Almost half of the participants noted positive changes in practices of spiritual or physical well-being, (14) self-actualization (13), and substance use reduction (14). All of the subjects reported some form of side effects during and after the sessions including jaw clenching, nervousness, jitteriness, fatigue, and insomnia lasting various lengths of time during treatment with one participant noting effects up to a week later. Given this was an early study, it noted its limitation as being that “Only phenomenological descriptions were obtained of the therapists’ observations and of the subjects’ experiences before, during and after the sessions.”

In a controlled study, individuals with and without a predisposition to depression either took MDMA or abstained in a social setting and were evaluated using the POMS and BDI at baseline and one hour after taking MDMA. The participants with a predisposition to depression showed a statistically significant decrease in depressive symptoms (Majumder et al., 2012).

Charles Grob’s first MDMA research with humans was initially designed to assess the drug’s effect in treating physical pain and psychological distress in cancer patients (Grob, 1995). However, the FDA required a redesign of the protocols, so it became a Phase 1 pilot study in healthy volunteers, investigating psychobiological effects of MDMA in the hopes of later completing the study’s original intent (Grob et al., 1995; Miller 2017). Safety was a key concern for the FDA, as prior research had reported a level of neurotoxicity with high-dose, long-term use of the compound. Reflecting on the Phase 1 study, Grob reported:

“[At] the end of the day we found that our subjects tolerated the MDMA experience very well. Two individuals of the eighteen people did have high blood pressure reactions. This is something one has to be wary of. One was an older individual who simply had labile blood pressure. His baseline blood pressure was not normal, but under the influence of the MDMA he did have a significant rise. The other subject was interesting because...on at least one other occasion he had received MDMA, and on this third occasion his blood pressure shot up...[earlier in the day] his friend gave him some of his asthma medications. So we learned that interactions with particular medications can potentially be somewhat risky, and individuals do need to be apprised of that” (Miller, 2017).

It would take another 20 years for the concept of Grob’s initial study to be revisited. Starting in 2015, Phil Wolfson and his team began to enroll 18 individuals with anxiety related to a life-threatening illness into a randomized pilot study (Wolfson et al., 2020). While the active group did show reduced symptoms of anxiety as measured by the STAI scale, with a mean reduction in anxiety scores greater than the placebo group’s, the difference between groups was not statistically significant—thought to be due to one outlier in the placebo



participants. If that individual's outcome was removed, the change in STAI scores between groups would have achieved statistical significance. Even so, the researchers stated:

"[T]hese findings provide preliminary evidence to support that MDMA-assisted psychotherapy may be a safe and feasible treatment for those with LTIs [life-threatening illnesses] for anxiety reduction and relief of other psychiatric symptoms associated with their illness. Study results support the feasibility of MDMA-assisted psychotherapy as a novel approach for potential long-term treatment of LTI-related anxiety."

A more recent review further speaks to MDMA's potential in treating LTI-related anxiety. A 2022 review evaluated 19 studies on the impact of psychedelic compounds including MDMA on existential distress, depression, and anxiety in terminally ill patients and found that:

"Recent (controlled) trials with LSD, psilocybin, ketamine, and MDMA are of higher methodological quality and indicate positive effects on existential and spiritual well-being, quality of life, acceptance, and reduction of anxiety and depression with few adverse and no serious adverse effects" (Schimmel et al., 2021).

Another potential anxiety-reducing treatment application of MDMA was noted in a 2016 report commenting on the compound's promise in addressing social anxiety in autistic adults using MDMA-assisted psychotherapy (Danforth et al., 2016). The publication indicated a high need for new therapies given few to no effective current treatments for social anxiety in this population. It reported:

"To date, MDMA has been administered to over 1,133 individuals for research purposes without the occurrence of unexpected drug-related SAEs [serious adverse events] that require expedited reporting per FDA regulations. Now that safety parameters for limited use of MDMA in clinical settings have been established, a case can be made to further develop MDMA-assisted therapeutic interventions that could support autistic adults in increasing social adaptability among the typically developing population."

A related randomized pilot trial launched in 2014 and concluded in 2017. The study included 12 autistic adults "with marked to very severe social anxiety" who received either MDMA or placebo during two eight-hour psychotherapy sessions, followed by three non-MDMA sessions (Danforth et al., 2018). Researchers measured participants' anxiety using Liebowitz Social Anxiety Scale at one month and six months, reporting significant improvement at one month. These results remained stable or continued to improve slightly for most participants at six months.



## MDMA AND THE BRAIN

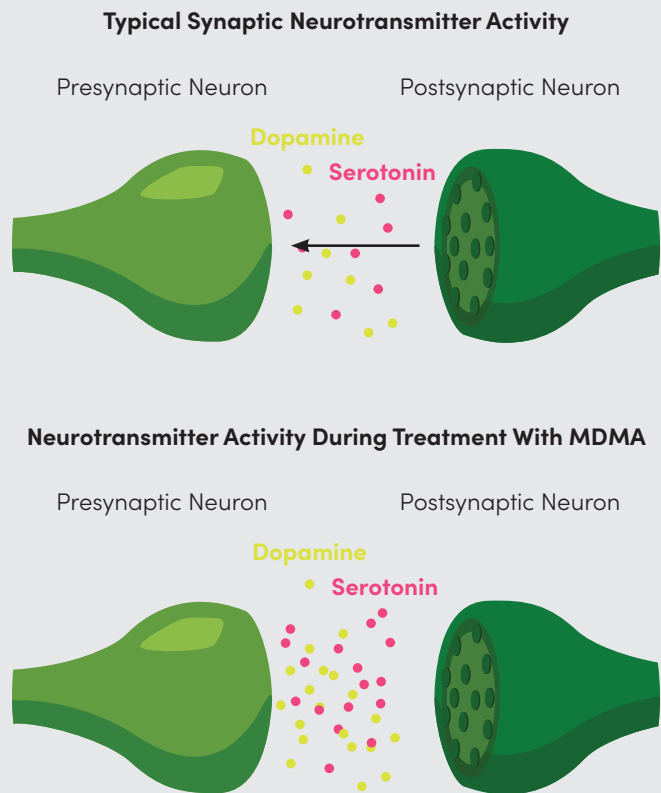
**M**DMMA differs from the classic psychedelics like psilocybin and LSD given its different mechanism of action and the resulting experience. MDMA is known as an empathic-entactogen; a psychoactive drug that produces experiences of emotional connection and openness (Farlex, n.d.). When using MDMA, people feel more empathetic and sympathetic and experience an increased sense of closeness to others and self. Furthermore, MDMA leads to prosocial behaviors and greater tolerance of one’s own feelings (Hysek et al., 2014).

MDMA is believed to exert its effects by affecting the levels of a number of different neurotransmitters in the brain, namely serotonin, dopamine, and norepinephrine (Mustafa et al., 2020). MDMA increases the levels of these neurotransmitters by interacting with their respective transporter proteins and receptors. Once released, MDMA also inhibits the reuptake of these neurotransmitters, further increasing the levels of serotonin and dopamine at the synapse.

Serotonin and dopamine are critical neurotransmitters that are associated with effective mood regulation and positive emotions. Serotonin plays a part in regulating mood and stimulating the production of dopamine, which, in turn, is associated with happiness, positive anticipation, satisfaction, and other positive emotions. The inability of serotonin to stimulate dopamine, whether due to lack of serotonin or another neurobiological deficit, has been found to play a key role in the onset of depression (Zangen et al., 2001). Conversely, people often engage in recreational and SUD drug use to increase levels of serotonin and dopamine for the pleasurable effects.

MDMA increases the levels of serotonin and dopamine in the brain by stimulating increases in serotonin production and reducing uptake, which results in increases in dopamine, as well as hormones such as oxytocin, that are responsible for the increased feelings of connectedness and openness.

**FIGURE 12. MDMA INCREASES SEROTONIN AND DOPAMINE LEVELS**



Among other neural activities, MDMA stimulates the increase of dopamine and serotonin, while it slows reuptake of serotonin, which leads to increased feelings of happiness, openness, and connectedness.

Note. The image above illustrates how MDMA increases levels of serotonin and dopamine in the brain, and reduces serotonin reuptake, which increases feelings of happiness, openness, and connectedness.

The increase in levels of these neurotransmitters allows a person undergoing MDMA-assisted therapy for a disorder like PTSD to more deeply and sincerely emotionally engage with the therapeutic process, often at levels of personal and emotional awareness beyond what would typically be accessible in a “normal” state, which contributes to the positive therapeutic outcomes seen in the research to date.

## MDMA RECOMMENDATIONS

BrainFutures recognizes MDMA-assisted therapy's efficacious, positive results for the treatment of PTSD, in particular long-term and refractory PTSD, with lasting reduction of symptoms often beyond 12 months after only one, two, or three sessions. Creating access to MDMA-assisted therapy for people with PTSD, including military personnel, would be a benefit to patients and to the mental health field. It would provide a treatment option beyond current antidepressant, anti-anxiety, and antipsychotic medications for PTSD. The compound is well-tolerated, and dose and frequency of therapeutic treatments keep patients below any potentially toxic levels observed in recreational and animal studies.

BrainFutures finds the evidence for MDMA in treating PTSD strong, and pending proven efficacy and safety in remaining FDA-required trials, BrainFutures recommends MDMA be adopted as a treatment option for PTSD and adequately covered by healthcare payers.

Preliminary research on MDMA for treating other anxiety disorders and depression are also promising, though additional studies are needed.



# LSD

BRAINFUTURES

## LSD / AT A GLANCE

### COMPOUND OVERVIEW

Following its synthesis in 1938 and subsequent discovery of its psychotropic effects in 1943—both by Swiss biochemist Albert Hofmann, who was researching stimulants for respiration and circulation—LSD went on to garner revolutionary popular interest that eventually transitioned into notoriety. In part, LSD fuelled the culture shifts of the 1960s while also finding its way into clinical psychiatry as an exciting and novel potential treatment for serious mental health disorders. Ultimately, LSD developed a pervasive negative reputation in mainstream society in large part due to its heyday of recreational use in the '60s, including reports of unsupervised “bad trips” and “flashbacks.” However, at the right doses and under the right therapeutic setting, research shows LSD to be generally well-tolerated. Research from the '50s and '60s focuses in large part on treating alcoholism, while newer research is seeking to evaluate LSD's role in addressing depression, SUD, and other mental health disorders.

### IN THIS REVIEW

Many of the LSD publications examined in this review include findings from the pre-1970 era, though using modern analysis techniques. More recent research on LSD-assisted therapy is still limited. BrainFutures' research reviews 34 studies with LSD (32 peer-reviewed), including five RCTs and five open-label studies with 507 participants, along with two meta-analyses and 19 reviews.<sup>12</sup> (The two meta-analyses analyzed ten trials and 619 participants, of which eight trials with 371 participants are not directly cited in this review.) Currently, there is one recruiting study on LSD for depression and one active or recruiting trial on LSD for cluster headaches. Early and current studies indicate that LSD PAT may be an effective treatment for SUD, most prominently alcoholism, as well as a potential treatment for depression and end-of-life anxiety.

### VOLUME AND TYPE OF RESEARCH

More than 9,000 papers have been published on LSD, its mechanisms of action, and effects in humans and animals. One major area of clinical research relevant to behavioral health is on LSD for the treatment of alcoholism, with over 1,100 publications on the topic. Research on LSD for all conditions, including alcoholism, includes more than 160 RCTs, 10 meta-analyses, and 783 reviews.

### AREAS OF RESEARCH SHOWING EFFICACY

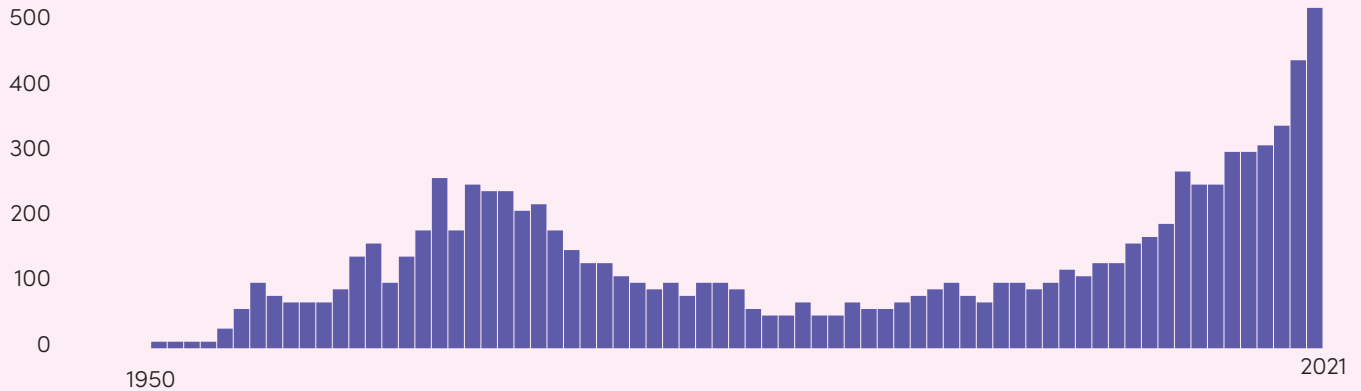
- Alcoholism
- Depression
- Schizophrenia
- End-of-Life Anxiety

### SAMPLE OF RESEARCH FINDINGS

- LSD-assisted therapy leads to a rapid reduction in alcoholic behavior and symptoms that can last up to six months.
- Early LSD research found improvements in “depressive reactions,” schizophrenia, and “anxiety reaction neurosis,” among other mental health states.
- LSD-assisted therapy has been found to reduce end-of-life anxiety and depression.
- Clinical studies to date show that LSD is generally well tolerated by participants and adverse events are typically mild and transient.

**FIGURE 13. LSD RESEARCH ACTIVITY (1950–2021)**

NUMBER OF STUDIES



Note. The above graph represents the increase in publications relating to LSD from 1950 to 2021. Adapted from PubMed (2022d). [Data set]. <https://pubmed.ncbi.nlm.nih.gov/?term=LSD>

**KEY TAKEAWAY**

The potential for LSD’s use in PAT is promising based on outcomes from early research. However, it has yet to find its way into modern studies at the level of rigor to be considered safe and efficacious by current clinical standards. Such research is likely to develop with the growth of the PAT field.

# LSD

**L**SD was first created without fanfare in 1938 by Swiss biochemist Albert Hofmann, PhD. when he synthesized LSD at the pharmaceutical company Sandoz Laboratories. This was done as an effort to discover an effective circulatory stimulant. Years later, in 1943, after accidental exposure while synthesizing a sample for testing, he experienced its consciousness-changing and mood-altering properties (Nichols, 2005). From there, LSD garnered great scientific and clinical research interest, and Sandoz supplied LSD under the name Delysid for medical research.

In the early years of LSD research, psychologists and psychiatrists conducted numerous trials and experiments seeking to investigate the drug's effect on ameliorating mental health issues (Miller, 2017). LSD was also used as a tool to observe a live model of what was considered to be psychosis to develop a greater understanding of mental health disorders and possible treatments (Miller, 2017). One of the clinicians who administered LSD in a therapeutic setting and became an early leading researcher in the field of LSD-assisted therapy was Dr. Stanislav Grof, MD, PhD. Grof has conducted over 4,000 LSD therapeutic sessions in Prague and in the United States, and explains how he (perhaps like his early PAT clinical peers) got started in this work:

“[T]he psychiatric department I was working in received a large supply of LSD-25 from the pharmaceutical company Sandoz in Basel, Switzerland. It came with a letter describing the serendipitous discovery of its psychedelic effect by Albert Hofmann... The letter accompanying the package suggested on the basis of the pilot studies conducted in Zurich that LSD could be used for inducing experimental psychosis...There was another suggestion that this

could be a kind of unconventional educational tool—that psychiatrists, psychologists, nurses and students would have the chance to spend a few hours in the world that seemed to be like the world of some of their patients” (Miller 2017).

LSD would go on to play a major supporting role in folk history from the 1950s–1970s. The CIA's Project MKULTRA experiments; Ken Kesey's book, *One Flew Over the Cuckoo's Nest*; Woodstock's LSD-tripping performers, festival goers and “acid tents;” Harvard researchers Timothy Leary and Richard Alpert's (Ram Dass) controversial experiments; and the Beatles' LSD-inspired song *Lucy in the Sky with Diamonds* are just a few examples of this compound's cultural influence. Some credited it with pivoting aspects of social consciousness, while others feared it was corrupting society. Under the framing of these latter concerns, along with other uncontrolled public use of psychedelics in the 1960s, it was made illegal in the U.S. in 1968 and eventually listed as a Schedule I substance under the 1970 Controlled Substance Act. However, important research on its therapeutic value had been done prior to and even during its zeitgeist moment.

One of these pioneering researchers was British psychiatrist Humphry Osmond, MD credited for coining the term “psychedelic.” In 1951, Osmond moved to Saskatchewan, Canada and established a lab to study LSD's effects, initially with schizophrenic patients and then with alcoholics, working with, among others, Canadian biochemist, physician and psychiatrist Dr. Abram Hoffer, MD, PhD. Osmond established the high-dose psychedelic treatment model—which engenders a transcendent state of consciousness—versus a low-dose psycholytic model meant to make psychotherapy more



effective through “a release of repressed psychic material, particularly in anxiety states and obsessional neurosis” (Grob, 1994).

In addition to early clinical explorations looking at LSD to treat alcoholism and investigating the effects of LSD on significant psychiatric disorders (key samples of which are highlighted below), it was even studied as a treatment for autism in children (Sigfoos et al., 2007). As one researcher remarked in 2005, “far from being fringe medical research, these LSD trials represented a fruitful, and indeed encouraging, branch of psychiatric research” but ultimately, according to the author, LSD early research did not persist for two reasons: 1) because of its association with reactive political and social movements, including student protests and other counterculture activities, and 2) because in the 1960s a new standard of evidence in research required randomized controlled trials, and LSD studies did not effectively meet the standard at that time (Dyck, 2005).

The last FDA-approved LSD clinical studies with humans in the U.S. were done in the 1980s (Miller, 2017). International clinical research on LSD has since continued (Liechti, 2017). In the early 2000s, a few research studies emerged that investigated the effects of LSD on various conditions. Modern study models are carefully designed to manage risk and provide for improved clinical control and safety. Initial findings are positive, and while this field is nascent, many researchers are saying that they would like to see large, rigorous trials to determine potential therapeutic uses and protocols for LSD as a psychedelic-assisted therapy agent.

Recent publications have primarily been reflections and reviews on early research and hypotheses about future applications. Unlike psilocybin, MDMA, and ketamine, LSD has not yet been used in rigorous Phase 2 trials, although more trials are underway, including investigations into the effects of microdosing LSD.

## TOLERABILITY OF LSD TREATMENT

Even with promising research, stories from the past and LSD’s reputation make safety a primary concern for any future therapeutic use. Reports vary but indicate that even with sometimes intense experiences, LSD is generally well-tolerated, and even more so in a suitable therapeutic setting.

Therapeutic doses of LSD range from 20 to 800  $\mu\text{g}$  (Fuentes et al., 2020), with medium-dose psycholytic sessions generally ranging from 150–200  $\mu\text{g}$ , and high-dose psychedelic sessions often between 250–500  $\mu\text{g}$  (Miller, 2017). Within 30 minutes of ingesting the drug, altered sensory and visual effects start to take place, including “intensified colors, movement of stationary objects, distortion to shapes and sounds, and changes in the sense of time” usually lasting up to 12 hours (Nichols, 2017).

## There has never been a death by overdose from LSD.

A review published in 2008 conducted a comprehensive analysis of the pharmacology of LSD, including interactions, tolerability, safety concerns, and other conditions of experience, reporting that there has never been a death by overdose from LSD (Passie et al., 2008). In other words, there is no defined LD50 (dose that would cause death) for LSD. In addition, while more than 10,000 people have used LSD under psychiatric supervision or in clinical trials, the suicide rate is extremely low, about equal to the rate of suicide in conventional psychotherapy (Passie et al., 2008).

The most outstanding negative characteristic of LSD is the “bad trip,” an intense reaction to the experience that includes anxiety or panic, usually accompanied by feelings of fear, loss of control, or fearing insanity or death (Passie et al., 2008). Even in the case of a bad

trip, however, the effects in a therapeutic setting seem to be transitory and resolve quickly with very few long-term adverse events reported (Johnson et al., 2008). Flashbacks are another popular concern with LSD use. In a 2017 review, the author explains:

“Clinically significant flashbacks are also defined as hallucinogen persisting perception disorder (HPPD). This disorder is considered rare and occurs almost exclusively in the context of illicit recreational use or/ and in patients with anxiety disorders and it typically will have a limited course of months to a year” (Liechti, 2017).

There are cautionary tales, however, that are important to learn from. A Danish report explained that in the 50s and 60s, nearly 400 Danes were subjects in LSD treatment therapy or clinical trials (Larsen, 2016). As a result of serious related events, including one homicide and two suicides, purportedly due to negligence on the part of the administering researchers, Denmark passed the Danish LSD Damages Law, awarding 154 of the participants compensation for damages. The report concluded that there may be some risk of adverse effects depending on the dose and number of treatments, and that in people with severe mental health issues, their condition could worsen. LSD may be better-tolerated in individuals without severe psychopathologies (Larsen, 2016).

A survey study authored by Dr. Nicholas Malleon, MD indicated that serious adverse effects, such as suicide, can occur as a result of LSD, but the author concluded that “if there is adequate psychiatric supervision and proper conditions for its administration the incidence of such reactions is not great” (Malleon, 1971). While the data are extremely limited, the author noted that in 1960, a researcher attempted to quantify this outcome (Cohen, 1960) through a “methodical survey of the pooled experience of psychiatrists” instead of individual case reports that may have been sensationalized. The review explains:

“[Cohen’s work] reported 44 replies sent out to 62 American investigators who had published papers or whose work was known to the author. Replies covered 5,000 subjects with 25,000 LSD or mescaline sessions. In this series, there were only two suicides that Cohen regarded as directly related to the LSD, and there were psychotic reactions (lasting more than 48 hours) at a rate of 0.8 per 1,000 experimental subjects and 1.8 per 1,000 patients” (Malleon, 1971).

Later that decade, Malleon’s own research collected survey responses from 73 doctors in the United Kingdom who had used LSD with patients. Data from 49,000 LSD sessions with 4,300 patients (and 450 LSD sessions with 170 experimental subjects) was collected. Malleon found a similarly low suicide rate, though the incidence of psychotic episodes lasting more than 48 hours were nine per 1,000 patients—higher than Cohen’s findings.

In *Adverse Reactions to Psychedelic Drugs: A Review of the Literature* (1984), Rick Strassman, MD reports:

“The relative roles of set and setting, motivations for drug use, personal and family history of mental illness, defensive style, and level of object relatedness, should all be used in careful selection, screening, and preparation of subjects for psychedelic research. It appears that, if these factors are carefully controlled, the incidence of acute and more long-term problems associated with their use can be kept to a minimum. The benefits that can be obtained in terms of an increased knowledge of psychedelic drug-induced altered mental states and their potential therapeutic roles, seems to justify these risks.”

More recent research that reviewed data from four double-blind, randomized, placebo-controlled, crossover studies including a total of 83 healthy subjects and 131 single-dose administrations of LSD found that a “single-dose administration of LSD is safe in regard to acute

psychological and physical harm in healthy subjects in a controlled research setting.” (Holze et al., 2021).

While individual studies report various findings, depending on study design, dose, predisposition of the participants in terms of mental health or life-threatening disease, and a variety of other factors, overall the findings on LSD are generally positive.

Recent research has explored the mechanism of action of LSD in the brain using modern brain imaging techniques, including arterial spin labeling, blood oxygen level-dependent measures, and magnetoencephalography, and confirmed that changes in brain activity are correlated with the subjective effects of the LSD experience (Carhart-Harris, Muthukumaraswamy et al., 2016). The study showed that increases in activity in the visual cortex were associated with hallucinations, but not necessarily with changes in perception associated with treatment benefits. Additionally, decreased brain activity in other areas was associated with the experiential qualities that are presumed to affect positive shifts in MH/SUDs. Both of these findings have implications for future research on LSD’s treatment potential in behavioral health. The study reports:

“LSD’s marked effects on the visual cortex did not significantly correlate with the drug’s other characteristic effects on consciousness, however. Rather, decreased connectivity between the parahippocampus and retrosplenial cortex (RSC) correlated strongly with ratings of “ego-dissolution” and “altered meaning,” implying the importance of this particular circuit for the maintenance of “self” or “ego” and its processing of “meaning”... The present results contribute important new insights into the characteristic hallucinatory and consciousness-altering properties of psychedelics that inform on how they can model certain pathological states and potentially treat others.”

A 2017 review referenced earlier in this report evaluated all LSD clinical studies in the past 25 years related to pharmacology, effects, experience, tolerability, and efficacious treatment outcomes (Liechti, 2017). The review looked at clinical studies over the past quarter century involving LSD with both healthy populations (five studies) and with patients (one study). The author’s findings, summarized in the abstract, state:

“In a controlled setting, LSD acutely induced bliss, audiovisual synesthesia, altered meaning of perceptions, derealization, depersonalization, and mystical experiences... Resting-state functional magnetic resonance studies showed that LSD acutely reduced the integrity of functional brain networks and increased connectivity between networks that normally are more dissociated... LSD acutely induced global increases in brain entropy that were associated with greater trait openness 14 days later. In patients with anxiety associated with life-threatening disease, anxiety was reduced for [two] months after two doses of LSD. In medical settings, no complications of LSD administration were observed.”

Research continues to investigate the possibility that LSD could contribute to a healthier brain, which could also support its potential in mental and behavioral health treatments. A 2021 pharmacological study found that healthy people who microdose with LSD show increases in brain-derived neurotrophic factor (BDNF) levels (Hutten et al., 2021). BDNF stimulates the growth of new brain cells and assists in healthy synaptic connections, improving learning and memory. Conversely, a drop in BDNF is correlated with cognitive decline and depression.

## LSD TREATMENT FOR ALCOHOLISM AND OTHER ADDICTIONS

A landmark study on the use of LSD to treat alcoholism occurred between 1957 and 1958 (Chwelos et al., 1959). This two-part investigation first treated 24 alcoholics with co-occurring mental health disorders, and then an additional 16 subjects with similar conditions, many of whom had tried Alcoholics Anonymous and failed to remain abstinent. The mental health disorders included character disorders, psychopathy, borderline personality disorder, and actual psychosis.

One of the notable characteristics of this study that likely influenced the field of modern day PAT was the study's environment. While the first study was done in a clinical location such as a psychiatric ward or an institutional setting, the second part of the study took place in a relaxed environment with music, visually stimulating art or symbolic objects, and with therapists who provided an emotionally supportive environment, many of whom had also had an LSD experience. The therapists encouraged the patients towards acceptance and responsibility for their alcoholism without moral judgment. This was perhaps one of the nascent beginnings of “set and setting.”

Outcome measures were defined as: “much improved” (abstinence), “improved” (reduced alcohol consumption), or “unchanged”. Interestingly, and possibly from the change in set and setting, only 12 of the original 24 patients who received treatment in an institutional environment had outcomes of “much improved” or “improved.” On the other hand, 15 of the 16 additional patients who received treatment in the revised set and setting showed outcomes of “much improved” or “improved.”

A landmark text, *The Use of LSD in Psychotherapy and Alcoholism* presented close to 700 pages of research, reviews, therapeutic processes, case studies,

and pharmacological and psychiatric considerations (Abramson, 1967). By and large, the presentations in this text noted significant progress in the treatment of psychiatric disorders and alcoholism using LSD-assisted therapy. Most of this research went dormant soon after publication with the listing of LSD as a Schedule I substance.

Another study that evaluated the impact of LSD treatment and recovery from alcoholism found that the use of LSD in therapy provided immediate disruption in the pattern of alcoholic drinking, but that over time—within 12 months—without continued support, most participants returned to drinking (Ludwig et al., 1969). The researchers acknowledged that, based on their study design and research findings, the failure of long-term success rate was most likely due to 1) lack of participant preparation before treatment, and 2) lack of follow-up therapeutic treatment after the LSD treatment. These findings are congruent with other research that has seen successful remission in cases where ongoing therapeutic treatment or other interventions were employed.

A major review of the research conducted in the early 1970s on the effect of LSD treatment for alcoholism looked at 31 studies that included 1,105 participants (Abuzzahab & Anderson, 1971). Of the studies, 13 were single, large-dose, open-label; five were single, large-dose, controlled trials; four were multiple, low-dose open-label; three were multiple low-dose with controls, and another six were undefined trials. Perhaps because of the varied dosages and different study designs, the researchers concluded that, “The overall effectiveness of this controversial treatment of alcoholics remains disappointing. It was difficult to reach meaningful generalizations from the variety of published investigations with different designs and variant criteria for improvement.”

In line with these conclusions, one earlier study evaluated the effects of LSD on alcoholism vs. dextroamphetamine (a stimulant used to treat ADHD and narcolepsy,

and used non-clinically as a performance and cognitive enhancer) in 72 participants (Hollister et al., 1969). The researchers found that LSD produced better results initially, but at six-month follow-up there were no significant differences between the two groups. The authors conceded that better controlled studies need to be done in order to truly evaluate the efficacy of LSD in treating alcoholism.

Based on promising research outcomes prior to 1970, many public movements and organizations for a time supported the use of LSD in the treatment of alcoholism. Osmond hoped that his research would support the idea that alcoholism is a disease and not a moral issue or a condition of weak willpower, as previously thought. LSD for the treatment of alcoholism, for a time, gained support from local provincial governments in Canada, some local chapters of Alcoholics Anonymous, and even Saskatchewan's Bureau on Alcoholism, which at one point initiated a public campaign to support LSD treatments for alcoholics. However, the controversy connected to recreational use and the subsequent War on Drugs, in combination with a lack of controlled trials, contributed to the end of this arm of research around 1970. More recent research builds on these earlier studies.

A 1998 review looked at previous studies and work that had been done since the ban on LSD research, particularly in the area of alcoholism, and noted that with modern study design and techniques (with safety and control considerations), further research could determine the true efficacy of the treatment (Mangini, 1998). The author states:

*"The possible value of LSD in a psychiatric or therapeutic context has been almost completely obscured by media sensationalism, unsupervised self-experimentation, poorly designed research, and misinformation. It is difficult to obtain legal permission to work with LSD, and there is no federal, institutional, or pharmaceutical industry support for*

*LSD research. Nevertheless, interest in its potential usefulness persists...The major part of the existing research on LSD has investigated its potential utility as a treatment for alcoholism. Since this program of research came to an end, progress in research design and treatment evaluation has made available tools and techniques that could help to resolve historic controversies and clarify confusion about its usefulness."*

The author also points out that at the time of publication in the late 1990s, 25 to 30 percent of hospital admissions were in some way related to alcohol and more than 52 percent of the American population consumed alcohol, with 10 to 12 percent of those at an alcoholic level—a fraction of whom ever get effective treatment, if any.

More recently, a 2018 report from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) stated that alcohol-related emergency room visits between 2006 and 2014 increased 47 percent overall, with visits related to acute alcohol consumption increasing by 40 percent and those related to chronic alcohol consumption increasing by 58 percent. The data showed that increases were higher among females, and highest across both sexes in the 45- to 54-year-old range, while the rates of admissions for 12- to 17-year-olds decreased over that period. During that same time, the medical costs of said visits increased from \$4.1 billion to \$15.3 billion (NIAAA, 2018).

Alcohol abuse and alcoholism is still a serious problem, and is often linked to mental health disorders as a cause, an outcome, or a co-occurring factor (Shivani et al., 2002). Novel effective treatments could be an asset to the medical profession, treating both alcohol use and mental health disorders.



**Overconsumption of alcohol is the third leading cause of death in the United States, and additional treatment options are needed.**

Another review analyzed the historical research of LSD in the treatment of alcoholism and addictions, and recommended continued research, citing data indicating that in the early 2000s, about 30 percent of the world’s population used illegal drugs with close to 200,000 deaths annually from drug and alcohol use (Liester, 2014). According to the data, SUD is a severe issue and threat to public health. Since 2006, millions of people have been addicted to prescription drugs, a trend that has currently evolved into a full-blown opioid crisis, leading to the deaths of more than 100,000 people and presenting an unmanageable threat to public health. Further, data in this review going back to 2001 indicate that overconsumption of alcohol is the third leading cause of death in the United States, and additional treatment options are needed as existing pharmacological interventions have limited success in treating alcoholism (Liester, 2014).

**“LSD is revealed as a potential therapeutic agent in psychiatry; the evidence to date is strongest for the use of LSD in the treatment of alcoholism.”**

A 2006 review mentioned above analyzed the research on the effectiveness of LSD in treating alcoholism over the span of 20 years from 1950 to 1970, and found that there were significant positive outcomes which indicate the treatment potential of LSD-assisted therapy (Dyck,

2006). For instance, a meta-analysis on six clinical trials—most occurring in the late 1960s and early 1970s—that investigated LSD as a treatment for alcoholism reported favorable results (Krebs & Johansen, 2012). A total of 536 participants received LSD as a treatment for “alcohol misuse,” with 59 percent reporting reductions in misuse compared to 38 percent in the placebo group. According to the researchers, “A single dose of LSD, in the context of various alcoholism treatment programs, is associated with a decrease in alcohol misuse.”

The most recent review of the clinical LSD literature was published in 2020 (Fuentes et al., 2020). After evaluating all trials from the 1950s through the 1970s, reviewers selected 11 studies that included 567 participants and concluded, “LSD is revealed as a potential therapeutic agent in psychiatry; the evidence to date is strongest for the use of LSD in the treatment of alcoholism.” They also stated, as others have, that new, modern studies that meet rigorous modern clinical protocols should be designed and implemented to verify and further investigate the potential of LSD in treating behavioral health disorders.

**LSD FOR DEPRESSION, SCHIZOPHRENIA, AND OTHER PSYCHIATRIC DISORDERS**

One of the earliest recorded trials on the effects of LSD on participants with “depressive reactions” took place in 1952 (Savage, 1952). Participants were given daily doses of LSD ranging from 20 µg to 100 µg. Published findings reported that:

“[Four] patients showed no improvement. In four cases, treatment was discontinued before proper evaluation could be made. Anxiety was a prominent reaction while less frequently euphoria was observed. In three patients who developed euphoria it served as an aid to psychotherapy by encouraging expression of feeling. In the others the heightened anxiety encouraged reticence rather than



confidence... However, LSD affords therapeutically valuable insights into unconscious processes by the medium of the hallucinations it produces.”

A 1957 paper explored the potential benefit of LSD in treating many forms of mental illness, primarily schizophrenia with an LSD and chlorpromazine (known more commonly under the brand name Thorazine) cocktail. Their findings show that 61 out of 100 participants improved or recovered following treatment. While the term psychedelic-assisted therapy did not exist at the time, they did indicate that, “When used as an adjunct to psychotherapy, LSD was of the greatest value in the obsessional and anxiety groups accompanied by mental tension.” Many studies in the 50s were not as specific and rigorous, and the protocols were varied depending on the patient and outcomes. For example, in an earlier study, Sandison, Spencer, and Whitelaw (1954) stated:

“Unless contraindications (e.g. the threat of psychosis) are present, one should persevere for at least [six] weeks or [six] to [eight] treatments before stopping. Many patients only started to produce material of value after [four] to [five] treatments. In some cases it may be necessary to continue treatment for at least [six] weeks and for [six] to [eight] treatments before stopping.”

Another early LSD-assisted therapy trial evaluated 110 participants, each diagnosed with a psychiatric disorder according to the DSM, who were treated with LSD as part of their therapy for up to 26 sessions, with an average of 6.2 sessions each (Chandler & Hartman, 1960). According to the research, therapists observed that the “introduction of LSD-25 effected a real breakthrough” even in some patients that had previously shown little to no improvement from earlier therapy. Therapists in the study reported that in 69 percent of the cases, LSD combined with therapy resulted in a “greater acceleration in the rate of therapeutic process.”

A similar study involved an outpatient therapy process where LSD was given in conjunction with therapy to 61 alcoholics and 39 non-alcoholics with other psychiatric diagnoses (MacLean et al., 1961). The treatment took place in a group setting with a psychiatrist, psychologist, psychiatric nurse, and music therapist present, after which the participants transitioned from the experience during an overnight stay. Based on follow-up interviews and other data collected between three and 18 months post treatment, the researchers found that 30 of the alcoholics and 22 of the other psychiatric patients showed much improvement in their condition and that 16 of the alcoholics and 13 of the psychiatric patients showed some improvement. The study reported, “It was concluded that LSD... is effective in the treatment of alcoholism and the psychiatric disabilities categorized as anxiety reaction neurosis and personality trait disturbances.”

#### END-OF-LIFE ANXIETY, GENERALIZED ANXIETY DISORDER, AND LSD TREATMENT

**B**eyond treating alcoholism and other psychiatric disorders, early studies with LSD researched the possibility of using LSD in alleviating the distress associated with life-threatening illnesses, in particular terminal cancer. These perhaps set the stage for other studies that came later using psilocybin and MDMA to investigate the psychedelic experience as a means to improving quality of life by alleviating anxiety related to the fear of death from illness.

In one study the researchers noted that for terminal cancer patients, their final months were often particularly difficult and “usually marked by increasing depression, psychological isolation, anxiety, and pain” as they attempt to come to terms with the failure of treatments and the inevitability of their impending death (Pahnke et al., 1969). This study noted:

“In recent years [the 1960s] considerable attention has been focused upon attempts to alleviate the

psychological stress and physical pain experienced by the dying cancer patient... but there has been little improvement in methods...the suffering caused by terminal cancer is an area urgently in need of more effective treatment.”

The authors of the study commented that research was showing that using LSD had both a significant analgesic effect and reduced depression and anxiety related to death. They suggested that with further studies LSD may one day prove to be an efficacious treatment for alleviating negative symptoms associated with life-threatening illness.

Dr. Walter Pahnke, MD was leading this line of research at the time of his death in 1971. Much of his work was carried forward by Stanislav Grof until Dr. Grof left the research world for Esalen Institute in 1973. Work with psychedelics and cancer patients continued at the Maryland Psychiatric Research Center, led by William Richards, PhD, with colleagues including John Rhead, PhD, Richard Yensen, PhD, and Albert Kurland, MD until 1976 (W. Richards, personal communication, January 27, 2022). Further investigations that often included detailed case studies of individual patient experiences, with and without terminal illness, are documented in publications and books from that time period (Richards et al., 1972, Grof & Halifax, 1977, Brandrup & Vanggaard, 1977; Kurland et al., 1972; Richards & Berendes, 1977).

A review of some of this research published in 1985 reflected on the progress of LSD research in treating terminal cancer patients by noting that traditional treatments to alleviate both physical and psychological suffering were largely unsuccessful, with patients heading to their final days often riddled with anxiety and fear (Kurland, 1985). The review pointed out that this line of research likely evolved from another study that was investigating the effectiveness of LSD on treating alcoholism in which one of the participants discovered that she had cancer

and became open to LSD treatment for her psychological disposition around the realization of her diagnosis. She experienced significant relief from the treatment, which led researchers to further investigate the possibilities of using LSD to treat terminally ill patients in order to alleviate psychological suffering.

In a double-blind, randomized, active placebo-controlled pilot study, 12 participants with life-threatening illness who also underwent psychotherapy sessions participated in two LSD-assisted sessions, two to three weeks apart. The active group of patients were given a high dose of LSD and the control group of patients received a low dose of LSD. After the initial blinded research, participants could choose to join an open-label study and knowingly engage in LSD-assisted psychotherapy sessions (Gasser et al., 2014). Using STAI to measure levels of anxiety, researchers found significant reduction in anxiety with large effect sizes and no adverse effects beyond one-day post-treatment for all participants receiving the active dose. Researchers also found that the reductions in anxiety persisted at a 12-month follow-up.

Other nascent research has found that LSD may be effective at reducing pain, which could have potential applications for end-of-life care and reduced use of potent prescription pain medications with potentially more serious side effects (Ramaekers et al., 2021).

Most recently, the FDA has cleared a U.S. biotech company to launch a Phase 2b study in early 2022 to test the efficacy of a “pharmacologically optimized” form of LSD in participants with GAD (MindMed, 2022a). The RCT dose-optimization trial plans to enroll 200 participants with GAD and investigate reductions in symptoms over three months following a single-dose administration. According to the company’s CEO, “This trial, the first commercial study of LSD in more than 40 years, builds on productive discussions with FDA and provides an opportunity to explore improvements in anxiety symptoms ...”

## LSD RECOMMENDATIONS

BrainFutures recognizes that the foundations of LSD research are close to 60 years old, with limited current studies underway. Even so, these original studies along with more modern research indicate that LSD may be an effective intervention for alcoholism treatment. In addition, LSD therapy has been found to alleviate symptoms of various mental health disorders. Though not currently on the short-list for potential approval or use in modern mental health practice, LSD may have a unique contribution to the field of PAT that will be revealed with more research in the years ahead.



# Ayahuasca (DMT)

## Ayahuasca (DMT) / AT A GLANCE

### COMPOUND OVERVIEW

N,N-dimethyltryptamine (DMT) is the key psychoactive component in ayahuasca and other similar traditional brews and mixtures, which have purportedly been used for centuries by Indigenous Amazonian tribes of South America for healing and ceremony. DMT is also bioavailable in synthesized crystalline form. Early studies on DMT, mostly from the 1960s and 1970s, sought primarily to evaluate mechanisms of action and biological effects on humans. A series of animal studies in the '70s and '80s used DMT and other substances to investigate serotonin pathways in animal brains. In the 1990s, Rick Strassman, MD brought the compound back to western attention with research studies, a book, and a mainstream movie by the same title, *DMT, The Spirit Molecule*. In his research, Strassman used synthetic DMT that was administered intravenously instead of the ayahuasca brew. While few modern clinical studies exist, the potential for this compound to positively affect serious mental health disorders and SUD is a subject of interest in the current field of psychedelic-assisted therapy research.

### IN THIS REVIEW

While most of the DMT research has been on its pharmacological effects and mechanisms of action, Brain-Futures' research reviews 28 studies with DMT (27 peer-reviewed), including six RCTs and six open-label studies<sup>13</sup> with 355 participants. Additionally, we include nine reviews related to DMT in MH/SUD treatments. Clinical evidence from these limited studies points to the potential effectiveness of DMT, and ayahuasca in particular, at treating depression, hopelessness, and anxiety, including TRD, major depression, suicidality, and addiction. Currently there are four active or recruiting studies on DMT for depression.

### VOLUME AND TYPE OF RESEARCH

Since the mid-1950s, DMT in its various forms has been cited in about 1,197 published papers. During this time, DMT has been the subject of 26 RCTs, 83 reviews, and five (peer-reviewed) open-label studies, primarily investigating mechanism of action and subjective response to the compound, with no meta-analyses to date.

### AREAS OF RESEARCH SHOWING EFFICACY

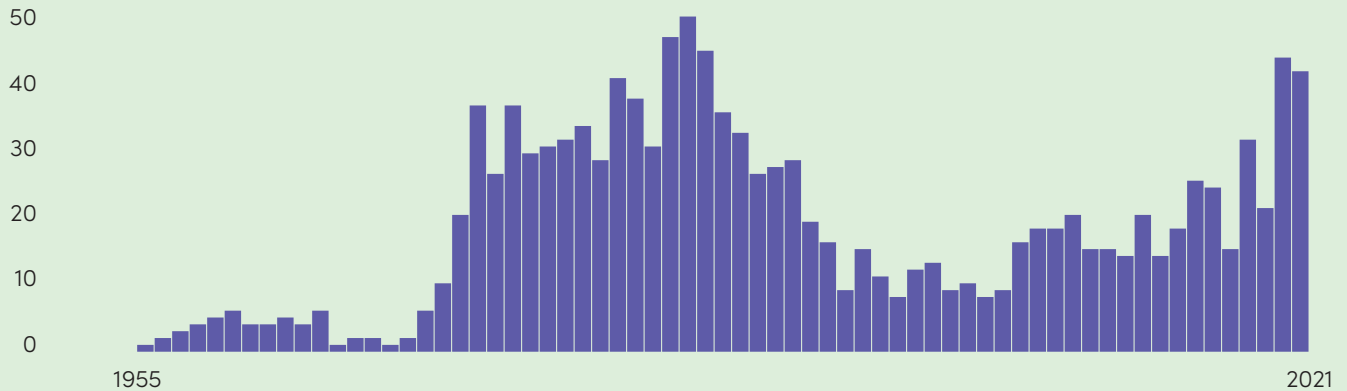
- Depression
- Major Depression
- Treatment-Resistant Depression
- Suicidality
- Addiction

### SAMPLE OF RESEARCH FINDINGS

- A single dose of ayahuasca led to significantly reduced symptoms of depression within 80 minutes and continuing through 21 days.
- Ayahuasca may be a powerful, rapid anti-suicidal treatment.
- Ayahuasca increases BDNF, a protein connected to increased neuronal growth and improved overall brain function.
- Ayahuasca treatment resulted in increased hopefulness, empowerment, mindfulness, and quality of life meaning while also eliciting reduction in alcohol, tobacco, and cocaine use.

**FIGURE 14. AYAHUASCA (DMT) RESEARCH ACTIVITY (1955–2021)**

NUMBER OF STUDIES



Note. The above graph represents the increase in publications relating to DMT from 1955 to 2021. Adapted from PubMed (2022a). [Data set]. <https://pubmed.ncbi.nlm.nih.gov/?term=%28dimethyltryptamine%29+OR+%28dimethyl+tryptamine%29&filter=years:1955-2021>

**KEY TAKEAWAY**

Today, DMT is still predominantly taken in ceremonial settings and within Indigenous cultural contexts in its brewed, botanical form as ayahuasca, even when used by non-Indigenous people. The research to date primarily investigates this form of use, which is unlikely to be broadly adopted by western allopathic and psychopharmacological clinicians. However, the benefits from the limited research, as well as the anecdotal reports, do show positive outcomes, which may create an opportunity for DMT, and perhaps ayahuasca, to find its way into the modern PAT paradigm.



# Ayahuasca

**A**yahuasca is a psychedelic, psychoactive mixture that contains DMT rendered orally bioactive by the presence of beta-carboline alkaloids—harmaline, harmine, and tetrahydroharmine, known as monoamine oxidase inhibitors (Aronson, 2016). It is traditionally compounded by brewing together the *Banisteriopsis caapi* vine, containing the beta-carboline alkaloids, and another plant containing DMT—usually *Psychotria viridis* (chacruna) or *Diplopterys cabrerana* (chaliponga)—and depending on the culture, region, and local flora, other plants may be added (International Center for Ethnobotanical Education, Research and Service [ICEERS], n.d.). Ayahuasca occurs under various names including yagé in Columbia and Ecuador, and caapi and daime in Brazil (Liana, n.d.; Tanev, n.d.). It has traditionally been used in South America by Indigenous cultures and shamans, where it continues to be used to this day. Though there has been limited evidence to verify how long ayahuasca has been in use, a ceremonial bundle recently recovered from Bolivia shows chemical residue of DMT and harmine (two primary ingredients of ayahuasca) carbon dated to be at least 1,000 years old (Miller et al., 2019). Ayahuasca is also well known as the sacrament of the Santo Daime, União do Vegetal, and Barquinha churches of Brazil (Hartogsohn, 2021; Grob et al, 1996; Mercante, 2006).

In the past decades, interest in its healing properties as well as a desire to participate in the reportedly profound traditional ceremonial experience has led to ayahuasca tourism in regions of its traditional use, as well as ayahuasca healing centers abroad, and an increasing number of ayahuasca community and religious ceremonies throughout the world, including in the U.S. As with most psychedelics in the U.S., DMT is listed as a

Schedule I substance. However, ayahuasca used in sacred and religious ceremonies is exempt under the Religious Freedom Restoration Act.

As summarized in a 2018 review, DMT was first synthesized in 1931 by Canadian chemist Richard Manske, PhD, but similar to LSD, it was not considered for psychiatric research purposes right away (Barker, 2018). Hungarian chemist, Stephen Szara MD would discover its hallucinogenic effects in 1956 when he self-administered the compound intramuscularly.

**Available research, though limited, consistently shows that the compound quickly reduces symptoms of TRD and can also be effective in the treatment of addictions.**

DMT through various means of delivery (e.g. intramuscular, intravenous, or inhalation of vapor) has also been researched, and some clinical studies have been conducted with the ayahuasca brew containing DMT. Regardless of the methodology, available research, though limited, consistently shows that the compound quickly reduces symptoms of TRD and can also be effective in the treatment of addictions.

Interestingly, *in vivo* and *in vitro* animal experiments have shown that ayahuasca stimulates the growth of new neurons in the hippocampus, increasing neurogenesis and “improving spatial learning and memory tasks” (Morales-Garcia et al., 2020). These researchers note that “mice performed better, compared to control non-treated

animals, in memory tests, which suggest a functional relevance for the DMT-induced new production of neurons in the hippocampus.”

### TOLERABILITY OF AYAHUASCA (DMT) TREATMENT

**A**fter Szara’s 1956 self-administration of DMT intramuscularly, one review summarized the researcher’s noted effects:

“DMT [effects, when] given intramuscularly, were similar to those of mescaline and LSD, including visual illusions and hallucinations, distortion of body image, speech disturbances, mood changes and euphoria or anxiety (dependent on set and setting). Several other studies have replicated these findings” (Barker, 2018).

The review went on to state that dose ranges for synthesized DMT differ based on the means of delivery, which can be intramuscular, intravenous, or inhalation of vapor, with onset of effects starting within minutes and lasting up to an hour. Comparatively, when ayahuasca is administered at 0.6–0.85 mg/kg DMT, subjective effects “usually appear within 60 min[utes], peak at 90 min[utes] and can last for approximately [four hours]” (Barker, 2018).

The potency and exact components and plants in ayahuasca can vary from region to region. The dose range of DMT in the brew varies both in concentration per milliliter and in the amount of milliliters ingested, depending on the traditional churches or Indigenous shamans administering it. Concentration of DMT can range between .16 mg/mL and 14.15 mg/mL with customary brew amounts ranging between 20mL and 200mL (ICEERS, n.d.)

With the *Banisteriopsis caapi* vine’s beta-carboline alkaloids acting as monoamine oxidase inhibitors, the orally ingested DMT can resist degradation in the human gut, passing into the bloodstream, crossing the blood-brain

barrier and exerting its strong psychoactive effects. Normally, oral DMT without a monoamine oxidase inhibitor present is very quickly metabolized by the human body and does not have a psychedelic effect (Barker, 2018).

Because of the combination of alkaloids and plant compounds, ayahuasca can be a purgative, thought by some traditional healers to lead to the release of energy and toxins through vomiting and other means. This is typical and expected as part of the ayahuasca experience. Other transient effects can include vivid visual imagery, sense of clairvoyance, impaired color vision, vertigo, anxiety, alteration in blood pressure and heart rate, and sweating (Artal, 2015; Gibbons & Arunotayanun, 2013; Walden, 2017).

Although limited in scope, the preponderance of clinical research on the therapeutic use of ayahuasca has been done on communal or ceremonial use of ayahuasca, primarily as practiced by the Santo Daime and União do Vegetal churches, where the brew is consumed (Hartogsohn, 2021; Grob et al, 1996). In some western clinical research settings, a synthesized version of DMT has been used (e.g., Strassman, 1994), or freeze-dried ayahuasca has been administered to better control for dose.

With any drug, toxicity and tolerability are always concerns that need to be carefully considered. In traditional cultures, Indigenous and mestizo people have been drinking ayahuasca for centuries without high instances of deleterious effects (Hay, 2020). More present are reports of positive effects, improved quality of life and longevity. While these are anecdotal, a handful of scientific investigations have attempted to evaluate the tolerability and toxicity of ayahuasca.

Strassman explored DMT’s subjective effects of graded doses on humans (Strassman, 1994). He used synthesized DMT given intravenously to 12 participants.

Through interviews and the Hallucinogen Rating Scale, effects were recorded at different dosing levels. Strassman reported:

“Psychological effects of IV DMT began almost immediately after administration, peaked at 90 to 120 seconds, and were almost completely resolved by 30 minutes... Hallucinogenic effects were seen after 0.2 and 0.4 mg/kg of dimethyltryptamine fumarate, and included a rapidly moving, brightly colored visual display of images. Auditory effects were less common. “Loss of control,” associated with a brief, but overwhelming “rush,” led to a dissociated state, where euphoria alternated or coexisted with anxiety... Lower doses, 0.1 and 0.05 mg/kg, were primarily affective and somaesthetic [body sensations], while 0.1 mg/kg elicited the least desirable effects.”

The study concludes that the data collected could be used as a basis for further human studies with DMT and to compare effects across compounds.

Strassman’s research was followed by a series of two single-dose studies which started in the late 1990s, and were designed to gain information on the general tolerability and human pharmacology of ayahuasca (Riba & Barbanoj, 2005). These focused on acute effects in a controlled study (using freeze-dried ayahuasca), something not done before. Volunteers were young, healthy, psychedelic-experienced participants, and results showed generally good tolerability. The pilot study of six males reported “a dose response pattern with subjective effect intensity and alkaloid plasma levels increasing with dose. Cardiovascular effects appeared moderate in intensity” and no other physiological measures were of concern. The final double-blind clinical trial was with 18 volunteers (three female). Cardiovascular changes following administration of ayahuasca compared to placebo showed the drug to be “relatively safe from a cardiovascular point of view” and blood analysis also did not raise any concerns. Although most volunteers experienced anxiety at times throughout the session, they still

reported the experience as pleasant, with effects lasting no longer than six hours.

An RCT of 10 healthy male volunteers were administered a medium-intensity dose of freeze-dried ayahuasca equivalent to 0.75 mg DMT/kg body weight (Alonso et al., 2015). The study found that ayahuasca induces “a temporary disruption of neural hierarchies governing the flow of information by reducing top-down control”—which is the processing of perception based on past experience and prior knowledge—and “enhancing bottom-up information transfer”—which is formation of perception built from direct real-time sensory input from stimuli in our environment. The authors concluded, “These changes could underlie the profound modifications of perception, cognitive processes, and experience of reality typically induced by these drugs.”

A comprehensive review of available worldwide published literature on ayahuasca evaluated the outcomes and potential toxicity of long-term ayahuasca use, and concluded:

“[Ayahuasca is] well tolerated, increased introspection and positive mood, altered visual perceptions, activated frontal and paralimbic regions and decreased default mode network activity. It also improved planning and inhibitory control and impaired working memory, and showed antidepressant and anti-addictive potentials ... [it] was not associated with increased psychopathology or cognitive deficits” (dos Santos, Balthazar, et al., 2016).

Another review of human studies sought to determine whether ayahuasca use, either clinically, recreationally, or in sacred ceremony, could lead to psychotic episodes or psychosis, and found that such an outcome is extremely rare, and typically connected to an individual with a family history or a predisposition to mental illness. They recommended psychiatric evaluation and pre-qualification prior to use to avoid this rare outcome (dos Santos et al., 2017).

A 2019 study involving 13 healthy participants looked at human brain activity from intravenous DMT (Timmerman et al., 2019). Using EEG readings, researchers analyzed the neurobiology of transitions in and out of altered states of consciousness, and participants also rated drug effect intensity every minute for 20 minutes. Researchers concluded:

“Importantly, the emergence of oscillatory activity within the delta and theta frequency bands was found to correlate with the peak of the experience—particularly its eyes-closed visual component. These findings highlight marked changes in oscillatory activity and signal diversity with DMT that parallel broad and specific components of the subjective experience, thus advancing our understanding of the neurobiological underpinnings of immersive states of consciousness... [R]esults may shed light on the mechanisms underpinning the antidepressant potential of DMT and DMT-related compounds. Increased alpha power and decreased delta power has been found in populations of depressed individuals and associations have been observed between signal diversity and fluctuations in mood including depressive states. It is reasonable to consider that the massive effects observed here under DMT may have implications for modelling [sic], and perhaps treating, psychopathology.”

In traditional cultures as well as the Santo Daime Church, concerns about the brew’s effects appear minimal. Families, including adolescents, take part in the sacrament. Research has shown that contrary to expected adverse outcomes from a “drug-concerned” perspective, adolescents who participated in ayahuasca ceremonies had considerably lower rates of anxiety, body dysmorphism, and attentional problems compared to “normal” adolescents (Da Silveria et al., 2005). Another study evaluated the neuropsychological aspects of ceremonial ayahuasca use in adolescents including attention, visual search, sequencing, psychomotor speed, verbal and visual

abilities, memory, and mental flexibility, and found no difference in measures compared to an age-, sex-, and education-matched control group (Doering-Silveira et al., 2005). Further, researchers found that teens who participated in the ayahuasca ceremonies were as healthy, thoughtful, considerate, and bonded to their families and peers as non-ayahuasca using teens (de Rios et al., 2005).

Although rare, it should be noted that reported deaths linked to participating in ayahuasca rituals do exist (Briceno, n.d.; Ray and Wilson, 2020; Morris, 2018). Given that ayahuasca brews often are mixed with various other plant ingredients, it is difficult to know what one or combination of ingredients may have contributed to an isolated fatality. Though reported deaths are few, with the increase of interest in ayahuasca, it is important to learn from these incidents. Participants should first investigate risks including interaction of certain foods and drugs (especially SSRIs) with monoamine oxidase inhibitors found in ayahuasca (Callaway and Grob 1998). Informed participants should also inquire about the brew ingredients and anticipated dosage of the batch they are ingesting, what medical support is available onsite where ayahuasca is to be consumed, as well as the expertise and reputation of those leading ayahuasca ceremonies.

#### AYAHUASCA (DMT) AS TREATMENT FOR DEPRESSION, HOPELESSNESS, AND ANXIETY

**S**tudies in adults who have participated in ayahuasca ceremonies, in the Santo Daime Church and elsewhere, have investigated the effectiveness of ayahuasca on treating depression, hopelessness, anxiety, addiction, and other mental and behavioral health issues. Attempts to evaluate the effectiveness of ayahuasca have been challenging as the ceremonial brew does not have a standardized concoction or amount. However, some researchers have used typical dosages to approximate effectiveness.

A 2007 study evaluated regular participants in the Santo Daime Church, using clinical outcome measurement tools—STAI, Addiction Severity Index (ASI), and the Beck Hopelessness Scale (BHS)—to evaluate the effects of ayahuasca consumption on anxiety, panic, and hopelessness in participants (Santos et al., 2007). The measures were taken one hour after ingesting ayahuasca in a double-blind, placebo-controlled method. Findings indicated that ayahuasca reduced panic and hopelessness, although it did not seem to have any significant effect on anxiety.

In a 2016 open-label study, a single dose of ayahuasca was administered in a psychiatric clinic with 17 participants with depression. Measures were evaluated using HAM-D, the MADRS, the BPRS, the Young Mania Rating Scale (YMRS), and the Clinician Administered Dissociative States Scale during treatment, and at one, seven, 14, and 21 days post treatment. Researchers found that a single dose of ayahuasca led to significantly reduced symptoms of depression within 80 minutes and continuing through 21 days. The ayahuasca was well-tolerated with the only transient adverse effect being vomiting, which is expected from this purgative (Sanchez et al., 2016).

A 2016 review analyzed 21 animal and human studies that reported on ayahuasca's effectiveness at reducing anxiety and depression, and reported that overall, in single-use and long-term use ayahuasca is associated with reduced symptoms of anxiety and depression in animals and humans (dos Santos, Osorio, et al., 2016). Similar to other study conclusions, the authors state, "Considering the need for new drugs that produce fewer adverse effects and are more effective in reducing anxiety and depression symptomatology, the described effects of ayahuasca and its alkaloids should be further investigated."

While the mechanism of ayahuasca is primarily thought to be along the serotonin pathways in the brain, some research has found that, similar to LSD studies, ayahuasca also increases BDNF, a protein connected to increased

neurogenesis and improved brain function (Nobrega de Almeida et al., 2019).

As the pharmacological actions and effects of ayahuasca on mental health are showing promise, another study found that set and setting may also hold significant value in alleviating symptoms. Traditional ayahuasca ceremonies typically consist of a community-based ritual underpinning a dusk-to-dawn event. Though the structure may differ, this community-based approach has been adopted by retreat-center ayahuasca sessions typically attended by largely non-Indigenous participants. In such a setting, researchers in a 2021 placebo-controlled study gave 14 participants ayahuasca and 16 participants a placebo (a combination of cocoa powder, unspecified vitamins, turmeric powder, quinoa, traces of coffee, and potato flour) (Uthaug, Mason et al., 2021). Using a series of tests—the multifaceted empathy test, and five questionnaires: the Ego Dissolution Inventory; the 5-Dimensional Altered States of Consciousness Rating Scale; the Depression, Anxiety, and Stress Scale 21; the Brief Symptom Inventory 18; and the Five Facets Mindfulness Questionnaire—researchers evaluated all participants' pre- and post-treatment levels of depression, anxiety and stress. They found that both the active and control groups showed improvements in the three mental health areas, and concluded:

*"Improvements in mental health of participants of ayahuasca ceremonies can be driven by non-pharmacological factors that constitute a placebo response but also by pharmacological factors that are related to the use of ayahuasca. These findings stress the importance of placebo-controlled designs in psychedelic research and the need to further explore the contribution of non-pharmacological factors to the psychedelic experience."*

Research is also finding that ayahuasca may improve certain brain biology, potentially being part of its mechanism of improving mental health symptoms in users.



A double-blind, randomized, placebo-controlled trial investigated outcomes related to depression with a single dose of ayahuasca and changes in BDNF in both depressed participants and non-depressed participants versus placebo. The study not only found reductions in depression, but also increases in BDNF in all groups that were treated with ayahuasca. BDNF is negatively correlated with depression—people with depression tend to have low BDNF, and increasing BDNF levels could alleviate depression. This study suggests one of the mechanisms of action in ayahuasca’s ability to alleviate depression could be increasing BDNF levels. BDNF contributes to the growth of neurons in the brain and is also known to increase productivity, mood, memory, and intelligence (Nobrega de Almeida et al., 2019).

#### AYAHUASCA (DMT) AS TREATMENT FOR ADDICTION

**A**s with other psychedelics, ayahuasca has not been found to be addictive, but rather, ayahuasca use is connected to reductions in addictive substance use. A research review by Amanda Nunes and colleagues (2016) investigated the anti-addictive qualities of ayahuasca by evaluating five animal studies and five human studies. The animal studies showed behavioral and biochemical improvements related to drug use. In four of the human studies, researchers found significant reductions in substance use and dependency, while one study did not show significant outcomes. They noted that these studies are promising, and warrant more controlled research to determine specific outcomes and mechanisms of action in behavioral health improvements, specifically addictions.

In a 2008 study, researchers interviewed and collected psychological measures and historical behavioral health information on 32 American members of the Santo Daime Church (Halpern et al., 2008). Members typically participated in weekly services, which usually include consumption of ayahuasca. Physical health was evaluated through exams and tests and found that the participants

were all physically healthy. Of the cohort, 19 had previously been assessed for some form of mental health disorder. Of those, 13 were in full remission, six in partial remission, and eight reported induction of remission after regular ayahuasca use. Similarly, 24 had a history of drug or alcohol dependence and, of those, 22 were in full remission, with five crediting church participation as the main catalyst for their recovery. Given the study design, researchers were not able to disentangle the effects of ayahuasca consumption on the participants’ outcomes versus church membership in general.

A Canadian study evaluated the effects of two ayahuasca ceremonies with 12 participants who had multiple behavioral health disorders, including SUD. The ceremonies took place during a four-day retreat that also included group counseling. The researchers concisely summarize their findings as follows:

*“Statistically significant improvements were demonstrated for scales assessing hopefulness, empowerment, mindfulness, and quality of life meaning and outlook subscales. Self-reported alcohol, tobacco and cocaine use declined, although cannabis and opiate use did not; reported reductions in problematic cocaine use were statistically significant. All study participants reported positive and lasting changes from participating in the retreat” (Thomas et al., 2013).*

#### AYAHUASCA (DMT) FOR TREATMENT-RESISTANT DEPRESSION AND MAJOR DEPRESSIVE DISORDER

There is some evidence that ayahuasca could be used to treat TRD and MDD. In a 2015 study, six participants who had been diagnosed with MDD, and who had not previously used ayahuasca or other drugs, participated in a single-session, open-label study in a psychiatric clinic (Osório et al., 2015). The ayahuasca brew was standardized for consistent levels of DMT and other alkaloids. The researchers state:



“Statistically significant reductions of up to 82 percent in depressive scores were observed between baseline and [one], [seven], and 21 days after [ayahuasca] administration, as measured on the HAM-D, the MADRS, and the Anxious-Depression subscale of the BPRS. These results suggest that ayahuasca has fast-acting anxiolytic and antidepressant effects in patients with a depressive disorder.”

## Researchers reported significant antidepressant effects of ayahuasca when compared with placebo

Similarly, a double-blind, randomized, placebo-controlled trial investigated the effects of a single dose of ayahuasca or placebo in 29 patients with TRD (Palhano-Fontes et al., 2019). Outcomes were measured using the MADRS and the HAM-D at baseline, and one day, two days, and seven days post-treatment. Researchers reported significant antidepressant effects of ayahuasca when compared with placebo at all time-points.

A Phase 1 study with 32 healthy, psychedelic-naïve participants showed the formulation of intravenous DMT to be well tolerated when administered in a dose-escalating protocol in combination with psychotherapy (Small Pharma, 2021). The study “demonstrated a favorable safety profile with no serious adverse events reported to-date.” A subsequent Phase 2a RCT trial will also explore DMT-assisted psychotherapy, this time in 42 patients with MDD, comparing the efficacy of one versus two doses of treatment.

### A NOTE ABOUT 5-MEO-DMT

**5**-MeO-DMT, a psychedelic alkaloid in the tryptamine class (Sherwood et al., 2020) occurs naturally (with significant concentration) in the bark of *Dictyoloma incanescens* in addition to the venom of the *Bufo alvarius* toad (Green, 2022). It is sometimes taken several hours following the ingestion of ayahuasca. This report does not evaluate the evidence of 5-MeO-DMT, as a 2021 review (Ermakova et al, 2021) confirmed that clinical studies in humans are limited. However, it is worth noting that several European companies are conducting research on 5-MeO-DMT for TRD (Carpenter, 2021) with a Phase 1 study underway by one, and completed by another—that has gone on to launch a Phase 2 trial (Reckweg et al., 2021). Additionally, a Canadian company is in preclinical trials looking at a 5-MeO-DMT “next generation” analog for use in clinical-based therapy (Mindset Pharma Inc., 2021).

## AYAHUASCA (DMT) AS AN INTERVENTION FOR SUICIDALITY

**I**n addition to effectively and rapidly alleviating symptoms of depression and improving brain function, ayahuasca has been found to concurrently reduce suicidality in patients with depression who are also suicidal. As with ketamine, the potential rapid anti-suicidal effects of ayahuasca could be a powerful treatment for patients with serious mental health disorders that could make room for more comprehensive and perhaps longer-term treatment for underlying depression or other mental health disorders.

A 2019 study evaluated the effect of a single dose of ayahuasca versus placebo on suicidality in 19 participants who had TRD (Zeifman et al., 2019). Large effect sizes—high effectiveness and significantly lower suicidality—were found at one, two, and seven days post-treatment, suggesting that ayahuasca may be a potential intervention for rapid reduction in suicidality.

A similar open-label trial gave a single dose of ayahuasca to 17 participants with recurrent MDD, 15 of whom were experiencing suicidality before treatment (Zeifman et al., 2020). Levels of suicidality were significantly reduced at one, seven, 14, and 21 days, with the largest effect size (greatest reduction) at 21 days post treatment.

## AYAHUASCA (DMT) RECOMMENDATIONS

Similar to LSD, ayahuasca (DMT) is not currently championed as a potential scalable mental health intervention in the U.S. Although clinical research is thin, limited studies do show that ayahuasca (DMT) has positive and promising outcomes in several areas including depression, suicidality, and addiction. While BrainFutures sees potential for ayahuasca (DMT) to be a treatment for these mental health and substance use disorders, for the time being, use of this compound currently is primarily ceremonial. Pharmaceutical innovations may afford more widespread clinical use.



# Ibogaine

BRAINFUTURES

# Ibogaine / AT A GLANCE

## COMPOUND OVERVIEW

Ibogaine, a compound derived from an African shrub, appears to have potential for treatment of opioid use disorder. Used indigenously in traditional rites-of-passage ceremonies, and therapeutically in non-U.S. clinics around the world where permissible, it has been found in case reports and open label studies to rapidly relieve individuals from the grips of addiction and withdrawal. It is currently being re-researched for the treatment of methadone withdrawal in Spain, alcoholism in Brazil, and opioid withdrawal in the U.K. and the Netherlands, with no ongoing studies in the U.S.

## IN THIS REVIEW

BrainFutures' research reviews 23 peer-reviewed studies with ibogaine, including three RCTs and six open-label studies totaling 387 participants, along with one meta-analysis (of animal studies) and 12 reviews. Overall, the investigators found ibogaine to be effective at ameliorating opioid addiction rapidly and for extended periods of time, and eliminating or attenuating withdrawal symptoms.

## VOLUME AND TYPE OF RESEARCH

Since 1950, just over 500 studies have been conducted on ibogaine in total, many evaluating the pharmacological effects and mechanisms of action. About 70 studies are related to ibogaine's capacity to treat opioid addiction in animals and humans. Of those, one RCT and seven reviews have been published.

## AREAS OF RESEARCH SHOWING EFFICACY

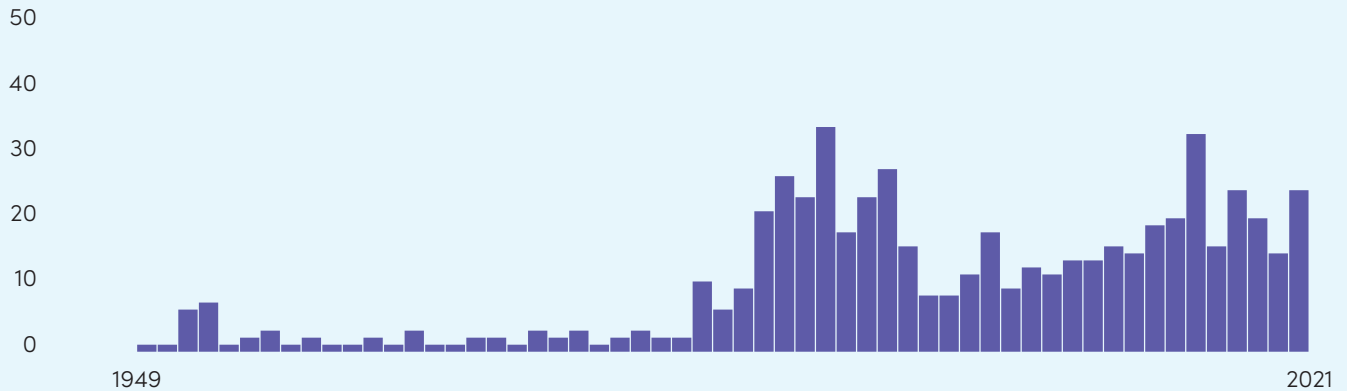
- Substance Use Disorder, including opioid addiction

## SAMPLE OF RESEARCH FINDINGS

- A single ibogaine treatment reduced opioid withdrawal symptoms and achieved opioid cessation or sustained reduced use in dependent individuals.
- Ibogaine treatment resulted in substantial reduction in use and withdrawal symptoms from oxycodone, heroin, or both at one, three, and 12 months post treatment.
- The iboga congener 18-MC (18-methoxycoronaridine) appears from animal and preliminary human studies to be non-psychedelic, with a stronger safety profile than ibogaine while maintaining similar anti-addictive properties.

**FIGURE 15. IBOGAINES RESEARCH ACTIVITY (1949–2021)**

NUMBER OF STUDIES



Note. The above graph represents the increase in publications relating to ibogaine from 1949 to 2021. Adapted from PubMed (2022b). [Data set]. <https://pubmed.ncbi.nlm.nih.gov/?term=ibogaine>

**KEY TAKEAWAY**

In the available research and anecdotal reports, ibogaine has been found to be effective at rapidly interrupting or reducing future opioid use in those with addiction, and in alleviating or eliminating withdrawal symptoms, including cravings. For the majority of participants, these results show long-term durability, often reported to last several months, and in some cases even years. Ibogaine does have a concerning side effect of lowering blood pressure in most individuals and/or extending the time it takes for the heart’s ventricle to contract and relax, which can be a co-factor in mortality as a rare event—and almost exclusively in cardiac-compromised individuals and/or in those who concealed other drug use. Thus, while the anti-addiction properties of ibogaine should not be understated, adequate patient screening is necessary before administering the compound. Additionally, strict monitoring during the dosing experience (and until subjective effects subside) is recommended. When weighing the risks of this intervention, consideration should be given to the high risks of rampant opioid addiction going unaddressed and the risks that some TAU used to address opioid addiction carry.

# Ibogaine

**I**bogaine is an alkaloid commonly extracted from the root bark of the *Tabernanthe iboga*, a West Central African shrub. For centuries, it has been used ritually and medicinally, mostly by people of the Bwiti religion from the Gabon and Cameroon regions (Richer, 2009).

In the 1800s, French and Belgian explorers first reported on the shrub's powerful effects as a stimulant, aphrodisiac, and performance enhancer, as well as an alleged vision-inducing agent when taken in higher doses, and in 1864, French physician and ethnobotanist Marie-Théophile Griffon du Bellay brought some of the initial specimens to Europe (Pope, 1969).

By 1901, researchers Jan Dybowski and Edouard Landrin were the first to make an extract of the iboga root, and called the alkaloid ibogaine (International Center for Ethnobotanical Education, Research and Service [ICEERS], 2019). For about a decade after ibogaine came on the scene, it was “recommended as a treatment for ‘asthenia’ at a dosage of 10 to 30 mg per day” (Brown, 2013). Initial interest in ibogaine's applications for mental health conditions, however, was modest. As one publication reports:

“The alkaloid was subsequently tested in Western clinical settings and was recommended as a stimulant for the treatment of convalescence and neurasthenia [physical and mental challenges and fatigue thought to be due to emotional causes]. Despite such recommendations, ibogaine never enjoyed wide clinical use and was neglected by researchers for almost 30 years” (Popik & Skolnick, 1999).

In the late 1930s, the compound started to be marketed in France as Lambarene, an 8-mg stimulant to help with depression and lack of physical strength and energy, among other conditions. It later went on to be sold as Iperdon, a 40-mg tonic and stimulant, and used by athletes as a performance enhancer (Popik & Skolnick, 1999).

By the later part of the 1950s, ibogaine was being explored as a catalyst for psychotherapeutic engagement. Chilean psychiatrist Dr. Claudio Naranjo, MD became among the most well-known clinicians using the compound as an adjunct to psychotherapy, and obtained a French patent for that purpose in 1969 (Myeboga, n.d.; Brown, 2013).

Ibogaine's potential for its most promising application as an addiction treatment was discovered quite unexpectedly in 1962. A 19-year-old New Yorker, Howard Lotsof, who had a heroin addiction, took ibogaine recreationally. When its effects dissipated some 30 hours later, so too did his craving for heroin (Pinchbeck, 2003). Lotsof also noticed that he did not experience any withdrawal symptoms, and soon shared the drug with a group of 20 psychedelic enthusiasts. Most were around the same age as Lotsof. Of the seven men from the group who had also been addicted to heroin, five immediately stopped using the drug following the session, and abstained for at least another six months (Brown, 2013; Alper et al., 2001).

Inspired by the potential of the compound, Lotsof became one of ibogaine's most ardent champions, a role that would prove pivotal toward advancing the drug's anti-addiction research. A major roadblock to that aim came shortly after Swiss chemist George Büchi, D.Sc.



first synthesized ibogaine in 1966 (Corkery, 2018). The following year, the compound became illegal in the U.S. and in other countries, and it eventually joined other psychedelics as a Schedule I drug in 1970. Like with other psychedelics, this meant that research dollars and federal approval were to be limited.

Lotsof continued to advocate for the U.S. Congress, federal agencies, and pharmaceutical companies to invest research dollars in studying ibogaine's potential. He obtained several patents for the drugs as a fast-acting treatment for narcotic, alcohol, and nicotine addictions (Brown, 2013). Lotsof also founded NDA International, Inc.—a drug research, development, and testing company (Brown, 2013). In the early 1990s, NDA International co-sponsored non-medicalized human studies in the Netherlands and in Panama in partnership with two organizations focused on addiction treatment—Dutch Addict Self-Help (DASH) and the International Coalition of Addict Self-Help (ICASH) (Hevesi, 2010; Brown, 2013). One of the goals was to gather effectiveness data from these informal studies. This research combined with available preclinical data encouraged the National Institute on Drug Abuse (NIDA) to eventually support more preclinical animal research on ibogaine for treating opioid addiction. This started in the early 1990s, but NIDA abandoned the effort within five years.

Prior to this decision, in 1993, the FDA had granted University of Miami researcher Deborah Mash, PhD and her team a Phase I pharmacokinetics and safety trial of ibogaine which was later revised and reapproved in 1995 to include cocaine-dependent subjects (Brown, 2013). After NIDA's 1995 decision to step away from human ibogaine research, the FDA wrote NIDA's director of Medications Development Division urging the agency to reconsider—the FDA recommended that NIDA fund at least a small Phase 1 safety study in humans, but to no avail (Doblin, n.d.). NIDA cited safety reasons as one of its concerns for pulling out (Oaklander, 2021). Mash

and her team tried applying for a NIDA grant based on some preliminary research, but funding was denied and the dose escalation trials at the University of Miami were not able to be completed (Doblin, n.d.; Brown, 2013).

Despite concerns from federal officials about ibogaine's risk potential as well as limited research from controlled studies, ibogaine's use as a treatment for SUDs grew by a reported 400 percent between 2001 and 2006, further bolstering an “ibogaine medical subculture” of clinical and lay practitioners across different parts of the world (Alper et al., 2008). An ethnographic study reported four distinct “scenes” of these providers types: medical model, made up of licensed physicians with treatment done in medical or clinical research facilities; lay provider/treatment guide, consisting of providers that lack medical credentials and in settings that are nonclinical; activist/self help, with providers who are ibogaine activists (eager to widen its use and acceptance), and also in nonclinical settings; and religious/spiritual, lay providers or traditional healers in a ceremonial or spiritual setting (Alper et al., 2008).

Preclinical studies in animals, case reports, and open-label studies in humans support anecdotal evidence of ibogaine's effectiveness in addressing opioid and other substance use addictions. Completed controlled trials would allow for further exploration of this compound's potential as an anti-addiction treatment. Some persistent safety concerns seem to impede this level of research from advancing more quickly (Brown, 2013) and are addressed in the “Tolerability of Ibogaine” section below.

Today, ibogaine is classified as a pharmaceutical in New Zealand, Brazil, and South Africa with administration privileges restricted to licensed medical practitioners (MAPS, 2017). The use of ibogaine as a treatment for addictions is also available in medical facilities in other countries, including in Mexico, Canada, and the UK, and Denmark.

## TOLERABILITY OF IBOGAIN

**C**linical dosage of ibogaine for anti-addiction treatment is generally at 15 to 20 mg/kg, given in only a single administration (Brown, 2013). The onset, duration, and quality of experiences is summarized in a 2013 review:

“The onset of the “acute” phase occurs within 1–2 hours of ingestion and lasts for 4–8 hours and is often marked by emotional intensity and the experience of location and interaction within a “waking dream.”... With ibogaine, commonly reported themes during the acute stage include visions of, and interrogatory exchanges with, ancestral or archetypal persons or beings; placement in and movement within a dream-like visual landscape; and panoramic recall of personal experiences or past events. Some reports indicate that these visions appear only when the viewer’s eyes are closed, and that when the eyes are open, people and things in the surrounding environment appear normal... The “evaluative” stage begins [four to eight] hours after ingestion and lasts for [eight to] 20 hours. During this phase the subject’s attention continues to be inwardly directed rather than towards external stimuli, and the emotional tone tends to diminish in intensity... The panoramic recall slows considerably or entirely as the patient reflects upon and evaluates the experiences of the acute phase. The material contemplated during this stage may consist of experiences from the dreamlike period as well as recollections of other memories and often concerns traumatic or highly emotional experiences, important personal relationships, or impactful decisions the patient has made. The onset of the final stage, called the “residual stimulation” phase is roughly 12 to 24 hours after ingestion; this period generally lasts for 24–72 hours or even longer. Reports of this phase suggest that the patient returns to a normal state of attention to the external environment during this time.

[D]rug dependent patients... reveal that the most common themes emerging from the interpretation of the experience included a sense of insight into destructive behaviors (86.7 [percent] of respondents), a felt need to become abstinent (68.3 [percent]), the experience of having been cleansed, healed, and reborn (50.0 [percent]), and the sense of having a second chance at life (40.0 [percent])” (Brown, 2013).

The review goes on to report that subjects “[experience] a sharp reduction in drug cravings and signs of withdrawal within one to two hours” lasting up to 18 hours, with an absence of cravings lasting for several days to a couple of months—though some case reports have these outcomes lasting years in some cases.

Mild side effects of ibogaine can begin immediately after administration of the compound, and may include dry mouth, ataxia (a lack of muscle control), nausea, and vomiting, which can last from 12 to 24 hours (Obembe, 2012).

A review of existing animal and human studies in 2008 also noted potentially neurotoxic and cardiotoxic side-effects of ibogaine (Mačiulaitis et al., 2008). Tremors and postural instability have been observed in human subjects, and in one study six out of 39 participants experienced significantly lowered resting pulse rate. Hypotension (low blood pressure) has also occurred in some cocaine-dependent subjects, requiring close monitoring (Mačiulaitis et al., 2008).

Although rare, serious adverse events related to ibogaine treatment have resulted in death. A 2015 review (Koenig and Hillber, 2015) indicated that between 1990 and 2008, 19 people died within 1.5–76 hours after ingesting large doses of ibogaine. Most died from cardiac arrest, and the majority also had some history of cardiovascular disease or some other significant health condition, often related to long-term substance abuse. Ibogaine’s toxicity

was not found to be a cause of any of these fatalities. The authors reported, “These adverse reactions were hypothesized to be associated with ibogaine’s propensity to induce cardiac arrhythmias.” They also stated that because most treatments are done underground or outside of documented settings, the number of people who have experienced adverse effects (and the total number who have engaged in the treatment) is unknown.

Building on the work of Koenig and Hillber (2015) and Alper (2012), Genis Ona, PhD and colleagues (2021) conducted a systematic review of reports of adverse effects in studies of ibogaine and noribogaine (psychoactive metabolite of ibogaine) from 2015–2020. The authors note that there has been little consistency in terms of dosage and study design, so it is difficult to draw broad conclusions. However, this review largely confirms earlier work that highlights potential cardiac side effects. The most common problem was QTc prolongation (when the heart takes longer than usual to contract and relax), as well as tachycardia (accelerated heart rate of 100+ beats per minute), and low blood pressure. Physical symptoms such as tremors and weakness were also found, as well as multiple reports of seizures. It is important to note that no prolonged adverse reactions to ibogaine were reported in controlled settings. The authors conclude by recognizing that the available safety data are insufficient: “Considering that a growing number of people worldwide are using these drugs in search for a treatment for substance use disorders, Phase [1 and 2] trials are urgent[ly] needed to assess their tolerance and safety, dose–effect relationships, and possible drug–drug interactions.”

In short, ibogaine treatment health risks are greater when a participant has pre-existing medical cardiac condition(s), when dosages are higher than normally indicated for SUD treatment, and/or when other drugs (e.g. opioids or other narcotics) are taken soon before or after ingesting ibogaine (Brown, 2013). It is also important to consider that currently there is limited long-term safety

data available on the intervention. In light of all of these considerations, treatment for patients with cardiovascular concerns (especially prolonged QTc Interval or hypertrophic cardiomyopathy) is contraindicated, and it is recommended that any session is conducted with proper medical supervision.

The ibogaine dose associated with better addiction treatment effectiveness is also associated with the above risks. Research has found that a lower dose does not present the same side effects and risk profile. In 2016, an RCT was completed on 21 healthy male volunteers with a low dose (20 mg total in a single administration) of ibogaine to analyze its effect on mood states and cognitive function, comparing psychometric test and mood rating results pre-intervention and two hours after administration (Forsyth et al., 2016). The low dose was reported to have “minimal influence” on either metric reading type. This may lead to further research to evaluate dosage risk versus efficacy.

Undoubtedly, serious side effects, including fatalities, from potential new treatment interventions must be given serious consideration. However, this assessment must also weigh the risks of a condition going untreated and the risks of treatments as usual. In the case of drug addictions, more than 840,000 Americans have died since 1999 from a drug overdose (CDC, 2021a)—meaning the risks of leaving this condition untreated are astronomically high. What is more, prescription medication given by doctors, including those meant to curb the addiction crisis, can add to this epidemic (CDC, 2021d). For instance, over the past 20 years, approximately 250,000 of the 840,000 overdose deaths in the U.S. involved prescription opioids. First-line FDA-approved TAU for opioid addiction fall into this category of prescription opioid drugs—methadone (opioid full agonist) and buprenorphine (a partial opioid agonist). These treatments have FDA black box warnings and carry their own overdose risk, including risk of death.

Although studies show that retention in these treatments is associated with lower mortality rates for people dependent on opioids (Sordo et al, 2017), maintaining treatment retention can often be problematic. With methadone, for example, both the required multiple trips per week to a clinician's office for drug administration (prior to being approved for self-administration) and the long-term need for treatment get in the way of treatment retention. Ultimately, methadone is responsible for 5,000 deaths per year, a sixfold increase over the past decade, and it is involved in 30 percent of accidental overdose deaths (CDC, 2012; Vestal, 2015). This is not to say that methadone should not be administered for opioid addiction treatment, rather that it too, like ibogaine, comes with risks.

Beyond the risk of death, methadone and buprenorphine carry other serious risks, such as addiction to the treatment drug and long-term health effects of the treatment drug. For all of these reasons, providers and patients are left looking for other effective anti-addiction treatment options. By comparison, ibogaine's risk profile—especially when given in a medical setting—is likely no greater than TAU, it is non-addictive as evidenced across studies, and it has potentially better outcomes than TAU. All of this means ibogaine should be a research priority in light of our current national addiction crisis that causes 50,000 people to die every year (National Center for Drug Abuse Statistics, 2019).

## “More Americans died from drug overdoses last year than ever before.”

A 2021 article in *Time* magazine summarizes these competing considerations. It states:

“More Americans died from drug overdoses last year than ever before, aggravated by the COVID-19 pandemic. Weekly counts of drug overdoses were

up to 45 percent higher in 2020 than in the same periods in 2019, according to research from the U.S. Centers for Disease Control and Prevention published in February. Available treatments can't meet the need. They aren't effective for everyone, may require long-term adherence and are sometimes addictive themselves... Ibogaine is one of the most promising psychedelics for addiction. Few people have heard of it, it's illicit in the U.S., and nobody does it for fun. It's not pleasant. It could kill you. But for extinguishing addiction—and a range of other issues—many people swear there's nothing like it” (Oaklander, 2021).

### IBOGAINÉ AS A POTENTIAL TREATMENT FOR SUBSTANCE USE DISORDERS

In the 1980s preclinical trials in animals began in an attempt to further validate or discount the anecdotal reports of ibogaine's outcomes in humans. The results from this strong body of preclinical evidence are largely consistent across studies and suggest: a) ibogaine chemically interrupts addiction to opioids, amphetamine, methamphetamine, cocaine, alcohol, and nicotine as evidenced by reductions in self-administration of the drugs; b) signs of attenuation of opioid withdrawal have also been observed; and c) safe levels of ibogaine are well-tolerated but monitoring of human patients is warranted to manage for any possible toxic effects (Glick & Maisonneuve, 2000; Alper et al., 2008; Belgers et al., 2016).

After Lotsof first observed ibogaine's potential as an anti-addiction treatment in the early 1960s, most research on its effect with humans has come from case reports from informal treatment networks across the world. The reports tend to provide consistent results—participants attest that the compound alleviated craving and withdrawal symptoms of their substance use disorders.

In 1999 Kenneth Alper, MD and colleagues completed a retrospective study that included many of these earlier reports. The study included 33 patients—26 who had sought treatment in the Netherlands for opioid addiction from 1989–1993, as well as the seven heroin addicts from Lostof’s group session in the 1960s. In this early nonmedical open label study, patient IV heroin use was treated with ibogaine at an average dose of 19 mg/kg. Outcomes resulted in successful withdrawal with no further drug-seeking behavior in 25 of the 33 participants “sustained throughout the 72-hour period of posttreatment observation” (Alper et al., 1999). One participant died during treatment, with researchers suspecting “surreptitious heroin use.” Of the remaining seven participants, the study stated that two patients experienced drug abstinence with attenuated withdrawal signs, four patients continued drug seeking behavior without withdrawal signs, and one patient showed drug seeking behavior with continued withdrawal signs.

These types of quasi-clinical treatments were taking place beyond just the U.S and the Netherlands. Reports of providers in Panama, Britain, Slovenia, the Czech Republic, Canada, Mexico, and Italy were also known (Brown, 2013; MAPS, 2003).

Alper and colleagues completed a 2007 ethnographic analysis of clients from this international network of informal treatment providers. More than 3,400 people had taken ibogaine as of 2006—68 percent of participants had done so to treat a substance-abuse disorder, and 53 percent were specifically wrestling with opioid dependence (Alper et al., 2008). After reviewing and analyzing the data, the study concluded that, “Ibogaine’s effect in opioid withdrawal is consistent with case series and preclinical evidence, and is unlikely to be mediated by placebo.”

A review in 2013 conducted by Thomas Brown, PhD offered an outcome study focused on ibogaine treatment for opioid addiction. It provided a literature review

covering preclinical studies, safety concerns, and findings thus far related to the compound’s treatment success with opioid-dependent patients. The review concluded by stating:

“In sum, the human studies of ibogaine treatment provide some preliminary support for the efficacy of ibogaine in alleviating the considerable discomforts of withdrawal from opiates and other addictive drugs, and thereby in facilitating detoxification from these substances in a comparatively painless manner... The limited research results achieved so far suggest that opiate and cocaine cravings are significantly reduced for up to [one] month following treatment and that a substantial minority of patients remain abstinent for several months.”

Brown’s review recommended future long-term outcome studies to better understand the durability of effect on ibogaine as an addiction treatment intervention. Two observation studies published in 2017 and 2018, including one led by Brown, helped answer that call.

In New Zealand, where ibogaine treatment is legally available, an open-label study on 14 participants (50 percent female) between ages 18 and 47 with opioid addiction was conducted (Noller et al., 2018). The study was designed to offer long-term follow-up data. Dependencies of the enrollees included methadone (10), codeine (three) and poppy seeds (one). Participants received staggered oral doses of 200 mg capsules over 24–96 hours for a total of 55 mg/kg of ibogaine with benzodiazepine and sleep aids. One death did occur during treatment while a participant was under medical supervision (and for which the provider was later found to have failed in their duty of care). With regard to remaining participants, the study found at the 12-month follow-up that “a single ibogaine treatment reduced opioid withdrawal symptoms and achieved opioid cessation or sustained reduced use in dependent individuals.” The unfortunate fatality did raise safety issues relative to the



importance of better standardized prescreening, dosing, and medical supervision protocols.

Another open-label observation study was conducted in Mexico, enlisting 30 individuals (five female) diagnosed with opioid dependence on oxycodone, heroin, or both (Brown & Alper, 2018). A mean total dose of  $1,540 \pm 920$  mg ibogaine was given. Outcomes were taken at one, three, six, nine, and 12 months post treatment. The study found that treatment with ibogaine led to substantial reduction in use and withdrawal symptoms at one, three and 12 months. At the one-month mark, 50 percent of the participants had been opioid free since treatment and 40 percent reported 75 percent reduction in their drug use; at the three-month follow-up, 33 percent reported being opioid-free for the past month. The study reports, “improvement in Drug Use scores was maximal at [one] month, and subsequently sustained from [three] to 12 months.” The researchers concluded that:

“Ibogaine was associated with substantive effects on opioid withdrawal symptoms and drug use in subjects for whom other treatments had been unsuccessful... ibogaine appeared to have a substantive treatment effect in opioid detoxification, and group statistics and individual trajectories appear to indicate an effect of reducing drug use at [one] month, which was sustained up to 12 months in a subgroup of subjects... No adverse medical events occurred in this study.”

Another review in 2018 was authored by Deborah Mash, PhD and colleagues. After NIDA funding dried up in the mid 1990s, Mash moved her studies off-shore to Saint Kitts, West Indies. This 2018 review looked at the methods and outcomes from ibogaine treatment for opioid use disorder at a 12-bed treatment facility on the island. Participants took part in a 12-day inpatient protocol designed to assess safety and open-label efficacy of ibogaine-assisted therapy for treating opioid or cocaine dependency. The review included 191 individuals

(47 female) from a series of treatment cohorts, who were given oral doses of ibogaine (8–12 mg/kg). The research concluded that ibogaine, “unlike a methadone or buprenorphine taper, is a rapid detoxification method, shortening the time needed for withdrawal to [two to three] days.” In addition, the study reported no significant adverse events “following administration of ibogaine in a dose range that was shown to be effective for blocking opioid withdrawal symptoms in this study.”

This 2018 review found that ibogaine treatment for opioid dependence in patients without preexisting conditions did not lead to cardiac side effects. Cardiac side effects were exclusively observed in some patients without preexisting conditions who were treated for cocaine dependence. Therefore, all participants were carefully screened prior to admission, and potential or occurring low blood pressure and low resting heart rate in the cocaine group was effectively mediated by IV fluids. The authors reinforce earlier review findings on ibogaine risks:

“Unfortunately, deaths related to ibogaine have been described for persons seeking detoxification from drugs and alcohol involving variable product purities of ibogaine (HCl or extract) (Alper et al., 2012; Noller et al., 2018). Many of the forensic investigations of ibogaine deaths lacked postmortem toxicologic measures of ibogaine or its metabolite noribogaine in blood (Alper et al., 2012). Ibogaine fatalities are frequently associated with higher doses of ibogaine (>20 mg/kg) which are well above those used in our study, suggesting that there is an increased risk for toxicity at higher doses depending on CYP2D6 genotype [a rating of person’s ability to metabolize drugs]. Also, multiple doses of ibogaine ‘stacked’ over time following the initial ‘flood’ dose were reported for many of these cases... A review of the available information suggests advanced drug-related comorbidities and contributing conditions, including cardiovascular disease and polydrug



abuse in the days or hours prior to ibogaine treatment may have contributed to the AEs and possible drug related fatalities (Kontrimavici et al., 2006; Kubiliene et al., 2008; Alper et al., 2012). Because ibogaine is a medicinal investigational product, these observations underscore the importance of strict inclusion/exclusion criteria to ensure patient safety” (Mash et al., 2018).

## “Ibogaine significantly decreased craving for cocaine and heroin during inpatient detoxification.”

Mash and colleagues’ previous research leading up to this review involved systematic investigations of ibogaine as a treatment for opioid withdrawal dating back to 2000. This early comparative study concluded that ibogaine showed efficacy as an inpatient detoxification treatment for cocaine and heroin users, with opiate cravings significantly reduced at 36 hours and one month, and further, depressive symptoms remained significantly alleviated at 30-day follow-up (Mash et al., 2000). The authors stated:

“Ibogaine significantly decreased craving for cocaine and heroin during inpatient detoxification. Self-reports of depressive symptoms were also significantly lower after ibogaine treatment and at 30 days after program discharge. Because ibogaine is cleared rapidly from the blood, the beneficial aftereffects of the drug on craving and depressed mood may be related to the effects of noribogaine [a metabolite of ibogaine that is produced in the body] on the central nervous system.”

Deepening this 2000 research, Mash and colleagues published a 2001 review hypothesizing that the mechanism

of action leading to successful withdrawal from opiates could be related to noribogaine, the psychoactive metabolite metabolized in the body from ibogaine following ingestion (Mash et al., 2001). In this study, the researchers used a single 800-mg dose of ibogaine, and withdrawal symptoms were rated at one hour before ibogaine dosing, and again at several intervals post-treatment. Withdrawal symptoms were significantly lower at 12 and 24 hours after dosing, at discharge approximately one week later, and at one-month follow-up.

When reflecting on the work she led in Saint Kitts over the past two decades, Mash noted:

“Not only were patients able to safely and successfully transition into sobriety, we found no evidence of additional abuse potential. Given the limitation in currently available treatments, ibogaine represents an enormous leap forward for [opioid use disorder] sufferers” (DemeRx, 2020).

Adding to the long-term outcomes for ibogaine treatment, an unpublished Dutch doctorandus thesis by Ehud Bastiaans collected survey data, based on the European Addiction Severity Index, to evaluate the post-treatment outcomes of 21 people who had undergone ibogaine treatment for opioid dependence (Bastiaans, 2004). The research found that 90 percent remained abstinent from all drugs for at least one week. The average length of abstinence for all participants was 3.5 years: 24 percent were entirely abstinent; 43 percent were free from opioids for an average of 1.5 years but may have used cannabis or alcohol; 33 percent returned to substance use although the majority were using smaller quantities of opioids. Relating to quality of life, 58 percent reported improvements in medical health, and 96 percent reported improvement in psychological well-being.

## RESEARCH ON COMPOUNDS RELATED TO IBOGAINE

**A**s the opioid crisis accelerates and current therapies fall short, the need for effective treatment options persists. Scientists and chemical engineers are looking for ways to modify ibogaine to preserve its powerful anti-addiction properties while reducing or eliminating serious adverse effects, in particular the risk of cardiovascular failure (Brown, 2013). The research behind three potentially promising compounds related to ibogaine—noribogaine, 18-methoxycoronaridine, and tabernanthol—are outlined below.

### NORIBOGAINE

Noribogaine is a metabolite of ibogaine. Researchers have speculated that this compound may be responsible for some of ibogaine's anti-withdrawal and anti-craving effects because it persists in the body much longer than ibogaine (Glue et al., 2015). Two clinical trials have explored the safety and tolerability of noribogaine: one Phase 1 RCT study published in 2015 with healthy subjects, and another RCT published in 2016 with opioid withdrawal syndrome patients (Glue et al., 2015; Glue et al., 2016). While the 2015 study found no adverse effects, some participants in the 2016 study experienced adverse side-effects, including QTc prolongation, which is associated with bradycardia (heart rate < 60 beats per minute) and arrhythmia (Ona, 2021, Köck et al., 2021). The 2016 study also did not find any statistically significant decrease in withdrawal symptoms. This study and later reviews have noted that the noribogaine dosage level used in this study (between 60 and 180 mg) may not have been large enough to elicit an anti-withdrawal effect (Ona, 2021; dos Santos, Bouso, & Hallak, 2016).

### 18-METHOXYCORONARIDINE (18-MC)

A synthetic derivative of ibogaine, 18-methoxycoronaridine is another promising compound. Animal studies

have shown that 18-MC has similar outcomes in terms of reduction of substance use, but without affecting heart rate.

In an early study of 18-MC on rats, Dr. Stanley Glick, MD, PhD and Dr. Isabelle Maisonneuve, PhD found that while the compound's effects on drug self-administration were equivalent to ibogaine, 18-MC appeared "much safer." The researchers concluded:

*"Even at high doses, 18-MC does not mimic ibogaine in producing neurotoxic (Purkinje cells in cerebellum) or cardiovascular (bradycardia) effects... Considered together, all of the data indicate that 18-MC should be safer than ibogaine and at least as efficacious as an anti-addictive medication" (Glick & Maisonneuve, 2000).*

Further studies have continued to bear out these initial findings. Koenig and Hilber's research (2015) stated:

*"[T]he ibogaine congener 18-MC is likely associated with a reduced risk of TdP arrhythmia induction, because it shows considerably lower affinity for hERG channels [essentially the potassium channel that, in-part, controls electrical activity to the heart] than ibogaine. We encourage researchers to develop ibogaine-like drugs with preserved anti-addictive properties."*

In 2021, a Phase 1 trial sponsored by a U.S company was completed with the aim to establish the "safety, tolerability, pharmacokinetics, and effects on cognitive activity of 18-MC in healthy volunteers" (MindMed, 2022b). The trial's topline results are expected to be released in early 2022. According to the company's CEO, the company expects to begin a Phase 2a trial to establish safety and efficacy of 18-MC in patients with opioid withdrawal syndrome in 2022. Interestingly, there is some evidence that 18-MC could also be used as an antiobesity treatment because it has been shown to be active on the sucrose reward circuit in the brain (Lavaud & Massiot, 2017).

## TABERNANTHALOG (TBG)

The ibogaine analog tabernanthalog has recently been synthesized and tested in rodents with promising results (Cameron et al., 2021). The study authors stated:

“[S]everal safety concerns have hindered the clinical development of ibogaine, including its toxicity, hallucinogenic potential and tendency to induce cardiac arrhythmias... [T]hrough careful chemical design, it is possible to modify a psychedelic compound to produce a safer, non-hallucinogenic variant that has therapeutic potential” (Cameron et al., 2021).

The research team is optimistic about the potential uses of TBG, including not only addiction treatment but also potentially comorbid conditions such as depression and PTSD (Peters & Olson, 2021). More studies are needed before TBG could be used to treat patient populations.

## FUTURE IBOGAIN STUDIES

As of January 2022, more rigorous ibogaine trials have been initiated and are ongoing, including a Phase 2 RCT on ibogaine for alcoholism in Brazil (dos Santos, 2021), a Phase 1/Phase 2a double-blind RCT on single-dose ibogaine for opioid withdrawal (DemeRX IB, Inc., 2021), an open-label, single dose trial on opioid dependence in the Netherlands (Radboud UMC, 2021), and a trial on ibogaine for methadone withdrawal in Spain (ICEERS, 2020). These new studies indicate that the international research community is taking the promise of ibogaine for addiction treatment seriously.

## IBOGAIN RECOMMENDATIONS

While ibogaine comes with documented health risks including death, it also demonstrates repeated success in treating addiction and in eliminating or attenuating withdrawal symptoms. Given the serious nature of our current opioid addiction and related death epidemic, BrainFutures sees value in ibogaine’s potential addiction-treatment capabilities. Considering that other treatments for opioid dependency also carry health risks—including addiction and long-term-use side effects not associated with ibogaine treatment—it is BrainFutures’ hope that ibogaine will garner more attention as a potential ally in the fight to curb addictions and reduce related deaths. To date, there are no completed Phase 1, 2, or 3 clinical trials on high-dose ibogaine (proper). Currently, the compound is only being researched in a limited capacity around the world, with no U.S. studies. In the years ahead, further controlled studies (including pharmacological engineering) of this powerful substance should be supported—enabling more rigorous research on ibogaine’s safety, efficacy, and effectiveness for addiction treatment.

The background features a complex, abstract pattern of overlapping circles and squares in various shades of purple, from light lavender to deep, dark violet, set against a black background. The shapes are arranged in a grid-like fashion, creating a sense of depth and movement.

# Mescaline

## Mescaline / AT A GLANCE

### COMPOUND OVERVIEW

Mescaline (3,4,5-trimethoxyphenethylamine), found in the peyote and San Pedro cacti (among others), has been used ceremonially for thousands of years by traditional tribes and communities, most notably the Huichol, Wixaritari, Cora, Tarahumara, and Yaqui from Mexico, and more recently in the North American Native American Church (Iron Rope et al., 2020). The compound was brought to wider western attention by Aldous Huxley in his book, *The Doors of Perception* where he narrated his experience with the substance (Huxley, 1954). Practically no modern, rigorous clinical research exists on the use of mescaline (including peyote and San Pedro) for the treatment of MH/SUD.

### IN THIS REVIEW

BrainFutures' research reviews nine peer-reviewed studies with mescaline, including, two comparative studies, two three survey studies, and two clinical trials, altogether involving a total of 814 participants. Two review articles and one animal study are also included. A robust number of rigorous clinical trials meeting today's research standards and exploring mescaline as an MH/SUD intervention are lacking, yet given the research to date, the potential for this compound to become an effective behavioral health treatment was identified.

### VOLUME AND TYPE OF RESEARCH

Since 1954, 230 studies involving mescaline at some level of therapeutic investigation have been published. There are a number of studies from the first half of the 20th century, yet these lacked modern day research methodology (and ethical standards). Most modern studies involving mescaline, including pre-clinical animal studies, have investigated mechanisms of action, biochemistry, prevalence of use (especially

among Native Americans), and illicit-drug-use-related adverse events. Modern clinical studies evaluating the effects of mescaline as a treatment for MH/SUD are still needed. Three clinical trials exploring mescaline's role in altered states of consciousness and effects on treating pain compared to other psychedelics are currently recruiting—two in Switzerland and one in Norway.

### AREAS OF RESEARCH SHOWING EFFICACY

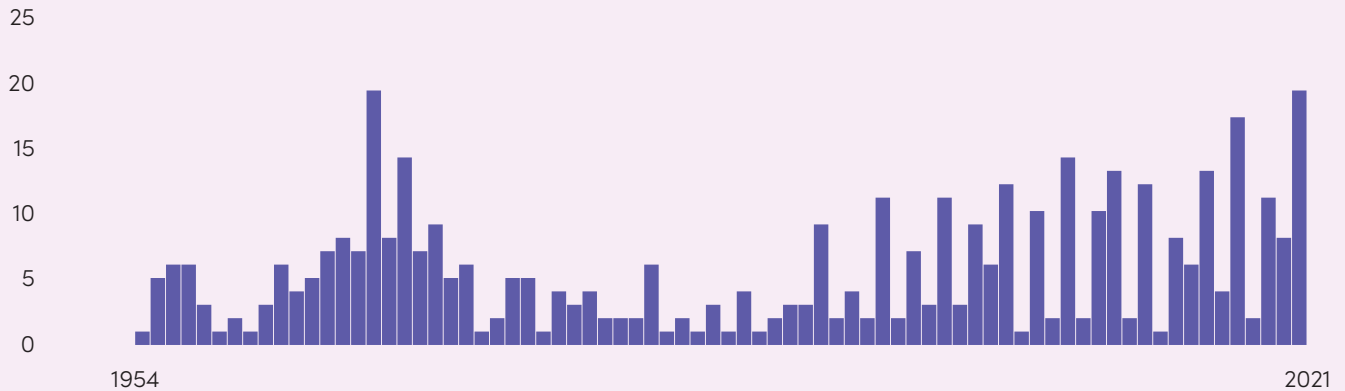
- Clinical research with mescaline is only beginning
- Self-report evidence shows strong effects of improving MH/SUD conditions

### SAMPLE OF RESEARCH FINDINGS

- Much of the currently available data comes from Indigenous populations in Mexico and North America who use mescaline as part of their religious ceremonies.
- Two studies have found no adverse effects as a result of long-term peyote use in Indigenous and traditional ceremonies.
- The majority of respondents in a survey study who indicated an underlying mental health disorder reported improvements in their disorder following mescaline use.

**FIGURE 16. Mescaline RESEARCH ACTIVITY (1954–2021)**

NUMBER OF STUDIES



Note. The above graph represents the increase in publications relating to mescaline from 1954 to 2021. Adapted from PubMed (2022f). [Data set]. <https://pubmed.ncbi.nlm.nih.gov/?term=mescaline+and+therapy&filter=years.1954-2021&sort=pubdate>

**KEY TAKEAWAY**

The published research on mescaline to date predominately investigates biochemical mechanisms of action and the subjective effects of the experience. A few reviews as well as survey and comparative studies provide the current basis for evaluating the effectiveness of mescaline as a compound for PAT. The limited research available shows positive outcomes with no notable negative effects, primarily in ceremonial and self-administered settings, and suggests that mescaline would be worthy of more rigorous clinical trials to investigate its effectiveness as a behavioral health treatment.



# Mescaline

**T**he human use of mescaline through peyote dates back at least 6,000 years as found in carbon-dated specimens (El-Seedi et al., 2005; Terry et al., 2006) and on petroglyphs in traditional art and stories. Peyote has long been used ceremonially by Indigenous people in what is now northern Mexico and southern Texas (Stewart, 1987). Similar to the history of psilocybe mushrooms, the use of peyote was largely forced underground during colonialization, but its traditional use never died out (Abbott, 2019). In fact, over the past century, mescaline use in ceremonial context through the consumption of peyote or San Pedro cacti has remained strong.

It is estimated that approximately **500,000** NAC members consume the peyote plant in ceremonies and/or as medicine.

Native Americans succeeded in incorporating the Native American Church (NAC) in 1918 as a way to preserve the sacramental use of peyote. Today it is estimated that approximately 500,000 NAC members consume the peyote plant in ceremonies and/or as medicine (Ermakova, 2019). Eligible legal use in the U.S. is limited to protections under the American Indian Religious Freedom Act (AIRF) of 1994.

Beyond traditional use, the pharmaceutical company Parke-Davis started to market a “peyote tincture as a respiratory stimulant and heart tonic in 1893,” which kicked off a series of turn-of-the-century researchers self-administering peyote to observe its effects and giving it to patients in failed attempts to gain insights into the

“psychotic phenomena associated with schizophrenia” (Abbott, 2019).

Mescaline was first synthesized in 1919 by Austrian chemist Ernst Späth and a year later Merck began to sell mescaline sulphate as an injectable solution (Jay, 2019). This new means of drug delivery enabled German psychiatrist Kurt Beringer to lead a series of human studies on the compound at Heidelberg University’s psychiatric hospital during the 1920s, aimed at better understanding the effects of the drug on patients. As one article writes:

“Beringer injected 60 experimental subjects with Merck’s mescaline solution, often several times, in doses ranging from 200 to 600 mg. His eventual report, *Der Meskalinrausch* (1927), included an appendix of over 200 pages of subjective reports, with detailed experiential accounts and occasional drawings of mescaline hallucinations. Beringer attempted to separate the effects of the drug into three categories: abnormal sensory phenomena, changes in conscious attitudes, and abnormal mental states, but found that they blurred together. His attempts to connect the subjects’ various responses with their different personality types were similarly inconclusive” (Jay, 2019).

In addition to early researchers attempting to use the drug to better understand schizophrenia and/or its treatment effect, psychologists in the 1930s gave it to both literary and visual artists, in part as an attempt to have them better capture in word and image the altered perceptions and experience induced by the drug (Jay, 2019). However, many of these kinds of mescaline experiments involving human subjects were ultimately abandoned due to unpleasant side effects, a lack of any consistently

positive outcomes, and a largely unsuccessful attempt to document any predictable results from consuming mescaline (Abbott, 2019).

In the 1940s, the U.S. Navy purportedly conducted experiments with mescaline (along with LSD) as a possible interrogation and recruitment drug under the name “Project Chatter,” although verifiable accounts remain limited (Alliance for Human Research Protection, 2015). Similar use of mescaline as a potential “truth serum” was attempted in concentration camps during World War II (Abbott, 2019).

Some of the early trials in the 1950s and 1960s involved combining mescaline with the antipsychotic chlorpromazine (also known under the brand name Thorazine) as an emergency psychiatric treatment for psychosis, or to induce psychosis as a treatment for schizophrenia and other disorders (e.g., Denber & Merlis, 1955). (These studies neither represented a PAT model of treatment nor have any recent research to support their validity.) Mescaline’s more mainstream popularity grew during this same period through the research work of British-Canadian psychiatrist Humphrey Osmond, as well through philosopher and writer Aldous Huxley’s narratives (Bisbee, et al, 2018). By 1965, mescaline, along with LSD, was no longer legal for non-clinical use (Jay, 2019).

Today, with growing interest in psychedelics in popular culture, current conservation issues that surround mescaline-containing plants are at risk of worsening. In natural form, in addition to the San Pedro cactus of the Andes, a primary source of mescaline is the peyote cactus (*Lophophora williamsii*), which grows only in a small area ranging from the southern border of Texas into northern Mexico, often referred to as peyote gardens (Jay, 2019; Iron Rope et al., 2020). These lands are considered sacred and harvesting peyote (now listed as a vulnerable species) is traditionally done as part of a pilgrimage

ritual (Iron Rope et al., 2020). Unfortunately, a number of issues have obstructed the preservation of peyote and threaten its traditional use. In an article, “Keeping the Sacred, Sacred: The Indigenous Peyote Conservation Initiative,” the authors summarize these factors as “lack of access to the private ranch lands in the gardens, improper and overharvesting, root-plowing, industrial agriculture, mining, oil and natural gas production, poaching, and illegal sales to non-Natives in the United States and Europe” (Iron Rope et al., 2020).

One critical issue relative to the growing demand for peyote is that the cactus cannot be successfully farmed at scale. It takes at least a decade for a peyote plant to mature to a harvestable fruit body. This is part of the reason why unsustainable harvesting practices as of late threaten both the plant’s future and traditional ceremonial practice.

Given these important ecological and cultural preservation issues, some of the emerging U.S. legislative efforts aimed at decriminalizing psychedelics include special clauses excluding peyote use (Lekhtman, 2022). To further support preservation concerns of this threatened plant, one solution when exploring potential future treatment applications could be to exclusively use synthetic mescaline (3,4,5-trimethoxy- $\beta$ -phenethylamine). Another avenue is to explore alternate naturally-derived options with the Echinopsis family of cacti that are fast-growing and amenable to growth in other climates (Bury, 2021).

Regardless of the compound source, mescaline has only limitedly been administered in today’s modern clinical trial setting to validate it as a potentially beneficial compound for mental and behavioral health. Nonetheless, data gathered from recent survey and comparative studies, as well as from reviews, point to the valuable therapeutic potential of this substance.

## TOLERABILITY OF Mescaline

**C**onsumption of cacti that contain mescaline generally triggers nausea and vomiting. However, some researchers theorize this may be due to the taste of the plant rather than any direct effect of mescaline since this side effect has not been observed in study participants who consumed synthetic mescaline (Dinis-Oliveira et al., 2019). Additional transient side effects may include intense visual imagery (psychedelic), modification in perception of time and space, a sense of euphoria, increased heart rate and/or body temperature, and impaired motor coordination (DEA, n.d.). More challenging psychological effects may include sensory alterations, paranoia, delusions, depersonalization, disorganized behavior, panic, and anxiety (Uthaug, Davis et al., 2021). Serious adverse events from mescaline are reported as rare, although the data are limited (Dinis-Oliveira et al., 2019). One retrospective review of the California poison center database for mescaline-related events reinforces claims of rare adverse events. It noted only 31 single-substance exposures to the drug over an 11-year period—an average of three events per year (Carstairs & Cantrell, 2010).

Research from the 1950s indicates that the lethal dose of mescaline is about 370 mg/kg (Speck, 1957). Typical ceremonial usage would result in the consumption of approximately 200 mg to 400 mg total (Dinis-Oliveira et al., 2019), about 70 times less than the lethal dose. Administered within this typical range, onset of effects generally begin within 45 to 60 minutes and last between four and eight hours but can last up to 12 hours (Tófoli & de Araujo, 2016; Iwanicki, 2018).

**Compared to the mescaline users who showed no neurological deficits, those who had previously abused alcohol showed significant deficits on every scale of the Mental Health Inventory.**

Researchers have attempted to establish whether mescaline leads to changes in the brain. One comparative study included long-term Native American Church users of peyote, non-users who were former alcoholics, as well as users with a minimal history of peyote and alcohol use. This comparison was done to evaluate any changes in neurological function, memory, attention, and executive functions. While no functional differences were found between the groups, compared to the mescaline users who showed no neurological deficits, those who had previously abused alcohol showed significant deficits on every scale of the Mental Health Inventory (MHI) (Halpern et al., 2005).

Another comparative study compared generations-long Huichol users of peyote to non-users to see if generational use affected any changes in gene expression or chromosomes and found no negative effect from the long-term use of peyote (Dorrance et al., 1975).

## Mescaline Research

**M**odern human research investigating mescaline as an MH/SUD treatment has been very limited. However, in addition to the few studies mentioned above, a 1992 RCT study measured the effects of mescaline on 12 healthy, male volunteers and found that the compound induced “the dissolution of ego-boundaries, visual hallucinations, and dimensions of ‘oceanic boundlessness’” among other sensations.” (Hermle et al., 1992). The researchers were primarily

interested in inducing a psychotomimetic state in order to create a comparison to the brains of schizophrenic patients. Longer-term or therapeutic outcomes from mescaline were not evaluated by this study.

## Data gathered from mescaline users in recent survey studies point to the valuable therapeutic potential of this substance.

Though other modern RCTs investigating mescaline as a treatment for mental and behavioral health are lacking, data gathered from mescaline users in a recent survey study point to the valuable therapeutic potential of this substance.

Researchers collected survey-based feedback from 452 respondents who had previous experiences with mescaline, 74 percent of whom said spiritual exploration motivated their desire to use mescaline. Interestingly, almost half reported having pre-existing depression or anxiety, 20 percent reported having a substance use disorder, and 17 percent had PTSD. Following their mescaline experiences, of the participants who indicated a MH/SUD, the majority reported improvements in their affective disorders as follows: 86 percent experienced relief from depression, 80 percent from anxiety, 76 percent saw improvements in PTSD symptoms, and almost 68 percent experienced reduced drug or alcohol misuse (Uthaug, Davis et al., 2021). The research team also noted that “Acute experiences of psychological insight during their mescaline experience were associated with increased odds of reporting improvement in depression, anxiety, AUD [alcohol use disorder] and DUD [drug use disorder]” (Agin-Liebes et al., 2021).

## Mescaline Recommendations

While findings from survey and comparative studies, reviews, and the historical traditional use of mescaline by Indigenous populations indicate that mescaline may have the potential to alleviate the symptoms of mental health and substance use disorders, evidence is currently inconclusive. Phase 1–3 randomized controlled trials are ultimately needed before this psychedelic can enter the pharmacopeia of PAT. Additionally, the source of the mescaline used for increased studies and potential future treatment should not endanger mescaline-containing plants or the traditional cultural practices for which they are used.

# Conclusion

**F**ollowing almost half a century of limited to no research on psychedelics, a resurgence in clinical investigations is showing high levels of efficacy, effectiveness, and safety for some of these compounds. Under proper conditions and protocols, at the right dosages and in combination with therapeutic support and supervision, several psychedelics are producing significant, positive treatment outcomes for some of the hardest-to-treat and even refractory mental health and substance use conditions. The research to date validates PAT as a highly effective tool in the work to alleviate our nation's ongoing mental health crisis and help lift the burdens of depression, anxiety, PTSD, and addiction that plague hundreds of millions of people around the world.

The overarching findings from this body of evidence indicate the following:

1. Psilocybin-assisted therapy is increasingly showing evidence of efficacy for the treatment of depression, including MDD and TRD, based on multiple randomized trials. Psilocybin has also been shown to be effective for anxiety and SUDs, specifically tobacco cessation.
2. A growing body of evidence points to ketamine, esketamine, and ketamine-assisted therapy being effective at rapidly reducing symptoms of depression, including MDD and TRD, as well as suicidality. Symptom relief from ketamine can last up to four weeks. In addition, ketamine has been shown to produce short-term reductions in anxiety, PTSD, and pain. Ketamine-assisted therapy has been shown to be effective for treating SUDs.
3. Based on multiple studies, including one successful FDA-approved Phase 3 clinical trial, MDMA-assisted therapy continues to demonstrate effectiveness at treating PTSD and anxiety following one or two treatments, with some of the research showing long-term response and remission rates.
4. LSD has fewer recent studies that meet today's standards of scientific rigor, yet it holds a significant body of research published prior to its Schedule I listing in 1970. Many of these early findings show LSD-assisted therapy to be effective at treating alcoholism, with newer research focusing on depression and anxiety.
5. DMT, in the form of ayahuasca and similar brews, has not been well-researched clinically, yet reports from a handful of studies over the past decade have shown DMT's promise for treating depression, including major depression and TRD, suicidality, and SUDs, with no lasting side effects.
6. Ibogaine is currently being researched in a limited capacity outside the U.S., yet a few studies are showing positive, effective results for the treatment of opioid addiction, including ongoing studies for methadone withdrawal and alcoholism.
7. Mescaline has largely not been the subject of modern formal clinical research trials. However, a self-report survey, comparative studies, and a number of reviews indicate that it could be effective at treating SUDs, especially alcoholism. Evidence of it reducing symptoms of PTSD, depression, and anxiety has also been indicated.

In the years ahead, technology, including adjunctive non-drug devices such as virtual reality, may also prove helpful in aiding the integration of meaningful psychedelic experiences and/or prolonging symptom reduction—all toward supporting long term positive behavioral changes occasioned by these compounds.

# Recommendations

**G**iven the current research and findings, the high potential for PAT to positively and significantly impact our current mental health crisis, the relative safety of PAT when used correctly, the anticipated significant cost savings for healthcare payers, employers and individuals, the powerful levels of investment in the space, and the change in public sentiment toward acceptance and approval of psychedelics, BrainFutures makes the following recommendations:

## 1. Certain PAT interventions with sufficient evidence levels for safety and efficacy should be rapidly adopted once approved by the FDA.

### FDA APPROVAL

Assuming remaining required trials continue to show efficacy and safety, BrainFutures endorses FDA approval for psilocybin and MDMA (when administered with assisted therapies), to support a more immediate inclusion of these interventions into the treatment protocols for MH/SUD conditions.

**These interventions have demonstrated positive outcomes and high levels of efficacy for treatment-resistant conditions.**

TAU, in particular psychopharmacology, while effective for some, has not been successful at tempering the growing mental health crisis. The powerful ability of these psychedelics to re-regulate brain activity related to mental health disorders, ideally in conjunction with psychotherapy, offers both novel mechanisms of action

and novel participant experiences compared to typical treatment medications such as SSRIs. When these compounds are combined with therapy that thoughtfully considers set and setting, these interventions have demonstrated positive outcomes and high levels of efficacy for treatment-resistant conditions and other MH/SUDs in many studies. Furthermore, for some patients, PAT has shown to produce longer-lasting outcomes and fewer enduring side effects than TAU.

In consideration of the current research presented in this review and the experience of expert clinicians in the field participating in PAT clinical trials, the case is clear for preparing now to incorporate these applications into the MH/SUD treatment toolbox. Given the dire need for new, effective treatments to address our current mental health crisis, upon anticipated FDA approval of psilocybin and MDMA for PAT, BrainFutures recommends fast and widespread adoption of these therapies.

### RIGHT TO TRY INCLUSION

Prior to FDA approval, BrainFutures also recommends that PAT interventions, especially using psilocybin, be made available now to patients with life-threatening or serious conditions through State and Federal Right to Try Acts (RTT). The federal Act, signed into law in 2018, supports the 41 state RTT laws, which allow eligible patients with severe conditions—who have exhausted available treatment options—access to investigational drugs which have completed a Phase 1 clinical trial with the FDA but remain under investigation in later stage trials and are not yet approved. Patients, physicians, drug manufacturers, and the DEA all must collaborate to ensure PAT will not encounter roadblocks when requests are made by providers (on behalf of their



patients) to manufacturers under the Acts. Because most PAT compounds are Schedule I drugs, the DEA needs to create a pathway to access and ensure that the Acts' immunity provisions prohibiting legal retaliation will be applicable to manufacturers responsibly distributing the compounds and providers utilizing them therapeutically for RTT-compliant purposes. BrainFutures recommends either a special registration, waiver, exception, or exemption be standard practice to afford this protection, and for the explicit process for attainment to be clear and publicly available on both the FDA's and DEA's websites.

## **2. Reimbursable and equitable access of approved psychedelic therapies is essential and all payers should adequately cover PAT treatments.**

BrainFutures advocates for insurance payers to make equitable widespread access of ketamine for the treatment of pain, depression (including MDD, TRD, and suicidality), anxiety disorders (including PTSD and SUDs) by making these reimbursable treatment events, inclusive of any concomitant psychosocial therapies.

Assuming that the FDA approves MDMA and psilocybin as PAT compounds, BrainFutures also recommends rapid coverage of these treatments from all payers.

Insurance coverage must reimburse these treatments at competitive rates, or providers will likely not accept that insurance. Higher out-of-pocket costs, whether due to out-of-network or no coverage, mean fewer people receive the care they need, especially those with more limited resources. Adequate provider reimbursement needs to include all PAT components, including assessment, therapeutic preparation, dosing/medication session (compound, therapy, and/or supervised observation), and integration therapy. Research and experience indicate that, in most cases, medication plus accompanying psychiatric therapies are more effective than either treatment alone.

Commercial and government payers, including the Veterans Administration, as well as self-insured employers, must adequately cover PAT to solidify a *safe, accessible, and reimbursable* healthcare payer network able to provide equitable access to these effective interventions. Currently, apart from limited access due to the Religious Freedom Restoration Act, psilocybin and MDMA PAT are only legally accessible through participation in approved clinical trials or through expensive international travel to jurisdictions where psychedelic use is permitted. Domestically, due to most of these compounds being listed as Schedule I, the current alternatives for access are various forms of unregulated psychedelic treatments, which typically come at a cost premium and carry legal and participation risks.

## **Ensuring affordable access to effective healthcare for all those in need of these treatments also supports mental health parity.**

Widespread insurance coverage at adequate rates is needed to build robust provider networks for psychedelic-assisted therapies, starting now with ketamine, and paving the way for MDMA- and psilocybin-assisted therapy following anticipated FDA approval in the coming several years. Ensuring affordable access to effective healthcare for all those in need of these treatments also supports mental health parity, and avoids litigation for noncompliance with the 2008 Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act.

In addition to the significant mental health benefits of PAT, some projected cost comparisons estimate that access to PAT interventions through traditional healthcare plans could save billions of dollars in healthcare expenses and employee absenteeism/presenteeism costs per year in the U.S., assuming sustained treatment efficacy rates (Blossom, 2021).

### **3. Public research dollars should be invested in advancing the field**

While this report concludes that (with continued demonstration of safety and efficacy in FDA clinical trials) psilocybin and MDMA PAT should be available for treatment as soon as legally possible, BrainFutures also supports further investigation of these compounds, as well as ketamine, to advance clinical applications for a broader array of conditions. Additional research is also needed to more thoroughly evaluate the potential applications of LSD, DMT, ibogaine, and mescaline. While private dollars have been responsible for psychedelic research over the last half century, public monies are additionally needed, and immediately, to support further studies into this class of interventions that hold extraordinary promise for some of the most debilitating mental health and substance use conditions.

Private and public investments, philanthropy, and shifts in public opinion over the past several years indicate a growing agreement on the value of PAT. To date, billions of dollars in commercial and private investment (Blossom, 2021) and hundreds of millions in philanthropic investment (Psychedelic Science Funders Collaborative, 2021) have been made in the PAT market. Simultaneously, a growing number of U.S. cities and states are taking legislative action to decriminalize or legalize psychedelic use and/or research, with surveys showing that the majority of Americans favor making psychedelics available for covered medicinal use (Blossom, 2021). State and federal governments owe it to U.S. citizens to join private support and invest in the most promising field of mental health research since the advent of antidepressants.

**BrainFutures envisions a future when the ongoing, high-level cooperation of researchers, regulators, lawmakers, licensed practitioners, and advocates overcomes waning barriers to PAT adoption and PAT becomes a historic, ground-breaking addition to best-in-class mental health and substance use treatments.**

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# Endnotes

1. An additional meta-analysis of animal studies is included in the report's ibogaine section.
2. Major depressive disorder (MDD) may be diagnosed in patients who are experiencing symptoms of depression for at least two weeks, including long-term feelings of hopelessness, sleep issues, anxiety, difficulty concentrating, and even thoughts of suicide or suicide attempts, among other possible symptoms. SAMHSA. (n.d.). Understanding major depressive disorder. U.S. Department of Health and Human Services. <https://www.samhsa.gov/sites/default/files/understanding-major-depressive-disorder.pdf>
3. According to Zhdanava et al. (2021), treatment-resistant depression is typically diagnosed after "Failure to respond or achieve remission after [two] or more trials of medication treatment for MDD of adequate dose and duration." Zhdanava, M., Pilon, D., Ghelerter, I., Chow, W., Joshi, K., Lefebvre, P., & Sheehan, J. (2021). The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. *The Journal of Clinical Psychiatry*, 82(2). <https://doi.org/10.4088/jcp.20m13699>
4. SAMHSA cautions when comparing 2020 SUD numbers with prior years due to several methodological considerations. For more details, see <https://www.samhsa.gov/data/release/2020-national-survey-drug-use-and-health-nsduh-releases>.
5. PTSD prevalence rates in U.S. combat Veterans depend on the research cohort and methodology used.
6. "Off-label use" of a drug is use that is other than what it was FDA-approved to treat. In this case, ketamine is approved for use as an anesthetic, and it is permissible to use it for other applications. Many approved drugs are used under these conditions. For example, while Wellbutrin (Bupropion) is FDA-approved to treat seasonal affective disorder and for smoking cessation, off-label it is used to treat bipolar-related depression, sexual dysfunction, and ADHD.
7. Due to the number of citations, the author of this paper has placed them here in a footnote for easier readability of the report. In-text citations include MedlinePlus, 2022a; University of Illinois, 2021b; MedlinePlus 2022b; Hudson et al., 2012; Fletcher, 2019; Mayo Clinic 2022; Lieber, 2018; Guina et al., 2015; Garcia and Santos, 2021; Connell, Zeier, & Thomas, 2013; Graham, Leckband, & Endow-Eyer, 2009; University of Illinois, 2021a; Mayo Clinic, 2022a; Mayo Clinic, 2022b; Mayo Clinic, 2022c; MedlinePlus, 2017b; Cleveland Clinic, n.d.; MedlinePlus, 2017a; MedlinePlus, 2018; Raskind et al., 2018; and Muench & Hamer, 2010.
8. One of the RCTs reviewed in this report is not peer-reviewed.
9. Two of the open-label studies reviewed in this report are not peer-reviewed.
10. Hofmann was well-known for synthesizing and discovering the psychedelic properties of LSD.
11. One of the open-label studies in this report is not peer-reviewed.
12. Two of the review studies included in this report are not peer reviewed.
13. One of the open-label studies reviewed is the preliminary result of a recent trial and is not peer-reviewed.

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BrainFutures was launched in 2015 by the nation's second oldest mental health advocacy organization, the Mental Health Association of Maryland (MHAMD). For more than 100 years, MHAMD has addressed the mental health needs of Marylanders of all ages through programs that educate the public, advance public policy, and monitor the quality of mental healthcare services. Building on this success, and bolstered by a cross-disciplinary advisory board of leading experts, BrainFutures brings together diverse stakeholders, policy-makers, funders, and influencers to accelerate and scaffold national adoption of effective practices targeting four main areas: youth, workforce, mental health treatment, and older adults. Breakthroughs in our understanding of the brain have the potential to improve learning outcomes for children, optimize functioning at work, enhance treatment for mental health or substance use problems, and maintain sharp thinking as we age.

BrainFutures writes evidence-based issue briefs and releases recommendations that fill knowledge gaps related to brain-focused applications targeting the above segments of society. These educational resources highlight the latest advances in brain plasticity and how their application is transforming quality of life for people of all ages. Through this process, we not only gain insight from experts and innovators, we also foster support for change, building coalitions and cross-disciplinary collaborations to advance both adoption and access to new breakthrough applications. Ultimately, by informing the public, cultivating influential relationships, and connecting communities of diverse advocates we help propel the change that is needed to make meaningful progress.

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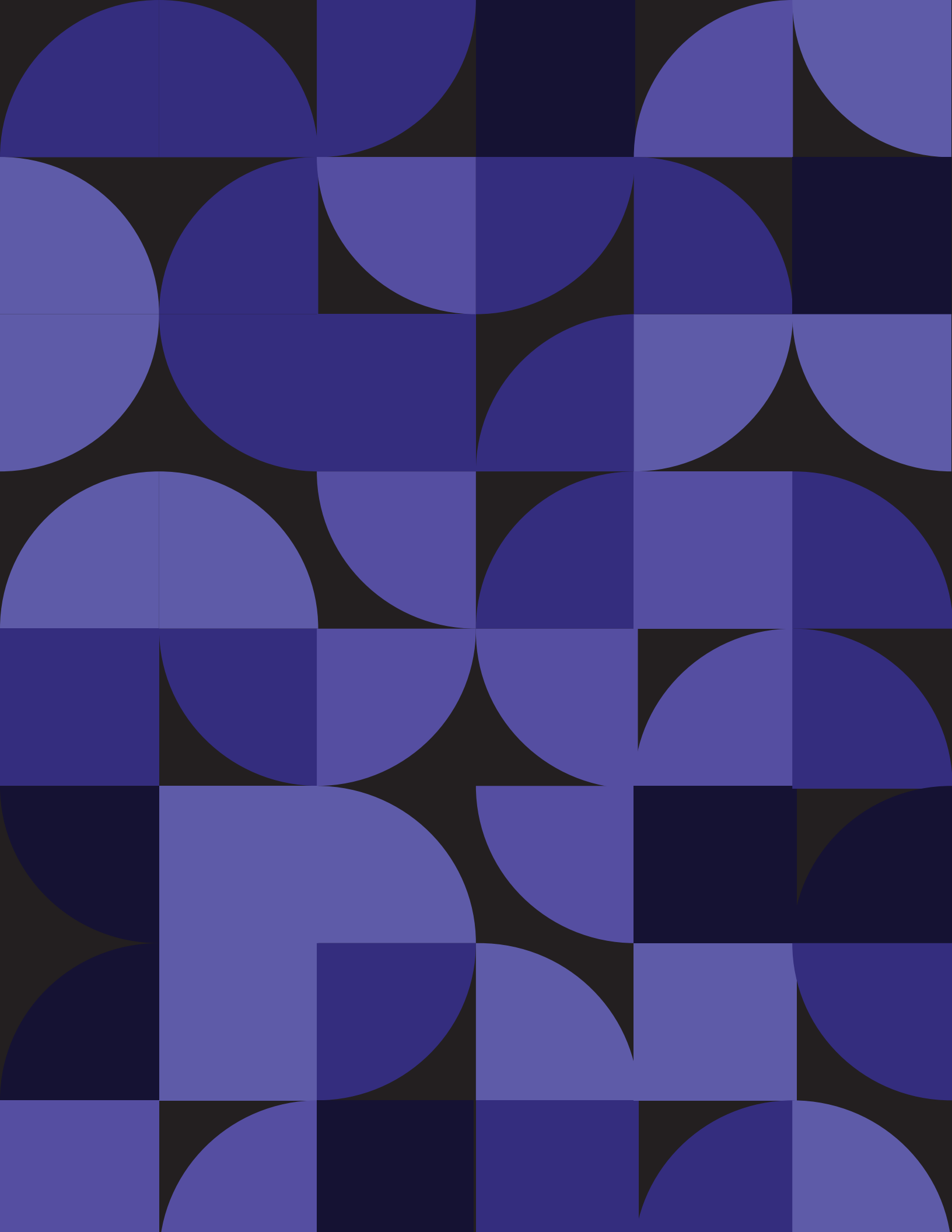
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