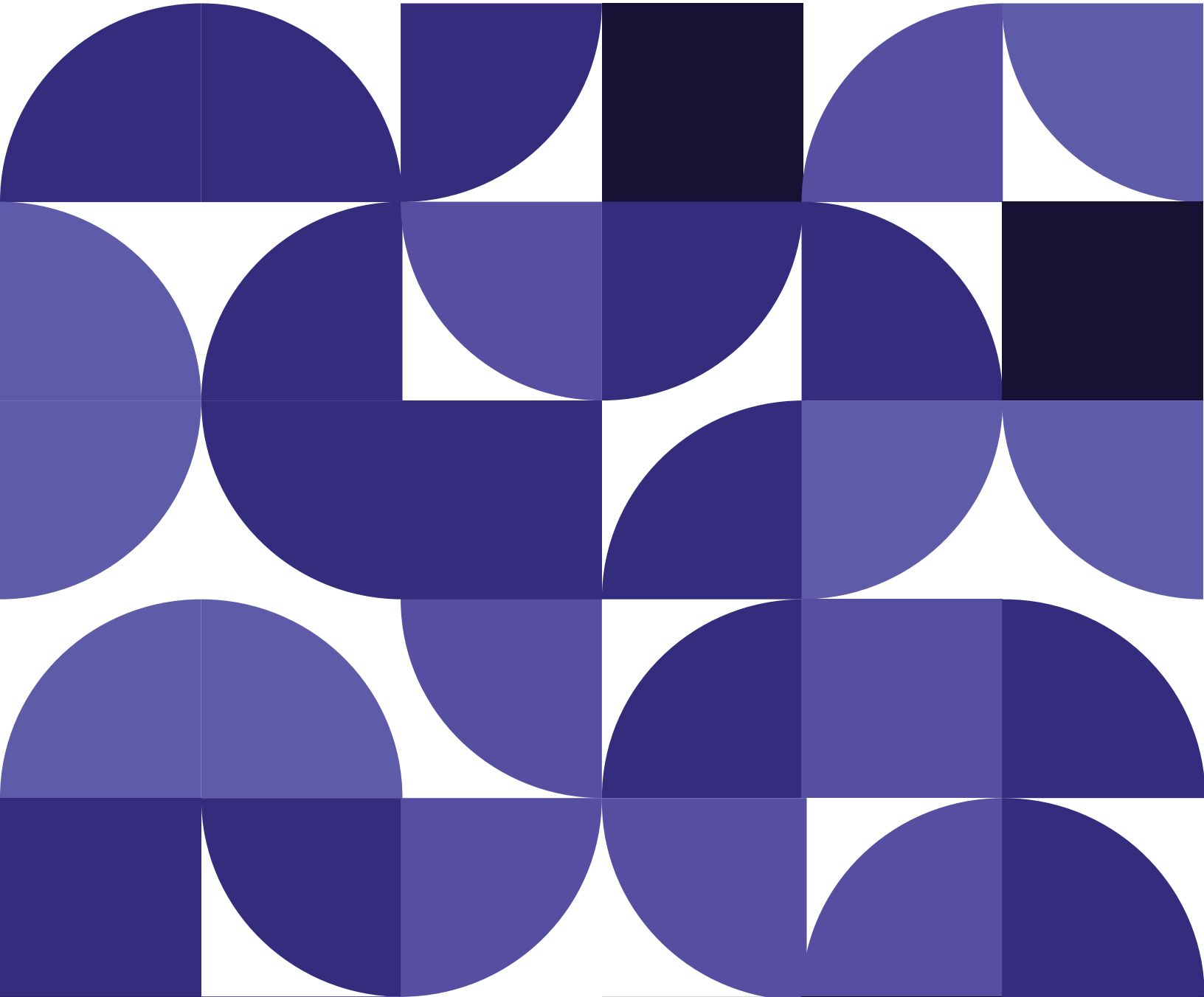
BRAINFUTURES

Psychedelic Medicine

Executive Summary



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Executive Summary

Psychedelic-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

THIS REPORT SUMMARIZES

46

RANDOMIZED CONTROLLED TRIALS

47

OPEN LABEL STUDIES

8

META-ANALYSES

84

REVIEWS

=4,650+

STUDY PARTICIPANTS INVOLVED

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[1] 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:

1. An additional meta-analysis of animal studies is included in the report's ibogaine section.

- 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

While 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

Increases 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

Taking 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.

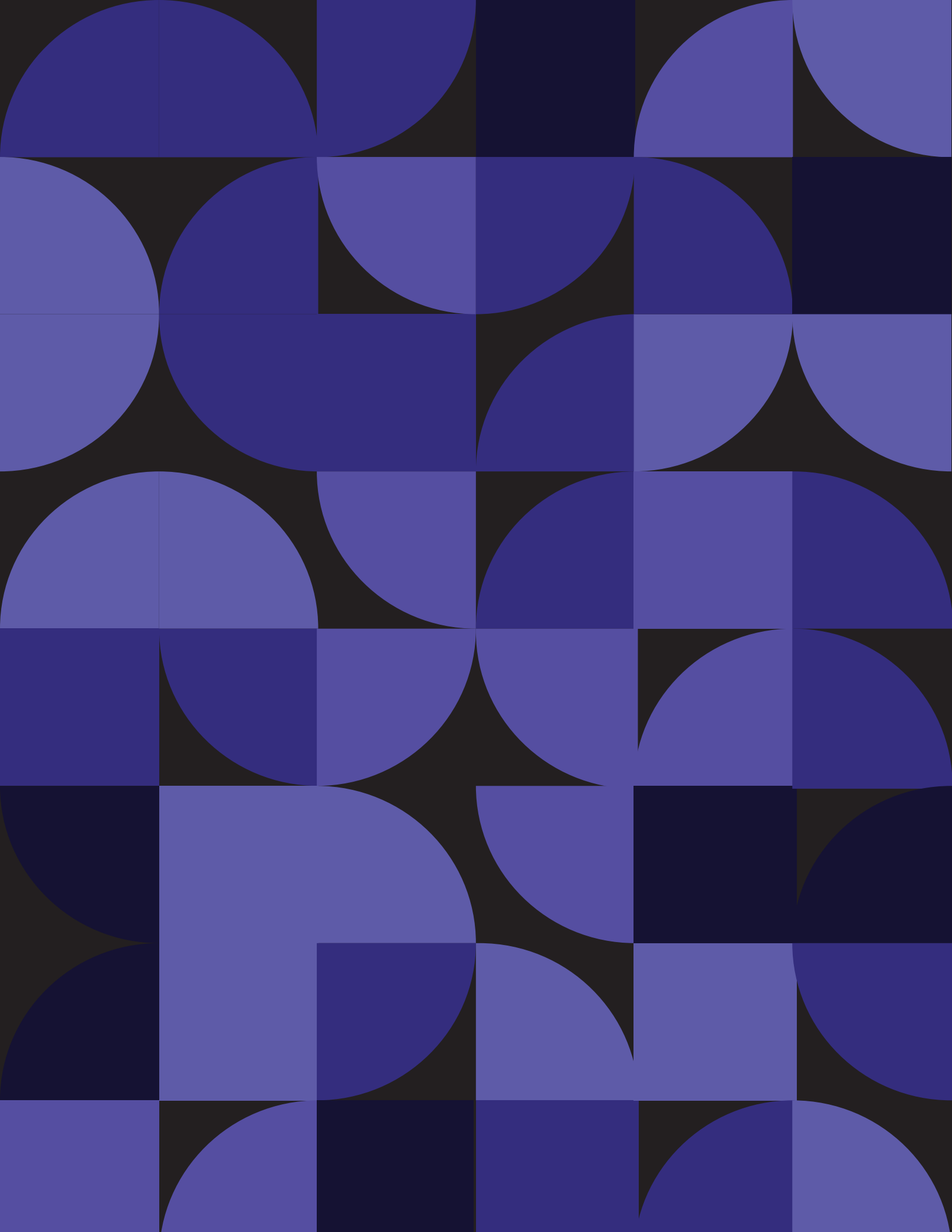
2. Reimbursable and equitable access to approved psychedelic therapies is essential and all payers should adequately cover PAT treatments.

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 healthcare-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.



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