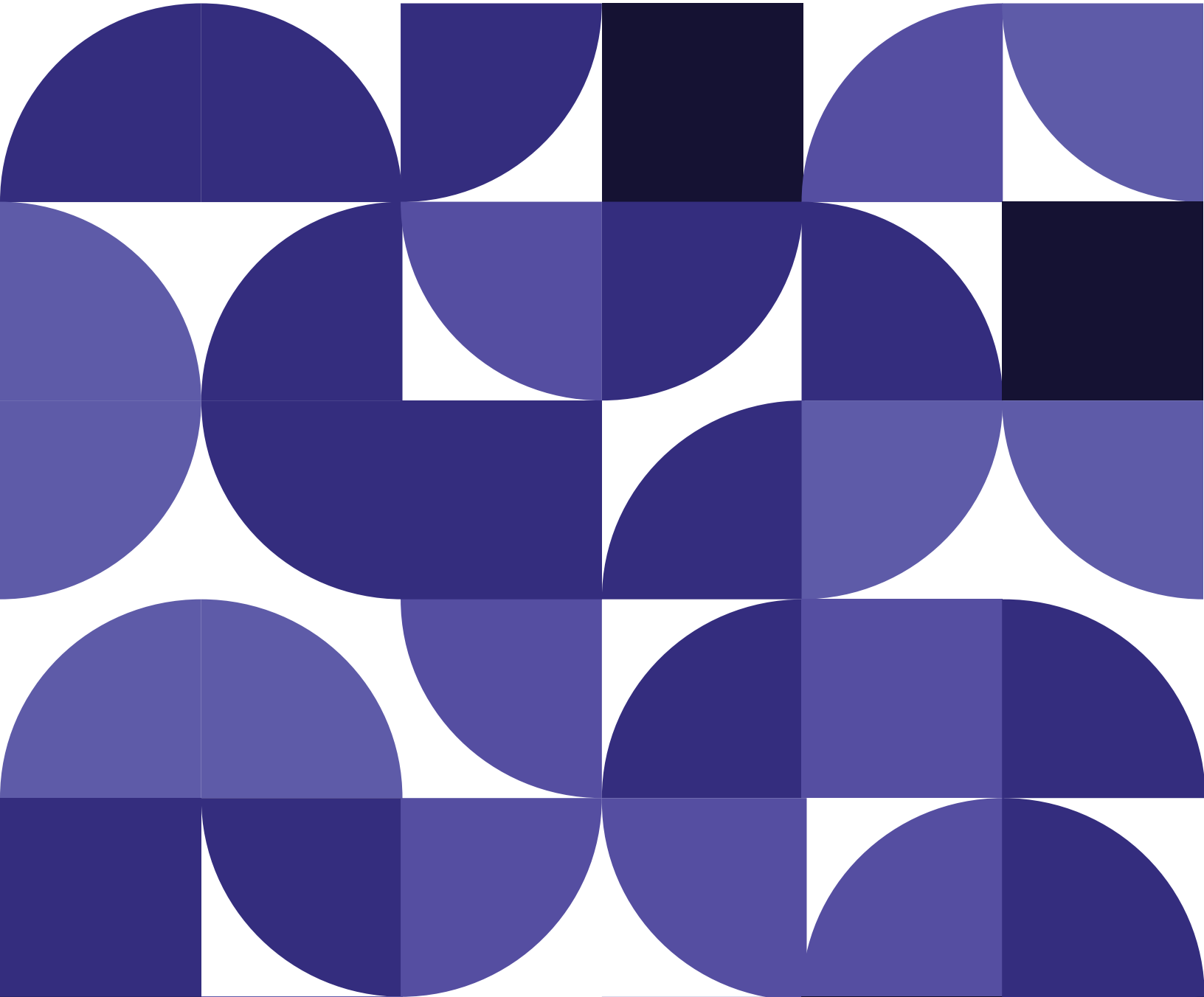
BRAINFUTURES

Psychedelic Medicine

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



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Psychedelic Medicine Clinical Research Summaries

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

BRAINFUTURES

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[8] and 16 open-label studies[9] 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.

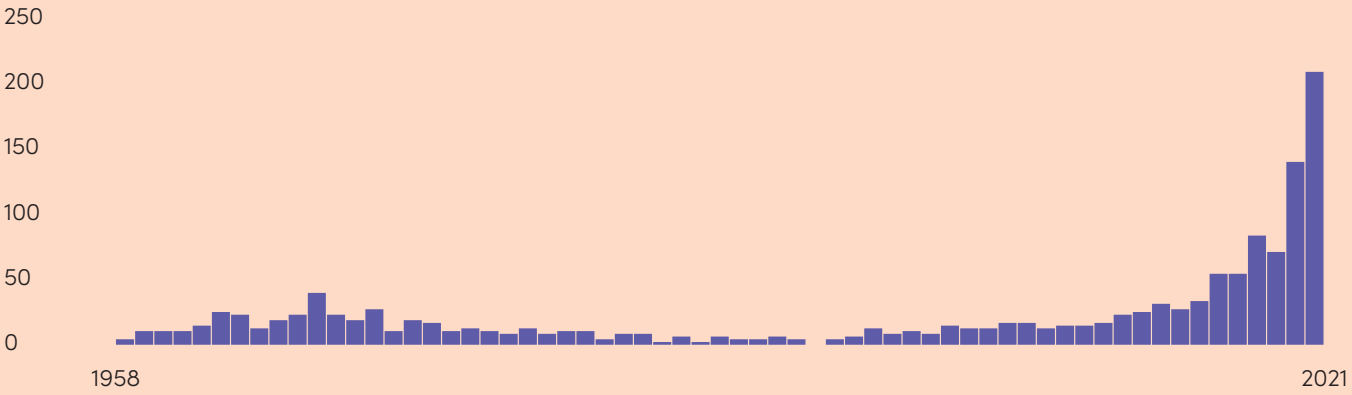
In addition to research on TRD and MDD, ongoing studies are exploring psilocybin as a treatment for a number of other conditions. The clinicaltrials.gov database shows these conditions include headaches (migraine, concussion, chronic cluster, and short-lasting unilateral neuralgiform headache attacks), 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

The 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, Olemec 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 amatuer 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).[10] 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).

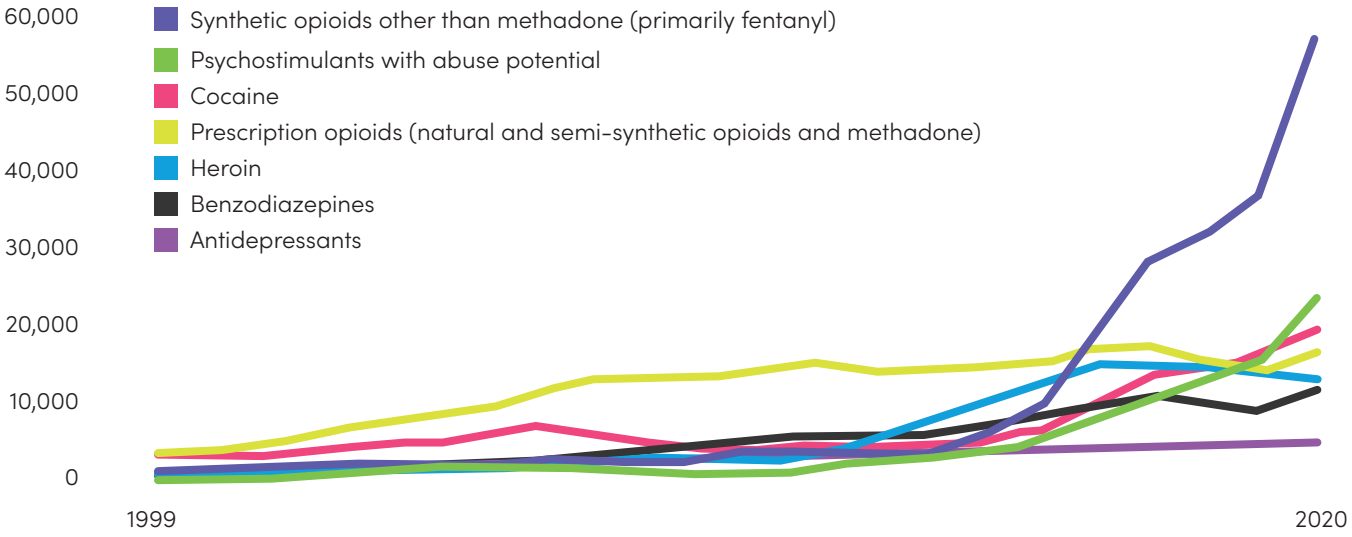
As demonstrated in studies overviewed below, the revival in research over recent years has been more clinically rigorous compared to the early experiments. Modern studies focus on both the effects of the experience and the neurological activity of psilocybin as mechanisms for effecting positive changes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

According 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:

> "TEAEs [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, Bolstrige 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

Defining 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. More so, 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-Liebes 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

Beyond 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-HT2A 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-HT1A 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.

BRAINFUTURES

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, policymakers, 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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