PSYCHCEs

Evaluating the Therapeutic Value of Psychedelics

Introduction

Emerging research shows the potential benefits of psychedelics in treating behavioral health disorders such as depression, anxiety, PTSD, addiction, and more. As a result, several prestigious universities and medical schools are dedicating resources to research in this area. Many speculate that this will be the next significant trend in behavioral health treatment.

The term psychedelic comes from the Greek words *psyche* (soul or mind) and *delein* (to manifest). Psychedelics have been used in ceremonial rituals for thousands of years and worldwide across numerous cultures. Clinical research into their effects had promising results in the 1950s and 60s. Unfortunately, the United Nations banned psychedelics almost entirely worldwide in 1971; even scientific research fell under the ban, halting any progress. Since the early 1990s, there has been a renaissance in psychedelic clinical research. This new research has shown the efficacy and safety of psychedelics in treating a range of psychological diagnoses (Luoma et al., 2019).

History

Research on psychedelics has been divided into three periods. The first wave of psychedelic research (1890–1940) was marked by the discovery of mescaline by Western science. The second wave (1940–1970) was marked by the synthesis of lysergic acid diethylamide and psilocybin. While this second wave is when clinical research took off, it did have its limitations that impacted many early clinical studies, such as a lack of validated clinical scales, absence of randomization, and limited controls. Despite this, these early researchers were able to show efficacy in the psychedelics they were studying. However, with the rise of the counterculture, Vietnam War protests, and the use of psychedelics as recreational drugs, the UN declared LSD and other similar substances a health and security risk and imposed the need for strict regulation. Regardless of the early research showing that psychedelics were mostly non-addictive and had potential therapeutic benefits, the United States Drug Enforcement Agency classified them as Schedule I substances (having no accepted medical use and a high potential for dependence) in 1970. This ban made it difficult for clinicians and researchers to prescribe them and led to the termination of psychedelic research in many countries, not only in the United States. The third wave of psychedelic research began in the 1990s in Germany, Switzerland, and the United States. These early third wave studies focused on establishing the safety of psychedelics on healthy volunteers

and led to more extensive clinical trials being approved. As we continue to ride this third wave of psychedelic research we are seeing the wide range of mental health diagnoses psychedelic-assisted therapy can treat safely and successfully (Luoma et al., 2019).

While the United States federal government does not recognize a medical use for most psychedelic drugs and continues to claim they have a potential for abuse, many universities now have permission to study psychedelics and use them in clinical trials with human volunteers. They are showing promising results for alternative treatments for several physical and mental disorders. Armed with these studies and anecdotal stories, advocates are calling for legalization. Their work has seen changes on individual state levels, with several states approving medical marijuana (37 States as of May 2022), and 27 States have decriminalized marijuana, while 19 have fully legalized it for recreational use. In addition, Oregon has recently passed a law to legalize psilocybin mushrooms. Despite this progress, psychedelics are expensive and difficult to acquire legally unless one is part of a clinical research trial (Eschner, 2022, DISA, 2022).

Types of Psychedelics

Psychedelics are divided into two categories: classic psychedelics, and non-classic psychedelics. Classic psychedelics are serotonin-receptor agonists, which include LSD, psilocybin, mescaline, and DMT (Luoma et al., 2019). These substances have long been known to produce perceptual disturbances and are derived from plants (i.e., ayahuasca brew or peyote) or fungi (i.e., ergot or psilocybin mushrooms). While many of these plants and fungi have been utilized for their ceremonial, religious, and healing value for centuries and still are in some cultures, they are illegal in many countries. Other psychedelic substances that have been researched for therapeutic purposes are usually classified as non-classic psychedelics, such as MDMA, which is a psychedelic and a stimulant; ketamine and ibogaine, which are psychedelics and dissociatives; or cannabis, which only has mild psychedelic effects (Luoma et al., 2019).

Classic Psychedelics

Typically, classic psychedelics are found in nature and have been used for centuries for religious, healing, and indigenous rituals. They are not known to be addictive or to have long-term negative effects. Classic psychedelics are serotonergic psychedelics because they achieve their effects by affecting the serotonin receptors in the brain, specifically the serotonin 2A (5-HT2A) receptor (Nichols & Hendricks, 2020).

Psilocybin

Psilocybin is the active chemical in "magic mushrooms." They have been used in religious and healing rituals in Mexico and other Central American countries for over 3000 years. When ingested, psilocybin causes alterations to a person's perceptions, emotion, and thought, leading to its classification as a hallucinogen or psychedelic drug. When taken orally, the effects begin after 30 minutes and are at their peak after 1-2 hours, and effects can then be felt for another 1-2 hours. Interest (and financing from private entrepreneurs) in psilocybin continues to grow with increased clinical studies and Oregon legalizing them in 2020 (although the law does not appear to be going into effect until 2023).

Potential mental health uses: In clinical trial research, psilocybin is administered in pill form to have consistent dosing versus its natural mushroom form. The research is finding it has the potential to treat substance use disorders, depression, and mood disorders in cancer patients. In addition, new research is studying it to treat PTSD, OCD, eating disorders, type 2 bipolar disorder, cluster migraines, and numerous other mental health diagnoses.

What it does: Psilocybin is metabolized into psilocin which activates serotonin 2A receptors and causes the change in consciousness a person experiences. Participants in trials report a sense of euphoria and increased awareness of their environment, with positive feelings lasting for months afterward.

Risks: Clinical trials with psilocybin are safe with no risk for drug abuse, no long-term change in perception, and no long-term psychosis or other change in functioning. Unpleasant effects that may be experienced during a dosing session include dizziness, disorientation, nausea, flushing, increased heart rate, and elevated blood pressure. Side effects reported within 24 hours of ingesting included headaches or head pain, fatigue, lack of energy, a "gone" feeling, lack of appetite, difficulty concentrating, and heavy or tired legs. Psilocybin can cause feelings of panic and anxiety and distressing hallucinations in some patients, so it is essential to have a trained therapist or guide with the participant (Eschner, 2022, Guss et al., 2020).

LSD (lysergic acid diethylamide)

LSD was created in 1938 by Albert Hofman, a Swiss chemist, to treat respiratory depression. In 1943 he discovered it was also a hallucinogenic after accidentally absorbing some topically on his skin. It was initially marketed as anesthesia and as a

drug to support psychoanalysis. However, as it became more popular in counterculture as a recreational drug, violent side effects or psychotic episodes were reported. It was then banned in the United States in the late 1960s and declared a Schedule 1 drug. LSD is a semi-synthetic drug that combines natural substances derived from ergot, a fungus that grows on rye and other cereal grains, and man-made non-organic chemical diethylamide. It is odorless and colorless, and a minuscule amount is sufficient to experience its hallucinogenic effects. Hallucinations typically begin within 60 minutes of ingestion and can last from 6 to 12 hours.

Potential mental health uses: LSD has shown promise for treating alcohol addiction and has been studied for other conditions such as depression, ADHD, pain management, and anxiety related to a life-threatening illness. Positive effects are a feeling of well-being, enhanced insight towards creativity, problem-solving, discovering a purpose, and mystical experiences.

What it does: LSD is an agonist at most serotonin receptors and can also cause modulation of the serotonergic, dopaminergic, and glutamatergic systems. After ingesting LSD, people report feelings of bliss, being able to see sounds, having mystical experiences, and a sense of closeness with others. LSD changes a person's perceptions, often involving the senses, thoughts, and emotions. Visual changes include brightened and more vivid colors, distorted shapes and coloring of objects and faces, blurred vision, and halos of light. Changes related to touch include pressure, shaking, and lightheadedness. Mood changes can lead to a sense of euphoria, peacefulness, bliss, dreaminess, heightened awareness, despair, anxiety, confusion, and rapid mood swings. Cognitive changes can involve a distorted perception of time, such as moving fast or slow, unusual insight, terrifying or accelerated thoughts, and a sense of transcendence. Physical reactions may include dilation of pupils, increased heart rate, increased blood pressure and a rise in body temperature, dizziness, sleeplessness, reduced appetite, dry mouth, sweating, numbness, weakness, and tremors.

Risks: A bad “trip” has caused some people to experience lasting psychological trauma. This is more likely to happen when someone takes a higher dose or uses LSD often. In a negative experience, individuals may experience paranoia, extreme fear, or a separation from self, and they may even believe that they are dying or in hell. In addition, it can trigger panic attacks, psychotic episodes, disturbing anxiety, paranoia, pain, schizophrenia, flashbacks, and a feeling of dying or going insane (Eschner, 2022, Davis, 2017).

Mescaline (Peyote)

The peyote cactus gets its common name from the Nahuatl language. The plant, Lophophora williamsii, is a small, button-shaped cactus that grows in the southern parts of the U.S. and Mexico. Native Americans have used peyote in their sacred ceremonies for thousands of years, specifically for its hallucinatory effects. Over 40 first nations tribes in the United States and Canada still use it in their sacred religious ceremonies. While the ritual varies from tribe to tribe (and may or may not include other spiritual aspects such as chanting, meditation, or cleansing ceremonies), the peyote is viewed as a sacred communion or religious sacrament.

Like other classic psychedelics, mescaline interacts with the 5-HT2A receptors in the brain, which impact how the body uses serotonin. Mescaline can be ingested by eating the dried crowns of the peyote cactus, boiling the cactus to make tea, and taking capsules containing peyote or mescaline. Once ingested, the effects may begin within an hour and can last for approximately 12 hours.

Potential mental health uses: Agins-Liebes et. al., (2021) surveyed 452 international respondents who met diagnostic criteria for depression, anxiety, post-traumatic stress disorder, alcohol or drug use disorders, and had an experience taking mescaline. Most reported improvements in mood, anxiety, and substance use disorders. Those who reported higher levels of improvement also described experiences of mystical-type, psychological insight, and ego dissolution effects.

What it does: Most people experience vivid hallucinations that affect multiple senses or a mixing of the senses. The hallucinogenic effects of mescaline appear to enhance colors and sounds, making everything feel richer and bolder. Others report a change in their field of vision, and the shifting and changing of solid objects. Visions are common with mescaline, especially when higher doses are taken. These visions feel very real to the person experiencing them, but they are not truly happening. These visions may be joyful or terrifying, meaningful or chaotic. They can also involve negative feelings, experiences, and emotions. Due to their altered perception of time, individuals may have severe anxiety or feel trapped within a negative loop or experience. Additionally, they may behave in ways that are not typical for them. Experiences, good and bad, are temporary, and the effects will fade as the body processes the mescaline out of the system.

Risks: Ingesting peyote may cause temporary physical reactions within the body, such as increased heart rate, numbness, tension, increased blood pressure, fever, chills, muscle weakness, headaches, dilated pupils, nausea, vomiting, sweating, and shivering.

Occasionally people report momentary flashbacks at a later time. These flashback moments can be small recall moments to vividly re-feeling the trip.

Overdosing is rare, and complications that require treatment generally involve problematic symptoms, such as dehydration from fever or vomiting. As with all hallucinogens, there is a concern for ongoing mental problems and disturbances called persistent psychosis. However, this is very rare (Johnson, 2020).

DMT (Dimethyltryptamine, Ayahuasca)

DMT is a hallucinogenic tryptamine drug that occurs naturally in many plants and animals. It is the active ingredient in the traditional South American brewed tea, ayahuasca. In addition, it has been used in religious rituals for centuries for its spiritual insight. DMT is also called the "spirit molecule" due to the intense psychedelic experience. It produces a brief but intense visual and auditory hallucinogenic experience. DMT is a white crystalline powder derived from a family of plants found in Mexico, South America, and parts of Asia, i.e., *Psychotria viridis* and *Banisteriopsis caapi*. It can be consumed by vaporization, be smoked in a pipe, or ingested orally in brews like ayahuasca. When smoked, the onset can be felt almost instantly. The effects peak for 3 to 5 minutes and gradually drop off with the duration of the effect totaling 30 to 45 minutes. When consumed as a tea, the effects begin in 30 to 45 minutes, peak after 2 to 3 hours, and are over in 4 to 6 hours (Porteous-Sebouhian, 2021).

Potential mental health uses: The first clinical trials to treat depression with DMT were conducted in January 2021 by the Centre for Psychedelic Research at Imperial College London. They have found that the DMT assists the brain in making new connections, breaking the ruminative and depressive thought process, and potentially undoing the triggering stress or event. In addition, there are none of the side effects that come with traditional antidepressants, and one session can see results that last three to six months. Additional ongoing studies are exploring its use in treating mood disorders, PTSD, and substance use disorders (Porteous-Sebouhian, 2021).

What it does: The psychological effects of DMT include euphoria, intense visual and auditory hallucinations, and an altered sense of space, time and body. People often report profound, life-changing experiences and complete shifts in their identity and reality. Some describe visiting other worlds, experiencing alternate realities, or near-death experiences.

Risks: Because DMT is structurally related to serotonin, it does have the potential to cause serotonin syndrome, particularly for those using antidepressants. Serotonin syndrome happens when the body accumulates an excessive amount of serotonin and is usually caused by taking a combination of different drugs. Too much serotonin can cause a range of symptoms, including agitation, confusion, high blood pressure, loss of muscle coordination, and a headache. Potential side effects from DMT include increased heart rate, increased blood pressure, chest pain or tightness, agitation, dilated pupils, rapid rhythmic movements of the eye, dizziness, nausea, vomiting, and diarrhea. In addition, DMT can cause seizures, respiratory arrest, and coma if a high dose is consumed. DMT could have serious consequences for those with pre-existing psychological problems or a mental illness, such as schizophrenia (Davis, 2017).

Non-Classic Psychedelics

Non-classic psychedelics tend to be synthetic, lab-created drugs. While they may impact the serotonin receptors, they also act on other neurotransmitters.

Ketamine

Ketamine was created in 1956 and is used as an anesthetic by veterinarians and in emergency or combat medicine. It is the one psychedelic that's never been illegal, hence researchers have been able to explore ketamine's potential as a mental health treatment and build a case for its use in humans. Ketamine is a dissociative drug.

Potential mental health uses: Many brain disorders are characterized by atrophy in the prefrontal cortex (schizophrenia, depression, and anxiety). There is strong evidence, though more research is needed, that ketamine promotes regrowth over time in neurons in the prefrontal cortex of people with psychiatric disorders. That may explain the near-immediate feelings of relief that users report, making it a successful treatment option for some suicidal patients. Esketamine is a form of ketamine that is more potent and can be taken intranasally, instead of intramuscularly or intravenously, which is how ketamine is usually administered. It has shown promise for treating major depression and treatment-resistant depression at a faster rate than other drugs, leading the FDA to approve its limited use in early 2019. Ketamine is currently being used to treat pain, major depressive disorder, mood disorders, addiction disorders, and PTSD.

What it does: Ketamine can create a sense of euphoria and detachment from reality. Blurred vision or hallucinations are common. At low doses, individuals may feel as if they

are floating or their body is numb. At a higher dose, people may temporarily be clumsy, forget where they are, or even who they are.

While most psychedelics operate by affecting the serotonin receptor (impacting mood and happiness), ketamine works differently. Ketamine affects the brain receptors that impact learning and memory. Both types of receptors are found in the prefrontal cortex of the brain, so this may explain why ketamine and other psychedelics have similar impacts on mental health. The prefrontal cortex communicates with all other brain regions and regulates mood, emotions, fear, and reward. Ketamine is an NMDA receptor antagonist, meaning it blocks the excitatory signaling of glutamate.

Besides its primary purpose as anesthesia, it can also be used as an analgesic, anti-obsessional, and antidepressant. It possesses neuroprotective and neuroplastic properties. The effects of ketamine on a person are dependent on the route of administration and dose, and the results can range from a slight perceptual disruption to paralysis and full dissociation to sedation.

Ketamine is used to treat mental health symptoms in one of two ways. The first, pharmaceutical or biochemical, is administered by a doctor to relieve psychiatric symptoms. The drug works through neurobiological mechanisms to provide symptom relief for up to two weeks. Without being offered any talk therapy or support, this may lead to dependence on ketamine to relieve symptoms. Long-term use can lead to kidney and bladder toxicity. In Ketamine-assisted therapy, there are two methods of treatment options. In the first, a low to moderate dose of ketamine is given to alter consciousness and facilitate psychotherapy, and while undergoing the ketamine experience the person is actively talking with a therapist. In the second treatment approach ketamine is given at a higher dose and the person experiences a major shift in perceptions typical of a classic psychedelic experience. The individual may have a mystical-type experience or feelings of ego dissolution. The person needs to be well prepared prior and receive support during and after this second type of treatment approach. Depending on the treatment approach, immediately after the ketamine effects dissipate or in the days or weeks afterwards, the person attends therapy to examine the experience. The goal of the process is to stabilize the positive behavioral changes, consolidate psychological material, resolve psychological issues, improve relationships, catalyze new insights, and enhance self-awareness. KAP is presumed to amplify the neurobiological properties of ketamine by addressing underlying psychological issues and bolstering transformational healing (Eschner, 2022; Psychedelic Support, 2022).

Risks: Ketamine is known for a specific and frightening side effect nicknamed the “k-hole.” While this is rare in clinical settings as the dose of ketamine is limited and the person is monitored, it can be a terrifying experience as individuals feel disassociated from themselves and their surroundings, including being unable to move or talk, leading to panic or feeling paranoid. Other negative effects may include anxiety, paranoid delusions, loss of coordination, disorientation, muscle trembles, psychotic episodes, psychological distress, and loss of airway function. When treating those with PTSD, traumatic memories may arise, and without proper support, these experiences can be harmful rather than therapeutic. (Eschner, 2022; Psychedelic Support, 2022).

MDMA (3,4-methylenedioxy-methamphetamine)

MDMA is a synthetic drug created in 1914 as an appetite suppressant. In the 1970's it was used as part of some psychotherapy treatments. It is an empathogen, meaning it increases an individual's feeling of empathy and compassion toward others. MDMA is commonly known as ecstasy. It gained popularity in the 1980s as a party drug, known for creating a sense of euphoria, intimacy and emotional warmth, increased energy, sensitivity to touch, and a distortion of time and of the senses. Effects last for 3-6 hours, but some withdrawal-type side effects may last for a week. These side effects can include insomnia, confusion, irritability, anxiety, depression, impulsiveness, aggression, decreased interest in sex, memory and attention problems, and reduced appetite (Eschner, 2022, Davis, 2017; Psychedelic Support, 2022).

Potential mental health uses: Interest in MDMA research was renewed in 2010 when the results from a study on treatment-resistant PTSD were published. Additional clinical trials have explored MDMA's potential as a treatment for other conditions like substance use disorder, social anxiety in autistic adults, anxiety related to life-threatening illness, anorexia nervosa, and binge eating disorders (Eschner, 2022, Davis, 2017; Psychedelic Support, 2022).

What it does: MDMA is an amphetamine derivative; it is often known by its street name, ecstasy, for the feeling of euphoria and connectedness it promotes in users. This feeling leads it to be classified as an empathogen (generating a state of empathy) or entactogen (generating relatedness) drug. It stimulates the release of neurotransmitters (serotonin, dopamine, and norepinephrine) and hormones (oxytocin, vasopressin, cortisol, and prolactin). The person may experience euphoria, heightened awareness and sensory perception, feelings of expansiveness, feelings of oneness and connection with others

and the universe, increased energy and alertness, and empathy (Eschner, 2022, Davis, 2017; Psychedelic Support, 2022).

Risks: MDMA can cause arrhythmia, cardiac collapse, hyperthermia, dehydration, and lasting kidney and organ damage, especially in people with related pre-existing conditions. MDMA causes a surge in serotonin during the trip but then leaves the body depleted, and it may take the brain days or weeks to replenish the neurotransmitter (Eschner, 2022, Davis, 2017; Psychedelic Support, 2022).

Ibogaine

Ibogaine is derived from the West African shrub Tabernanthe iboga. It is a psychoactive alkaloid that, in small doses, acts as a stimulant, while larger doses produce a psychedelic experience. Historically it was used in healing ceremonies and initiations in the Bwiti religion in Western Africa. It was used in France as an antidepressant and stimulant from the 1930s-1960s. It has been found to reduce withdrawal symptoms from opiates, alcohol, nicotine, and psychostimulants and temporarily eliminate substance cravings. Ibogaine's use to treat addictions seems to have been found accidentally in 1962 when heroin user Howard Lotsof tried it recreationally and found that his desire to use heroin was gone after his experience with ibogaine. Although he had several friends try it with similar results, at the time, he could not convince anyone to research the drug, as it was classified as an illegal substance. It takes 30-180 minutes for the onset of high and then the person tends to progress through different stages beginning with a visionary phase that lasts 4-8 hours, an introspective phase that lasts 8-20 hours followed by a stimulatory phase of 24-72 hours. Current treatment and research are in countries where it is legal such as Mexico and New Zealand (Noller et al., 2018; Psychedelic Support, 2022).

Potential mental health uses: Ibogaine is not only seen as a treatment for substance use, but it has also had positive results with PTSD, mood disorders, and anxiety. In addition, studies of ibogaine treatment of substance use have shown a reduction in withdrawal symptoms, reductions in drug cravings and use, and with some, a complete cessation of drug use (Noller et al., 2018; Psychedelic Support, 2022).

What it does: During treatment, ibogaine allows the evocation and reprocessing of traumatic memories and brings about therapeutic and meaningful visions of spiritual and autobiographical content, which are of central relevance in addressing PTSD-related psychological content (Noller et al., 2018; Psychedelic Support, 2022).

Risks: The primary adverse effects of ibogaine include cardiovascular effects (e.g., Q-wave/T-wave interval prolongation, bradycardia, arrhythmias, and in rare cases, sudden cardiac death), ataxia, nausea, and vomiting, and psychological effects (e.g., auditory and visual hallucinations, re-experiencing traumatic memories, acute fear, distress, or guilt). Due to these cardiac risks, a medical screening that includes an ECG/EKG is extremely important, as there have been reports of death. (Noller et al., 2018; Psychedelic Support, 2022).

Cannabis

Cannabaceae is a flowering plant that has a range of psychoactive effects varying by species. There is historical evidence that it has been used for its mental health effects for centuries. A Chinese medicinal book describes its use between 200 BCE and 200 CE as an anti-senility herb; in Assyrian culture, it was documented to be used for grief and sorrow; and in 1500 BCE in India, it was used for its anti-anxiety properties. Research is exploring what the different phytocannabinoid effects are and what combinations may have specifically indicated therapeutic uses. While there have been numerous studies on the efficacy of cannabis for physical conditions (reducing pain, muscle spasticity, chemotherapy-induced nausea and vomiting, and unmanageable childhood epilepsy), the research has been limited on its use for treating psychological conditions (Saris et al., 2020; Psychedelic Support, 2022).

Potential mental health uses: CBD has shown to reduce social anxiety, and ongoing studies are looking at CBD/THC combination ratios to best treat generalized anxiety disorder. THC use appears to help those with PTSD by improving mental health, coping, and improving sleep. THC and CBD have been shown to reduce insomnia, particularly when they are linked to pain, anxiety, and PTSD. Cannabis use does appear to help adults with ADHD, but much of this is anecdotal and more studies with higher numbers of research participants are needed. High levels of THC use do appear to worsen depression (Saris et al., 2020; Psychedelic Support, 2022).

What it does: The endocannabinoid system has been found to be a modulator of anxiety and mood, with recent data showing that cannabinoids may interact with specific brain regions, including the medial prefrontal cortex, amygdaloid complex, bed nucleus of stria terminalis, and hippocampus while also influencing the hypothalamic-pituitary-adrenal axis, immune system activation, and neuroplastic mechanisms (Saris et al., 2020; Psychedelic Support, 2022).

In cannabis-assisted therapy, a person consumes cannabis with the goal of exploring emotions, thoughts, and sensations under the guidance of a therapist. A person may find it easier to work through difficult emotions under the relaxing effects of cannabis which may allow them to have a different self-view point (Saris et al., 2020; Psychedelic Support, 2022).

Risks: The main risk factors observed in clinical trials were coordination problems, dizziness, disorientation, euphoria, drowsiness or fatigue, dry mouth, nausea, and gastrointestinal upsets. Long-term use can lead to respiratory issues. It can cause anxiety, panic attacks, or paranoia for some people. There is an increased risk of psychosis or worsening of schizophrenia symptoms for those at high genetic risk (Saris et al., 2020; Psychedelic Support, 2022).

Therapeutic Uses of Psychedelics

Cancer-related psychological distress

Anxiety affects 40% of those diagnosed with a life-threatening disease (which is where a vast majority of the research has been focused). The anxiety can manifest as apprehension regarding future danger or misfortune, feelings of dysphoria or somatic symptoms of tension, and often coexists with depression. It is linked to decreased quality of life, reduced treatment adherence, prolonged hospitalization, increased disability, and hopelessness, all of which lead to reduced survival rates. The pharmacological and psychosocial interventions that are used to manage this type of anxiety have limited efficacy, and as such, they often fail to provide satisfactory emotional relief (Muttoni et al., 2019).

A study of 51 patients with life-threatening cancer diagnoses, who also had depression or anxiety, found that high-dose psilocybin, when given with psychological support, improved symptoms and quality of life. At the six months follow-up, about 80 percent of participants continued to show clinically significant decreases in anxiety and depressed mood (Marks, 2022).

A small study with 12 participants found that LSD-assisted psychotherapy lessened illness-related anxiety among people with a life-threatening diagnosis. At the one-year follow-up after treatment, researchers found that those decreases in anxiety had lasted (Marks, 2022).

Depression

Depression is a multifaceted condition with varying ranges of severity, characterized by episodes of mood disturbances and other symptoms such as anhedonia, psychomotor complaints, feelings of guilt, and suicidal tendencies. According to the World Health Organization, depression affects over 350 million individuals and is the leading global cause of disability. The discovery of mainstream antidepressants has largely revolutionized the treatment of depression, but up to 60% of patients remain inadequately treated. This is often due to antidepressants' delayed therapeutic effect, side effects leading to non-compliance, or inherent non-responsiveness to them (Muttoni et al., 2019).

In a small study comparing 15 adults with Major Depressive Disorder to a waitlist control group of 12 adults who received no treatment, researchers reported that two doses of psilocybin, given with supportive psychotherapy, significantly reduced depressive symptoms. During the four-week follow-up over half of the study participants were in remission (Marks, 2022).

A 2022 published study of a small group of participants with depression found that among those who received supportive therapy and two doses of psilocybin, 75% still had some response to the treatment and 58% were in complete remission from depression. Another study reviewing National Survey on Drug Use and Health data found that psilocybin use was linked with a reduced risk of major depressive episodes (Law, 2022).

A study published in Nature Medicine revealed that psilocybin appears to increase the brain's neuroplasticity, the ability for neural networks to shift and rewire. Researchers found that it helped to build more connections between different parts of the brain, while also reducing interactions between brain areas connected with depression, therefore seeming to reduce patients' depressive symptoms (Law, 2022).

A small 2018 study found intranasal esketamine, administered in conjunction with conventional antidepressant treatment, reduced depressive symptoms and suicidal thoughts significantly in patients with depression and high suicide risk. In another study, ketamine given with standard antidepressant treatment was found to significantly reduce suicidal thoughts and behaviors within 24 hours among people with depression who were at risk of suicide (Marks, 2022).

In March 2022 researchers released results they found looking at 537 people who had received ketamine assisted therapy in a clinical setting between 2016 and 2020. They

found that more than half of them experienced an an improvement in their symptoms and almost 30% were in remission. 73% of people with suicidal thoughts and behaviors reported a decrease in these symptoms. The researchers noted that there were some negative side effects for some; 8% of people experienced worsened depression, and 6% reported increased suicidal thoughts or behaviors after starting ketamine therapy (Marks, 2022).

Addictions - Alcohol

In a trial for alcohol dependent participants, those who received up to 2 doses of psilocybin with motivational enhancement therapy experienced a reduction in alcohol consumption sustained through the 9-month follow-up (Nichols and Hendricks, 2020).

A similar study into alcohol use disorder at NYU School of Medicine found that abstinence among those with alcohol addiction increased significantly following the use of psilocybin (Law, 2022).

Addictions - Smoking

A Johns Hopkins University study with 15 participants receiving two to three moderate to high-level doses of psilocybin found that the majority were able to maintain their smoking cessation for at least 16 months (Law, 2022).

In a trial for smoking cessation treatment, participants could receive up to three administrations of psilocybin, the first on the quit date, the second two weeks later, and a third 8 weeks after the quit date. Participants also received cognitive behavioral therapy. Results were 80% successful abstinence at 6 months post quit date and 60% 2.5 years after (Nichols and Hendricks, 2020).

Addictions - Cocaine, Opioids, Marijuana

Observational studies and research have found that psilocybin is associated with a reduced risk of using substances like cocaine, marijuana, and opioids (Law, 2022).

An observational study of ayahuasca-assisted therapy for addictions among First Nations individuals in Canada found that participating in up to two ayahuasca ceremonies was associated with reductions in alcohol, tobacco, and cocaine use (Nichols and Hendricks, 2020).

Post Traumatic Stress Disorder

It is estimated that 12 million people suffer from PTSD in the United States alone with an estimate of 350 million people worldwide.

Some of the most promising clinical trial research on MDMA as a mental health treatment has come out of studies with those diagnosed with Post-Traumatic Stress Disorder. In one study where 90 participants diagnosed with PTSD were treated with MDMA-assisted therapy, researchers found that after 18 weeks post-treatment 67 percent of people no longer met the diagnostic criteria for PTSD (Marks, 2022).

How do Psychedelics work?

There are two components that work together to produce the profound effects experienced by psychedelics: a biological component, and a psychological component. Biological components consist of how the psychedelic impacts the person's brain, be that on neurotransmitters and hormones (as discussed earlier), improving neuroplasticity and the brain's default mode network, or their anti-inflammatory properties. The psychological impact is harder to study and there are a number of different theories on how one experiences the dissolution of ego, awe, and feelings of connectedness that also appear to play an important role in the experiences and outcomes. Explanations at the neurological and psychological levels should be viewed as connected and complementary, not as incompatible or competing (Muttoni et.al., 2019).

Biological

Biochemically, classic psychedelics are 5-HT2A receptor agonists. The serotonergic system has long been implicated in the regulation of complex emotional behaviors. Psychedelics, as serotonergic agonists, enhance amygdala inhibition; the resulting reduction in amygdala reactivity correlates with increases in a positive mood (Muttoni et.al., 2019).

Increased serotonergic signaling by psychedelics also reduces amygdala activation in response to threat-related visual stimuli. This is because the processing of threat-related visual stimuli can be modulated via feedback connections from the amygdala to the visual cortex. Increased amygdala reactivity is associated with increased attentional focus on negative reactiveness of environmental or social stimuli. This effectively blocks out the processing of positive information since the capacity of the visual cortex to

process multiple stimuli is limited. Accordingly, hyper-connectivity between the amygdala and visual cortex has been linked to increased threat processing and anxiety. Therefore, decreasing threat sensitivity in the visual cortex with psychedelic administration can lead to top-down suppression of negative stimuli, thus acutely shifting emotional biases from negative to positive stimuli. This has important therapeutic implications for anxiety and depression, as the persistence of negative cognitive biases is a central feature of these disorders (Muttoni et.al., 2019).

Another possible mechanism of therapeutic action is the modulation of glutamatergic neurotransmission induced by 5HT 2A receptor agonism. Higher cortical glutamate concentration indirectly stimulates the expression of brain-derived neurotrophic factor (BDNF), which is associated with increased neurogenesis and neuroplasticity. As depression has been linked to deficient neurogenesis and neurotrophic activity, normalization of BDNF levels can have therapeutic effects (Muttoni et.al., 2019).

In addition to modulating amygdala reactivity, psychedelics decrease connectivity within the default mode network (DMN). DMN hyper-connectivity has been linked to depression and anxiety and may contribute to the negative self-referential thoughts present in these conditions. Therefore, by decreasing DMN activity, psychedelics may exert beneficial effects (Muttoni et.al., 2019).

One theory proposes that network connectivity is abnormal in the depressed state and that after the desynchronization and hyperconnectivity produced by classic psychedelics, the Default Mode Network (DMN) resets to a normal non-depressed state of synchronicity and connectivity. A modification of this theory to address the long-lasting effects after a single treatment involves the anti-inflammatory effects of classic psychedelics. In this scenario, the classic psychedelic treatment will not only reset the DMN but also reduce and eliminate comorbid neuroinflammation, preventing the brain from relapsing to an abnormal state again due to persistent neuroinflammation. Another factor that may contribute to antidepressant effects is the ability of 5-HT2A receptor agonists to rapidly induce dendritic spine growth and density, similar to what has been observed for ketamine, which can also elicit significant and rapid antidepressant effects. The effects of ketamine, however, are not long-lasting and typically subside after a few weeks. This may be due to the lack of anti-inflammatory properties associated with ketamine (Nichols and Hendricks, 2020).

The anti-inflammatory effects of classic psychedelics may also contribute to their efficacy to treat drug addiction at the cellular level. Neuroinflammation has been found to be associated with aspects of drug addiction including cocaine seeking, opioid dependence,

and alcohol use disorder. Conversely, nicotine has been shown to impair immune responses within the central nervous system, and whereas nicotine itself has inhibitory effects on immune cell activation, other components of tobacco smoke likely produce the bulk of immune cell dysfunction in smokers. Psychedelics may also improve symptoms of depression by reducing inflammation. 5-HT2A receptor activation in immune cells can modulate the immune system, resulting in lower circulating levels of pro-inflammatory cytokines like tumor necrosis factor-α and interleukin-6. As high levels of these have been associated with depressive illness, normalization could produce antidepressant effects (Nichols and Hendricks, 2020; Muttoni et.al., 2019).

Similar to the potential therapeutic effects of classic psychedelics to treat depression, there are likely psychological and physiological components to the efficacy of classic psychedelics to treat addiction. Unlike with depression, where there is currently no evidence definitively establishing a physiological component, there is data from animal models demonstrating that classic psychedelics have efficacy to block drug-seeking behaviors ranging from cocaine self-administration to alcohol preference. The simplest explanation is that classic psychedelics, which nonselectively activate both 5-HT2A and 5-HT2C receptors, have therapeutic effects by activating 5-HT2C receptors and that this activity overcomes the effects of 5-HT2A receptor activation to produce an overall net decrease of dopamine release in the mesolimbic system. A reduction in the dopaminergic response would be predicted to reduce craving and drug-seeking behavior. (Nichols and Hendricks, 2020).

Psychological

Some studies are finding the extent to which psychedelics occasion a mystical-type experience predicts therapeutic outcomes. Research indicates that the intensity of mystical experiences elicited by psychedelics predicts changes in depression, alcohol consumption, trait openness, smoking cessation outcomes, negative affect, and end of life depression and anxiety. These results suggest the possibility that some of the efficacy of psychedelic substances may occur through their ability to create mystical-type experiences characterized by a sense of sacredness; a feeling of unity and interconnectedness with all things; a transcendence of space and time; feelings of peace, joy, bliss, awe or amazement; and a sense that this experience is an objective truth about reality. (Luoma et al., 2019).

At the psychological level, the emotion of awe might be responsible for the effects of classic psychedelics. Awe is experienced whenever humans encounter stimuli so vast

and novel that they must alter their understanding of reality. Nature, religious or spiritual practices, and music are common elicitors of awe. At the core of awe's acute effects are the small self, which involves attention being directed away from the self, feelings of unity with others and the environment, and diminishment of individualistic tendencies. From the perspective of the social functional approach to emotions in which emotions aid in the coordination of social interaction, awe is believed to be the quintessential binding emotion that drives social integration and cooperation, which are crucial to evolutionary success. Classic psychedelics may ultimately produce profound awe. Thus, for those suffering from addiction marked by considerable disruption in social functioning, an experience that highlights the discrepancy between the individualistic pursuit of drug rewards and the collective pursuit of a cause greater than self (e.g., family, community) may provide the motivation for sustained sobriety. For those suffering from end-of-life distress, depression, or other conditions characterized by maladaptive, self-directed rumination, attention directed away from the self and toward the transcendent may account for improvements in anxiety and mood. Of course, these effects may be reflected in the biological/physiological mechanisms mentioned above. These are hypotheses to be tested by future research (Nichols and Hendricks, 2020).

The neurological foundations of awe have not yet been investigated, so the following section is speculative, based on Hendricks (2018) research. He proposed two areas to support the theory of awe as a component of treatment.

First are findings from human brain imaging. Classic psychedelics produce acute default mode network disintegration and whole brain integration (by way of augmented global functional connectivity), in which there is increased communication between all brain networks, despite a decrease in communication within those networks. These effects are associated with self-reported ratings of ego dissolution post-classic psychedelic administration. The increase in functional connectivity in the bilateral temporoparietal junction and bilateral insular cortex (structures associated with the self-other boundary, orienting oneself in physical space, and out-of-body experiences) are among the most strongly correlated with ego-dissolution. Considering the conceptual overlap between ego dissolution and the small self-characteristic of awe's effects, these findings suggest that increased global functional connectivity could well be important to both awe and classic psychedelic-occasioned mystical experience (Hendricks, 2018).

Second are findings related to serotonergic activity. Serotonin plays an important role in social dominance, which is in turn associated with increased drug administration, risk-taking, and aggression in rats, as well as some antisocial behavior in humans. Classic

psychedelics primarily act as serotonin 2A receptor agonists and down-regulate serotonin-2A receptors in the prefrontal cortex. These findings imply a potential, molecular link between an emotion (awe) that promotes subservience of one's own needs in favor of the greater social good, a type of submission or humility that contrasts with dominance, and classic psychedelic-occasioned mystical experience (Hendricks, 2018).

A lasting indication of classic psychedelic occasioned mystical experience may be a sense of connectedness or oneness with others and the external universe. It is this heightened feeling of connectivity or wholeness that may account for the promising effects of classic psychedelic-assisted psychotherapy across a range of applications. It is possible that this connectedness is key to understanding the therapeutic potential of classic psychedelics, which may or may not involve awe, as the catalyst of this effect. For those suffering from depression, end-of-life distress, or other conditions marked by rumination, attention diverted away from the self and toward the transcendent (family, community, the external universe, a belief system) is likely experienced as liberating if not sublime. For those struggling with addictive disorders characterized by social dysfunction, the experience of discrepancy between the compulsive pursuit of a hedonic pleasure and commitment to a cause greater than self may fuel the desire for sustained abstinence. For those involved in transgressive behavior, a profound experience highlighting the inter-relatedness and interconnectedness of all life may foster greater empathy and concern for the welfare of others (Hendricks, 2018).

In addition to their neurobiological mechanisms, psychedelics also elicit highly meaningful and spiritually significant experiences that are conducive to their therapeutic potential. In clinical trials, up to 87% of participants have attributed increased life satisfaction or well-being to these psycho-spiritual experiences. Furthermore, the intensity of the mystical experience seems to be predictive of long-term therapeutic efficacy. This is because it creates a "window of opportunity" in which changes in unhealthy thoughts, emotions, and behaviors can take place in a psychotherapeutic context. Specifically, the heightened state of consciousness induced by these drugs interrupts the rigid and pathological pattern of negative and compulsive thoughts present in anxiety and depression. This contributes to mental flexibility and leads to enduring positive changes in attitudes, moods, perspectives, values, and behavior. Some have termed this phenomenon an 'inverse posttraumatic stress disorder-like effect' in which a highly significant and positive experience causes lasting beneficial changes, as opposed to a single traumatic event causing chronic distress (Muttoni et.al., 2019).

Overall, psychedelics are able to provoke profound psycho-spiritual experiences as well as modulate neural circuits implicated in mood and affective disorders, to reduce their symptoms (Muttoni et.al., 2019).

Kelley O'Donnell, MD, Ph.D., an assistant professor of psychiatry at the New York University (NYU) Grossman School of Medicine and a researcher at the NYU Langone Center for Psychedelic Medicine, states that psychedelic drugs allow patients to access parts of themselves that are ordinarily inaccessible. She explains, "The human brain is fundamentally a learning machine, and it derives its power from its ability to learn and recognize patterns and use those patterns to predict the future. It seems that psychedelics make that pattern much more flexible, so you have a window of opportunity to reopen a period of development, so even after the psychedelic experience, you can make choices and establish new patterns." (Marks, 2022).

Psychedelic Assisted Therapy

Most clinical trials incorporating psychedelic-assisted therapy involve supportive psychotherapy that consists of a period of preparation, followed by a dose of psychedelics in the presence of one or more therapists, and concluding with one or more integration sessions. Dosing and integration sessions may repeat multiple times and be spaced at different intervals depending on the study. Historically, psychedelic-assisted therapy has been shaped and guided by psychodynamic, humanistic, and transpersonal theories. Most of the psychotherapy involved in past and published trials has relied on these principles. Newer and ongoing studies are incorporating contemporary evidence-based psychotherapies, such as motivational interviewing and Acceptance and Commitment Therapy (Luoma et al., 2019).

Most clinical trials and treatment models for psychedelic-assisted therapy include three parts to the intervention: preparation for the dosing session, support during the session, and integration post-dosing session. This model focuses on set, setting, preparation, integration, and establishing and maintaining a supportive therapeutic relationship to work through the effects of the psychedelic experience.

Preparatory sessions focus on developing therapist-participant rapport, gathering participant history, and psycho-education on the psychedelic experience, therapeutic model to be used, and participant expectations. Logistics of the dosing session are explained such as the expected time it will last, music that will be played, setting boundaries for interactions with the participant and therapist, and safety protocols.

These preparatory sessions are important, as research has found the subjective effects of the psychedelic experience are strongly influenced by environmental and psychological factors. Having participants set their mindset and intention prior to the experience includes exploring their beliefs, hopes, fears, traumas, personalities and temperament, expectations, and fantasies. The setting where the experience will take place not only includes the physical space but who and what will also be in the room - therapist or guide, music, artwork, and safety equipment. Addressing all of these factors helps maximize safety and minimize risk, thereby setting the stage for a successful dosing session.

During dosing sessions, therapists provide emotional support but are non-directive. They may encourage the participant to explore the difficult thoughts, sensations, or memories that are experienced during the psychedelic experience. The therapist is there to also provide for any immediate needs for comfort or safety. Safety equipment for medical monitoring includes a blood pressure and pulse monitor and locked areas for protocol materials and records. Safety also includes having access to treatment for possible reactions to the medicine. This includes rescue medications and basic and advanced cardiac life support. The therapist also ensures the participants' physical safety when moving about the room or using the bathroom, and also makes sure that the individual remains hydrated. It is also important the participant has a designated support person who has been briefed on the process and can monitor the person after the dosing session and who can provide transportation home.

The integration phase usually happens the day following the dosing session. The participants' experience is explored in-depth and therapeutic techniques are used to explore insights participants had and reinforce specific aspects of the experience to support the desired changes in thoughts and behaviors.

While most clinical trials follow this basic model, there is variation based on the condition being treated and the therapeutic orientation of the clinicians or researchers. Some programs use evidence-based therapeutic interventions while others use non-specific supportive psycho-therapeutic methods. Examples of evidence-based treatments include Yale’s use of Acceptance and Commitment Therapy in their psilocybin-assisted therapy for depression, and the New York University School of Medicine's use of Motivational Enhancement Therapy and Cognitive Behavior Therapy in their psilocybin-assisted therapy to treat Alcohol Use Disorder. Non-specific supportive models trials are attempting to establish the drug's effects versus the therapeutic effects of the experience. In psychological support only models instead of a “therapist” there is

a “sitter, guide or monitor.” The role of the guide is to support the participants as they use psychedelic medicine to find their inner healing within their own psyche (Guss et al., 2020).

While different psychedelics and mental health diagnoses may have varied treatment protocols, three examples Yale’s Psilocybin Assisted Therapy Treatment for Depression (Guss et al., 2020), MAPS MDMA-PT protocol and a general Ketamine Assisted Clinic-Based Treatment. Yale’s program follows a very specific treatment protocol that sets up the importance of psychoeducational sessions prior to the experiential session and the follow-up sessions to debrief and have some additional post-psychoeducational sessions. The table below lays out the session of each focus and how ACT is utilized to support the psilocybin experience and address the participants' depression symptoms. Prior to the first session, there is a screening and consent process that includes gathering participant history, establishing therapeutic rapport, signing necessary consents, answering participant questions, and commitment from the participant to comply with protocols.

Yale’s Psilocybin Assisted Therapy Treatment for Depression (Guss et al., 2020)

Session Name	**Session Overview and Ways ACT is Employed**
Preparatory Psychoeducation Session #1 (2 hours)	Therapist aims to establish a therapeutic alliance through • Listening to the participant’s narrative of depression and treatment history to understand patterns of psychological inflexibility that are most prominent; • Psychoeducation regarding the psilocybin experience, therapeutic boundaries (e.g., touch) and safety measures; • Teaching grounding techniques including diaphragmatic breathing; • Assisting the participant in setting an intention for medication session #1.

Medication Session #1 (at 1 week)	• In line with the supportive stance during medication sessions, the therapist does not provide significant ACT interventions or feedback. • ACT-based clinical formulation continues as the therapist listens to emergent narratives and notes instances of psychological flexibility and inflexibility, especially present moment awareness, self-as-context, and experiential avoidance.
Debriefing Session #1 (1-2 hours, day after medication session)	• Therapist elicits a complete narrative of the participant's experience during the medication session. • Identify and explore aspects of the participant's narrative that engage with ACT principles, as well as instances when they moved toward or away from psychological flexibility
Debriefing Session #2 (1-2 hours, 1-week after the medication session)	Therapist and participant continue to review and reflect on the participant's: • Psilocybin experience, including any emotional, mental, or lifestyle changes that followed the dosing session. • Values, by discussing the participant's completed Valued Living Questionnaire, and the relative importance of valued domains of living. • Experiences living in accordance with or not living in alignment with their values.

Preparatory Psychoeducation Session #2
 	
(2 hours, at 4 weeks)
	• Conduct psychoeducation regarding:
	  • The cognitive processes and behaviors that contribute to depression from an ACT perspective (i.e. cognitive fusion, experiential avoidance, reason-giving, etc.);
	  • How depressive patterns can be changed through an interactive process between the principles of ACT and the experience with psilocybin; and
	  • Mindfulness practice.
	• Through this process, the therapist aims to induce “creative hopelessness.”
	• Assisting the participant in setting an intention for medication session #2.

Medication Session #2 (at 5 weeks)	Same as medication session #1
Debriefing Session #3 (1-2 hours, day after medication session)	Therapist elicits complete narrative of participant’s experience during medication session, exploring: • Aspects of the experience in relation to ACT principles discussed previously. • Metaphors derived from psilocybin experience or from ACT (i.e. house and furniture metaphor) to aid in the understanding of the principles, such as self-as-context.

Debriefing Session #4 (1-2 hours, 1 week after medication session)	Using the ACT Matrix if helpful, therapist and participant continue to review and reflect on the participant's medication experience and changes that have taken place, to explore: • What the participant values most; • How to put their values into action. Therapist may shift toward a more directive behavioral approach to help the participant to define precise actions they can take to start living in accordance with their values.
Follow-up Sessions #1 and #2 (2 and 4 weeks after medication session #2)	Therapist continues to explore and reinforce: • Insights gained from the psilocybin experience while assessing for changes in psychological flexibility; • How the dosing and therapy sessions brought each ACT process to light, using the ACT hexaflex; • Relevant ACT concepts • Successful behavioral changes and committed actions are taken • Mindfulness practices and other concrete ways the study experience can be translated into lasting changes. Therapist leads termination discussions and plans for post-study follow-up care for the participant.

MDMA-Assisted Therapy

MDMA-assisted therapy is delivered during three 8-hour sessions, scheduled three to five weeks apart, along with 12 non-drug therapy sessions to aid with preparation and integration.

MAPS MDMA-PT

(Hutchison & Bressi, 2018)

Preparatory Stage 2-3 90 minutes session	• Rapport Building with 2 therapists, 1 male & 1 female • Patient is oriented to the treatment model • Patient is given psychoeducation on MDMA
MDMA assisted session 6 hours	• Therapists are non-directive but offer empathetic support • Patient may initiate discussions or have periods of quiet reflection with optional music • Discussion of traumatic content generally emerges spontaneously, although patients agree to have therapists introduce it if this does not occur.
Monitoring Overnight	• Patient has an overnight stay in the clinical setting post-MDMA session to continue to monitor vitals and for any adverse psychological reactions.
7 Days of Phone Check-ins	• Co-therapists check in by phone daily for one-week
Integration Sessions (3) 90 minute sessions over subsequent weeks post-dosing session	• Goal is to integrate insights from the experience
Above cycle repeated 2-3 times	• This cycle of drug-assisted sessions and follow-up therapy is administered a total of 2–3 times. • The overall course of treatment includes approximately 18 hours of non-drug psychotherapy and 16–24 hours of MDMA-assisted psychotherapy

Ketamine-Assisted Therapy

(McInnes & Yu, 2020)

Preparation	• Screening Tests: Liver function, pregnancy, urine drug screen • Vital Signs: including height and weight • Consent forms signed • Psychoeducation on ketamine and expectation management
Administration	• Patient sits or lies comfortably with eyes closed, focusing inward • Target dose is to provide mood elevation and dissociation while limiting mild side effects • Confirm steady gait, stable blood pressure and transportation home prior to release from dosing session
Integration	• The most important aspect of integration is for patients to create a meaningful narrative of healing for themselves. • Therapeutic techniques to support integration include: guided imagery, mindfulness, Emotion Modulation Therapy, Mindful Self Compassion, Cognitive Behavioral Therapy, and Dialectical Behavioral Therapy

While the drugs and therapeutic treatments may vary, there are similarities amongst most psychedelic-assisted therapy protocols with the preparatory phase, the dosing phase, and the integration phase. Strengths of successful programs incorporate behavioral therapy sessions into the psychedelic treatment and the programs heavily screen for patients that have potential risks for a negative reaction (Nichols and Hendricks, 2020).

Code of Ethics

The Multidisciplinary Association for Psychedelic Studies (MAPS) is non-profit research and educational organization that develops legal, medical, and cultural contexts for people to benefit from the careful uses of psychedelics and marijuana. They have established a code of ethics for psychedelic psychotherapy. The purpose of the code of ethics is to "protect the safety and welfare of participants" and "outline ethical principles governing treatment decisions made by providers delivering psychedelic psychotherapy." Since psychedelic assisted therapy involves deep work with trauma and attachment in non-ordinary states of consciousness, there are unique ethical considerations practitioners need to be aware of. These considerations include the need for sensitivity regarding consent, the potential for greater participant suggestibility, and the potential for greater and more complex transference and countertransference. MAPS has identified twelve key standards as part of the code of ethics; a more detailed description of each standard can be found at: maps.org (MAPS, 2021).

- **Safety:** We commit to the safety of study participants, patients, and clients.
- **Confidentiality and Privacy:** We respect the privacy of participants and uphold professional standards of confidentiality.
- **Transparency:** We respect each participant's right to make informed choices.
- **Therapeutic Alliance and Trust:** We act in accordance with the trust placed in us by participants.
- **Touch:** When using touch in our practice, we always obtain consent and offer touch only for therapeutic purposes.
- **Sexual Boundaries:** We do not engage in sexual touch with participants.
- **Diversity:** We respect the value of diversity, as it is expressed in the various backgrounds, identities, and experiences of participants and colleagues.
- **Special Considerations for Non-Ordinary States of Consciousness:** We attend to special considerations when working therapeutically with participants in non-ordinary states of consciousness.
- **Finances:** We maintain clear communication with participants about fees and aspire to increase financial access to services.

- **Competence:** We practice within our scope of competence, training, and experience specific to the populations we are working with and the modalities we offer.
- **Relationship to Colleagues and the Profession:** We establish and maintain compassionate and positive working relationships with colleagues, in a spirit of mutual respect and collaboration.
- **Relationship to Self:** We commit to ongoing personal and professional self-reflection regarding ethics and integrity (MAPS, 2021).

Established Research Centers and their Focus

The number of centers and clinical trials in psychedelics is growing exponentially every year. For example, in 2018, Hendricks reported 15 clinical trials in the United States reporting on clinicaltrials.gov. In May 2022 there were 96 active studies taking place in the United States according to clinicaltrials.gov. Some of the studies in 2022 were researching psychedelics for frontline healthcare workers during the COVID-19 pandemic, psilocybin for the treatment of binge eating disorder, OCD, Major Depressive Disorder, addictions disorders, chronic lyme disease, and PTSD. Below are some of the key research centers in psychedelics and psychedelic-assisted therapy (clinicaltrials.gov):

John Hopkins: The Center for Psychedelic and Consciousness Research

John Hopkins was the first to receive regulatory approval in the United States in 2000 for research of psychedelics in healthy, psychedelic-naive volunteers. In 2006 they published their results on the safety and positive effects of a single dose of psilocybin; they claim their work is what reinvigorated the worldwide study of psychedelics, and they continue to be the leading research facility in the United States for work with psychedelics. Their research has shown the positive effects of psychedelics in treating those with substance abuse, emotional distress caused by life-threatening illnesses, and depression. Their ongoing research on psilocybin includes the treatment of opioid addiction, Alzheimer's disease, post-traumatic stress disorder (PTSD), post-treatment Lyme disease syndrome, anorexia nervosa, and alcohol use in people with major depression (John Hopkins Center for Psychedelic and Consciousness Research, 2022).

NYU: Center for Psychedelic Medicine

NYU focuses on psychiatry, medicine, and preclinical research. The center's goal is to generate knowledge, train scientists and clinicians, and ensure accurate dissemination of information surrounding the clinical use of psychedelics. Their psychiatry research is studying Classic Hallucinogens for Addiction, Mood, and Anxiety Disorders; Cannabidiol for Alcohol Use Disorder; and MDMA for Trauma- and Stressor-Related Disorders. Their medicine branch of research is focused on Cannabidiol for chronic non-cancer pain, and their preclinical section explores the Mechanism of Psychedelic-Induced Change in Animal Models of Psychiatric Disorders (Center for Psychedelic Medicine, 2022).

UC Berkeley: Berkeley Center for the Science of Psychedelics

The UC Berkeley Center for the Science of Psychedelics (BCSP) states their mission is to explore psychedelics as tools for understanding the brain and mind, enhancing well-being, and deepening spirituality. Their goal is to investigate the short- and long-term effects of psychedelics on human cognition, perception, and emotion; assist in the training of practitioners to support the use of these medicines in culturally appropriate, spiritually significant, and medically safe ways; and offer authoritative, evidence-based, and culturally inclusive journalism about the field (Berkeley Center for the Science of Psychedelics, 2022).

Imperial College London: Centre for Psychedelic Research

The Centre focuses its research on using psychedelics in mental health care. Their goal is to gather clinical evidence to become the prototype for future licensed psychedelic treatment facilities. Their early research looked at the brain effects of LSD using modern brain imaging and was the first to study psilocybin for treating severe depression and neuroimaging research with psilocybin, MDMA, and DMT. Current research is comparing psilocybin therapy with a conventional antidepressant drug in patients with depression and another study utilizing psilocybin to treat patients with anorexia (Centre for Psychedelic Research, 2022).

Risks

Psychedelics do come with some risks; they are contraindicated with certain medications and pre-existing health conditions, and there are adverse side effects with each

psychedelic drug. The set and setting can also impact the outcome of the experience. There are three categories of risk in consuming classic psychedelics. The first is the potential for a bad trip that may consist of anxiousness, confusion, or delusions. These can be safely managed in a clinical research setting. The second is the potential to trigger an underlying psychotic disorder or to experience a prolonged psychotic reaction. Clinical trials screen potential participants heavily for any history of psychotic disorders. The third risk category involves short-term physiological effects. These include increased blood pressure and heart rate during the active effects of the psychedelic; therefore, those with cardiac disease history should also be excluded from clinical trials. Other uncomfortable but non-life-threatening side effects of ingesting classic psychedelics include headaches, nausea, and vomiting (Johnson et al., 2019).

Limitations

- Those participating in clinical studies are heavily screened for any underlying conditions, both mentally and physically.
- Clinical study sizes are still in small groups of the population, and therefore results may be stretched to apply to the general population.
- Psychedelics are not a cure for chronic mental illness; while results do appear to last weeks or months, they do begin to gradually fade. There have not been enough follow-up studies to determine what best practices may be to maintain remission (traditional antidepressants, brain stimulation, repeated psychedelic dosing, psychedelic microdoses, or other options).
- Studies have all been relatively short-term, and there is an ongoing need for follow-up studies to determine the long-term risks and benefits of psychedelic treatment.
- Due to limited clinical studies, psychedelics have not been able to show they are a superior treatment to current psychopharmacology.
- Psychedelics are not an approved treatment in the United States, and therefore to legally experience them, one must travel outside the country or be admitted into a clinical trial (Bender & Hellerstein, 2022).

At this time, the only way to legally seek treatment with psychedelics is through clinical trials (other than ketamine and cannabis, depending on one's state of residence).

Clinical trials of psychedelics for a variety of conditions are taking place across the United States. One place to research open trials that are seeking participants is through clinicaltrials.gov. While they can be difficult to find or have long waiting lists, it is safer to try psychedelics as part of a study than on one's own. In clinical trials, patients attend appointments to prepare for their psychedelic experience, complete the dosing procedure in a professional environment where any side effects can be managed and attend post-dosing sessions where they can process their psychedelic experience. There are some treatment clinics in and outside of the United States but one should be aware of the minimal regulatory checks and balances that may or may not be involved based on state or country. (Eschner, 2022).

Microdosing

Microdosing psychedelics is the practice of taking small doses of a substance every few days for mental health benefits without the hallucinogenic effects. While microdosing has grown in popularity there is limited scientific research to support the claimed benefits. There is also limited research on the harmful effects it might have; for example, there is some evidence long-term psilocybin, even at microdose levels, can over time damage the heart. A study on LSD and rats found that microdosing led the rats to show signs of psychiatric illness (these symptoms included aggression and poor grooming habits). As with psilocybin, LSD may also cause heart strain by overworking the neurons around the heart. Some research is finding that the positive effects people are reporting from microdosing are in actuality caused by the placebo effect (Eschner, 2022; Anderson et. al., 2019).

Anderson et. al. (2019) conducted anonymous online surveys of 278 microdosers to see what benefits and challenges they self-reported. The top five benefits of microdosing that were reported were: Improved mood (26.6%), Improved focus (14.8%), Creativity (12.9%), Self-efficacy (11.3%), and improved energy (10.5%). The top five challenges of microdosing per survey respondents were: Illegality (29.5%), Physiological discomfort (18%), Impaired focus (8.8%), Increased anxiety (6.7%), and Impaired energy (7.2%). Respondents were allowed to list up to three benefits and three challenges. While these results sound promising, the researchers of this study acknowledge the limitations due to subjective self-report, recall bias, and placebo effects. More microdosing research is needed to help inform future psychedelic treatment options, including contrasting full-dose and microdose psychedelic therapies and what potential there may be for mix-dose treatments.

Future Research Needs

Although research shows promising results, there are still many unknowns. We need larger scale clinical trials, the FDA will need to determine how the drugs will be prescribed and administered, and clear protocols will need to be established on self-administration versus psychedelic-assisted therapy. As mental health difficulties continue to rise in our communities people are desperate to find relief. The results from many of the psychedelic trials are showing more hope for people than traditional medications, especially for those with hard to treat diagnoses (Marks, 2022).

Case Studies

In 2015, Kirk Rutter participated in a psilocybin-assisted treatment program with the Imperial College London for his depression. He reports he had been diagnosed with it for years but it had worsened with the death of his mother in 2011 and a break-up that was followed by a car accident. He shared it felt as if his brain was stuck in an automatic circuit of negative thinking. He reports the treatment helped him look at grief differently and realize that holding on to it wasn't helping, nor was he betraying anyone by letting it go. He shared within a week of treatment he could feel a sense of optimism and openness he had not felt for a long time. He was fearful that the negative automatic thoughts would eventually return, but after five years his depression has not returned (Tullis, 2021).

Jon Lubecky reports being desperate when he signed up for a clinical study with the Multidisciplinary Association for Psychedelic Studies to treat PTSD with MDMA. He reports he felt tortured by his memories of his Iraq tours and had attempted suicide five times. Other symptoms he experienced were nightmares and panic attacks when in public. He explained when the MDMA started to take effect he was able to talk through things that he had never brought up to anyone before and it was ok, he didn't have a panic attack, he didn't emotionally shut down and he didn't become overemotional. He reports his PTSD is now 100% gone and he even feels he may be more mentally healthy than he was even before experiencing PTSD (Carrol, 2021).

Joan had struggled with an eating disorder since she was a teenager. Not only did she suffer from dangerously low weight she had no energy to participate in activities that normally brought her joy such as hiking and traveling. All of this led to also having symptoms of depression, anxiety and suicidal ideations. Joan tried numerous treatment strategies, including long term residential programs, but nothing seemed to give her

long term results. Discouraged, she turned to experimenting with the psychedelic underground trying to find some relief,and these brief moments of respite encouraged her to explore Emotion Focused Ketamine-Assisted Psychotherapy. She reports after two sessions she was able to think about things more rationally, and has fewer obsessive thoughts about her daily calorie intake. She has been able to gain a little weight while still feeling emotionally comfortable and not panicking about it and she has been able to have more energy to do the things she loves (Ferenstein, 2022).

In 2013 Marcus Capone retired from the U.S. Navy Seals after 13 years. His wife reports she and their children had become afraid of him and tip-toed around when he was home. Everything seemed to worsen with his retirement, including depression, anger, headaches, anxiety, alcohol intake, impulsivity and nightmares. His wife reports his cognitive functioning declined to the point he got lost driving to one of his daughters sporting events. None of the traditional medications he was being prescribed to treat his PTSD, depression, and anxiety seemed to be helping. One of his Navy friends had similar struggles and shared his experience traveling outside the country to be able to legally take ibogaine. IN 2017, he decided in 2017 to go to Mexico and tried it for himself. He shares it was his first psychedelic experience, lasting 12 hours and sometimes awful, re-experiencing some of the worst times of his life. Afterwards he reports he felt like he finally put down a heavy load he had been carrying for years. He didn't want to drink and stayed completely sober for a year after the experience. He was able to think clearly, no longer had moments of impulsivity and no longer experienced anxiety or depression. His wife reports she feels she has her husband back (Oaklander, 2021).

Conclusion

Psychedelic drugs aren't simple substances. More time and research are needed to build a clear understanding of their effects on the brain and best practices for use in medical treatments. Current research does appear to support the use of psychedelic treatments when other forms of traditional drugs and therapy have been unsuccessful. And as with any drug, not everyone is going to respond in the same way. Instantly changing one's life or curing a mental illness is not a realistic expectation for psychedelic treatment. However, psychedelics do give people an opportunity to experience new consciousness that may allow them to create new patterns of thoughts, emotions, and behaviors (Eschner, 2022; Marks, 2022).

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