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THE PAST, PRESENT AND FUTURE OF PSYCHEDELIC MEDICINE

By

Helen Claire Merrill-McNulty

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A thesis submitted to the faculty of The University of Mississippi in fulfillment of the requirements of the Sally McDonnell Barksdale Honors College

Oxford

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Approved by:

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Advisor: Dr. Noa Valcarcel

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Reader: Dr. Jason Paris

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Reader: Dr. Saumen Chakraborty

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## Abstract

This thesis is a systematic literature review that will articulate the need for psychedelics as a treatment for several mental illnesses and ailments. Starting with the origins of psychedelics used in South American religious ceremonies and their development and early trials in the mid 20<sup>th</sup> century as well as the legal battles of psychedelics in American society. Additionally, this thesis examines the chemical structure, pharmacology, and safety of psychedelics. An in-depth examination of psychedelics as a therapy for treatment-resistant depression, depression and anxiety as a result of a cancer diagnosis, nicotine addiction and alcoholism, OCD, PTSD, and cluster headaches will be conducted as well as potential therapeutic uses for treating inflammation and the possibility of using psychedelics for tissue regeneration. Present-day studies that are currently in Phase 2 and Phase 3 of trials will also be explored including the contemporary challenges psychedelics face as becoming a part of modern society and their mainstream use as a therapy for mental illnesses.

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## Introduction

For some time now, some drugs that have been classified as illicit and illegal now are being studied for their potential therapeutic effects on the body and mind alike. The most well-known illicit drug that has been researched for having positive effects on health is marijuana. Marijuana also provides a good model for drug legalization, in terms of research and controversy.

The most common use of marijuana is for the control of pain that is not caused by inflammation, such as chronic or neuropathic pain. It has also been used to help treat rare forms of epilepsy, used with chemotherapy, vomiting, nausea and weight loss from patients with HIV/AIDS. It can also be used in lieu of opiates to eliminate the chance of dependence on opiates.

The level of legality of marijuana varies from jurisdiction to jurisdiction. Marijuana is legal in some way, shape or form in 29 states as well as Washington D.C. but it still illegal at the federal level. People are still hesitant about legalizing it in full as there are still questions remain related to its safety or long-term effects.

Psychedelics are one of these drug classifications that could have potential positive health effects. Drugs in this class include classic hallucinogens such as lyseric acid diethylamide (LSD), methylenedioxymethamphetamine (MDMA), psilocybin, and or N,N-Dimethyl-5-methoxytryptamine (DMT). The main reason why the therapeutic use of psychedelics is being explored stems from the difficulty of treating several mental illnesses such an anxiety,

depression, obsessive compulsive disorder, post-traumatic stress disorder, alcoholism and nicotine addiction. At the moment, the standard course of treatment usually involves psychotherapy alone or in combination with selective serotonin-receptor inhibitors (SSRIs) or other antidepressants.

As with marijuana, the research and the therapeutic use of psychedelics has been challenging due to its legal status but it is currently experiencing important advances that might lead to its introduction in common medical practice in the near future.

### Methods

The articles found for this literature review were done systematically. This was done through OneSearch and keywords such as psychedelics, hallucinogens, LSD, mescaline, MDMA, DMT, psilocybin, psychedelic clinical use, history of psychedelics, PTSD psychedelics, depression psychedelics, OCD psychedelics, tissue regeneration psychedelics, cluster headaches psychedelics, substance abuse psychedelics, cancer patients psychedelics. The search settings were set to scholarly journal articles. This brought up 6,142 results. The articles, with the exception of the history of psychedelics, were set within the past 20 years which narrowed down the results to 1,531 hits. Of those 1,531 hits, the terms OCD, depression, anxiety, cluster headaches, substance abuse, cancer patients, inflammation, tissue regeneration where these keywords must be included in the articles with the keyword's psychedelics, hallucinogens, LSD, mescaline, MDMA, DMT, psilocybin. This narrowed down the results to 217 hits. These articles were then examined individually through the abstracts to determine if there was sufficient data and results that could support the claims for psychedelic medicine, this narrowed down the results to 107 hits that are the basis of this literature review.

### History and Legality of Psychedelics

Psychedelics have been used for centuries by indigenous peoples with records of the earliest use of psychotropic plants dating back 5700 years used in Northeastern Mexico where they were used during religious ceremonies (Bruhn et al. 2002). It was formally introduced into Western society by Arthur Heffner in 1897 when he was able to isolate the compound mescaline from the peyote cactus and again in 1938 when chemist Albert Hoffman synthesized lysergic acid diethylamide (LSD) from ergot alkaloids. However, the hallucinogenic properties weren't fully understood until 1943 when Hoffman accidentally ingested the 25th derivative of lysergic acid and experienced intense hallucinations. Hoffman also synthesized psilocybin in 1958 (J.D. Moreno 2016) (Rucker, Iliff, and Nutt 2017) (Hoffman 2013)

Psychedelics were an integral part of the counter-culture movement during the 1960s after LSD became popular by several authors including Timothy Leary. This led to the increased and often illegitimate use of psychedelics by sham psychiatrists, as well as "LSD parties" (Novak 1997). In 1957, the term "magic mushrooms" was coined by LIFE magazine (Wasson 1957). At the beginning of the 1960s, Dr. Sidney Cohen began to question the safety of psychedelics, particularly LSD. He had previously taken a positive stance on psychedelic use, defending that if used properly, psychedelics could be very effective and helpful for people suffering from depression and anxiety alike. However, as the illicit use of psychedelics increased and a larger amount of the population began misusing the drug, he began to take a more cynical and bleak stance towards the subject (Novak 1997).

Around this time, Congress tightened regulations for experimental drugs, including psychedelics, as a consequence of reports of severe birth defects in children whose mothers had taken thalidomide for morning sickness. In October of 1962, the FDA introduced Kefauver-Harris Drug Amendments to limit the use of these experimental drugs. Following this



amendment, Sandoz stopped the production of LSD and psilocybin in 1965 (Stevens 1987). The use and regulation of magic mushrooms, LSD and mescaline were quite liberal until 1967 when the United Nations decided to classify all psychedelics as a Schedule I drug, effectively taking it off the shelves and making it nearly impossible to obtain. In 1968, Dr. Cohen helped to create the NIMH Division of Narcotics Addiction and Drug Abuse where he became the very first director. Around this time, the attitudes towards psychedelics turned increasingly sour as the so-called “war on drugs” initiative became mainstream and their effectiveness and safety were called into question ((Rucker, Iliff, and Nutt 2017). In 1970, President Richard Nixon passed the Controlled Substances Act effectively creating five schedules or drug levels based on therapeutic and abuse potential. LSD and psilocybin were placed in the most restrictive category, Schedule I, which requires special permits and licenses to obtain access to. (Lee, Johnson, and Griffiths 1992) In 1981, the Common Rule was adopted making behavioral and biomedical research indistinguishable and as a result, the amount of research dwindled until the turn of the 21st century (J.D. Moreno 2016).

However, this did not mean that research completely ceased. Instead, research was driven underground. Some people began to synthesize psychedelics for the main purpose of street sales while others wanted to find a similar hallucinogen that could be sold on the market, legally. Dr. Alexander Shulgin on the other hand, wanted to continue experimentation with psychedelics for therapeutic use. He first tried to experiment on animals with little success so he decided to experiment on himself. He was working for Dow Chemicals at that time and decided to leave the company to go back to school to learn more about chemistry. He eventually got a license to perform research with schedule I drugs. He published a book called PIHKAL (Phenethylamines I Have Known And Loved) which details his life and his study of psychedelics (Shulgin and

Shulgin 2002). This was the beginning of the end for Shulgin. After he published this book his relationship with the DEA quickly began to deteriorate and he began to be inspected more often and eventually he got his license revoked.

Beginning in the early 1990s, the interest in psychedelics was rejuvenated (Strassman 1996). In 2006, several researchers published that people who had a psychedelic experience reported it being one of the top five most influential, meaningful and important experiences in their life - comparable with the birth of a child (RR Griffiths, Richards, and McCann 2006). Since then, the research on psychedelics has gradually returned.

### Chemical Structure of Psychedelics

Under the Controlled Substances Act, all psychedelics are classified as Schedule I drugs by the DEA. Drugs are classified as Schedule I when they have no current acceptable medical use, their safety is questionable, and they present the highest abuse potential.

Psilocybin (C<sub>12</sub>H<sub>17</sub>N<sub>2</sub>O<sub>4</sub>P), the active ingredient in magic mushrooms, otherwise known by its street name shrooms, is a tryptamine alkaloid which is a tertiary amino compound and an organic phosphate. Tryptamines are derived from the amino acid tryptophan and can be found in over 200 species of Basidiomycota mushrooms, where both the caps and stems contain active psilocybin. Psilocybin has a N,N-dimethyltryptamine carrying an additional phosphoryloxy substituent at the fourth position (Medicine and NIH).

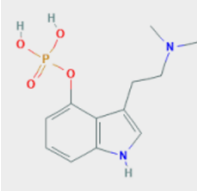
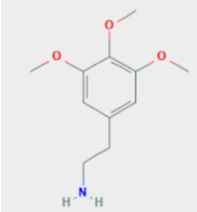
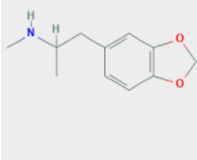
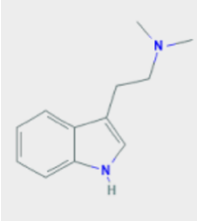
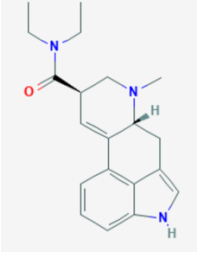
Mescaline (C<sub>11</sub>H<sub>17</sub>NO<sub>3</sub>) is a phenethylamine alkaloid which is a member of the methoxybenzene family and a primary amino compound. Phenethylamines are organic compounds, natural monoamine alkaloid and trace amine. Mescaline is found in several cacti plants including the peyote cactus, the San Pedro cactus, and the Peruvian Torch cactus. In

mescaline, the phenethylamine is substituted at the third, fourth and fifth positions by methoxy groups (Medicine and NIH).

MDMA (C<sub>11</sub>H<sub>15</sub>NO<sub>2</sub>), or 3,4-methylenedioxyamphetamine, otherwise known as molly or ecstasy is a ring-substituted amphetamine derivative in the same class as methamphetamine (meth) and structurally related to mescaline. MDMA was developed by a German pharmaceutical company in 1912. As a member of benzodioxoles, the 1,3-benzodioxole is substituted by a 2-methylamino propyl group at the fifth position (Medicine and NIH)

DMT (C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O), or N,N-Dimethyl-5-methoxytryptamine is a tryptamine alkaloid, an aromatic ether and a tertiary amino compound. substituted by a methoxy group at the fifth position and is derived from a bufotenin. DMT is found in several plant species such as ayahuasca and the Colorado River toad. It is used in South American religious and spiritual rituals as well (Medicine and NIH).

Lysergic acid diethylamide (C<sub>20</sub>H<sub>25</sub>N<sub>3</sub>O), otherwise known as acid is an ergoline alkaloid which is an organic heterotetracyclic compound and a monocarboxylic acid amide. Ergoline alkaloids are in fungi and some flowering plant species, including the Mexican species *Turbina corymbosa*. Lysergic acid diethylamide is the result from the formation of lysergic acid and diethylamine (Medicine and NIH).

Name	Chemical Formula	Compound Type	Where it's Found	Picture
Psilocybin	$C_{12}H_{17}N_2O_4P$	Tryptamine alkaloid	200 species of Basidiomycota mushrooms	
Mescaline	$C_{11}H_{17}NO_3$	Phenethylamines	Peyote, San Pedro and Peruvian Torch cactus	
MDMA (3,4-methylenedioxymethamphetamine)	$C_{11}H_{15}NO_2$	Amphetamine derivative	Made in a lab	
DMT (N,N-Dimethyl-5-methoxytryptamine)	$C_{13}H_{18}N_2O$	Tryptamine alkaloid	Ayahuasca and Colorado River Toad	
LSD (lysergic acid diethylamide)	$C_{20}H_{25}N_3O$	Ergoline alkaloid	Turbina corymbosa plant	

## Pharmacology of Psychedelics

The majority of compounds within the psychedelic class of drugs function as non-selective serotonin agonists with psychoactive effects primarily thought to be related to agonism of the 5-hydroxytryptamine 2A (5-HT<sub>2A</sub>) receptor subtype. The 5-HT<sub>2A</sub> receptor is a G protein-coupled receptor (GPCR) that preferentially couples with a G<sub>q</sub>-protein, stimulating the subsequent activation of phospholipase C and the signaling cascade that leads to the activation of protein kinase C and mobilization of Ca<sup>2+</sup> from intracellular stores (Thomas, Malcolm, and Lastra 2017).

The first experiment to illustrate this mechanisms in humans was a clinical study in 1998. It clearly showed that the hallucinogenic effects of psilocybin were blocked by the 5-HT<sub>2A</sub> receptor-selective antagonist ketanserin. With this data and observations, a direct correlation could be made that the experiences felt from psilocybin were due to the activation of the 5-HT<sub>2A</sub> receptor (Vollenweider et al. 1998).

Unfortunately, that is the only definitive evidence in humans that is available as to what the actual mechanisms of psychedelics are in the human brain. All psychedelic drugs are chemically related but they are not identical in terms of their mechanisms of action. The pharmacology of each of these psychedelics are incredibly diverse and have a wide range of effects on the brain which can lead to a high risk of interactions with other drugs or conditions. We do not completely understand how psychedelics work which makes it difficult to understand the dose-response relationships, duration of action and toxicity of psychedelic medication. These must be known or at least have a basic understanding of them in order to ensure the efficacy and safety of psychedelics (Sellers and Leiderman 2017).

However, in the past ten to fifteen years, technology imaging technology has greatly improved so that it has allowed scientists to see the effects of psychedelics on the brain firsthand. These new technologies have revealed that brain activity is organized into functional networks, known as resting-state networks (RSNs). Scanning of these networks has allowed scientists to learn extensively about how psychiatric illnesses can disturb these delicate networks. These altered states coming from obsessive-compulsive disorder, depression, anxiety and many more illnesses can be detected by blood oxygen level-dependent fMRI. (Yuan et al. 2016). The greatest improvements in symptoms occur in patients who have a powerful, mystic, transcendent experience. (RR Griffiths et al. 2006). In a study, it was found that psilocybin decreased the connectivity within an important brain network called the default mode network (DMN). Using BOLD fMRI the researchers were able to observe decreased brain activity in the posterior cingulate cortex as well as in the medial prefrontal cortex, which are typically overactive in patients with major depression. (Robin L. Carhart-Harris et al. 2017). This is all exceptionally promising in the possibility of treating major depression.

### Safety of Psychedelics

Research has shown that psychedelics are much more physiologically safe than opiates (Jaffe 1985). The peripheral activation of the 5-HT<sub>2A</sub> receptor is associated with increased vascular which can lead to thrombus formation, platelet aggregation and coronary artery spasms (Nagatomo et al. 2004). 5-HT<sub>2A</sub> receptors are also responsible for the constriction of the portal venous system. When taken in an uncontrolled environment, paranoia and distress can result from it.

Even when massive doses of LSD were consumed (1000-7000ug compared to the normal 100-200ug dose), the individuals survived with hospital treatment without any known long term adverse effects. Despite the unpleasant symptoms of hyperthermia, respiratory problems or being in a comatose state, they could be saved (Klock, Boerner, and Becker 1974).

Mescaline, still commonly used and legally allowed for use by Native American tribes and churches, has not been shown to cause neurological deficits. This was investigated by assessing cognitive function using the Rand Mental Health Inventory where no significant deficits were observed (Halpern et al. 2005).

Regarding MDMA, there have been reports of increased feelings of anxiety, depressed mood and irritability, as well as more general feelings of dizziness, fatigue, headache, tight jaw, and nausea in over 40% of the participants which typically subsided over the next seven days. This was after active doses of MDMA ranging from 75-125 mg were administered in six randomized, double-blind, controlled clinical trials from April 2004 to February 2017. There were no changes in neurocognitive function observed, which means that the MDMA did not cause any neuro deficits and their cognitive level stayed the same. There were however, four reported cases of suicidal ideation but there was no suicidal behavior during the treatment period of dosing. (Mithoefer et al. 2019).

When psilocybin is administered in a controlled setting, typically under the supervision of a qualified health professional, it can cause delayed headaches with differences of severity and incidence according to dosage (Johnson, Sewell, and Griffiths 2012). However, when psilocybin is ingested by a person with other medical conditions, it can have severe, harmful effects as illustrated by a hepatitis C-infected 25-year old man who developed rather severe

rhabdomyolysis, renal failure, encephalopathy and cortical blindness but was able to recover over several months back to full health (Bickel et al. 2005).

The main adverse effects reported with the use of psychedelics is impaired judgement which is a major concern when used recreationally, or a heightened and altered sense of self, which have occasionally led to accidental deaths (i.e. by jumping off a building because the individual thought that they could fly). (Keeler and Reifler 1967)

### Therapeutic Uses of Psychedelics

In recent years, there has been great speculation about the potential therapeutic effect of psychedelics for patients afflicted by a variety of mental illnesses. There was quite a bit of research done prior to the passing of the Controlled Substances Act of 1970. After this legislation passed and was put into effect, clinical research about this potential treatment option for mental conditions essentially ceased until the 2000s. (L. Grinspoon and Bakalar 1997). However, research with controlled substances remains challenging and few studies have been able to be conducted with appropriate sample size and study design until recently.

### Depression

Depression is a very prevalent and debilitating mental illness affecting over 17 million adults and almost 2 million children in the United States (Major Depression 2017) and is the leading cause of suicides and disability worldwide (WHO 2017). It affects women twice as much as men, including postpartum and major depression (Prevalence of Depression Among Adults 20 and Over 2017).

The current standard method to treat depression is to use cognitive behavioral therapy (CBT) alone or in conjunction with one or several antidepressant medications such as selective



serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs), with around 50% of patients noticing an improvement in symptoms (Pharmacists) 2020). CBT therapy alone can be very effective for mild and situational depression but patients diagnosed with major depression are usually subjected to the trial-and-error method to find the right antidepressant. One antidepressant may improve the condition for one patient but can make another patient worse off or have no effect at all. Those who suffer from treatment-resistant depression sometimes have to resort to more aggressive forms of treatment such as electroconvulsive therapy (ECT) which is very effective but has many unwanted side effects and some argue that the risks outweigh the benefits (Kerner and Prudic 2014). These problems highlight the need for alternative, safer treatments. One of these options are psychedelics.

Recently, there have been open-label studies of ayahuasca, an ancient compound used in religious ceremonies by the South American indigenous populations near the Amazon Basin. The compound is extracted from the *Psychotria viridis* and *Banisteriopsis cappi* plants. It has been legal for spiritual practices in Brazil since 1987 (Frecska, Bokor, and Winkelman 2016).

In 2015, ayahuasca was given in a single dose to 17 participants who were diagnosed with major depressive disorder. The severity of depression in these individuals was measured by two scales, the Hamilton Depression Rating scale (HAM-D) & the Montgomery-Aesberg Depression Rating Scale (MADRS) before and after the ayahuasca was administered. Within hours, study participants experienced a notable decrease in depressive symptoms which was maintained for up to three weeks (Osorio et al. 2015). Despite these hopeful outcomes, the relevance of these results is compromised by the sample size and the lack of a control group in the experimental design.

In 2019, another trial was done using the same depression measuring scales but this time a bit larger and using a placebo-controlled group. In this study, ayahuasca showed a significant improvement in depressive symptoms compared to placebo. This study confirmed the potential prospects of therapeutic effects on patients suffering from major depression (Palhano-Fontes et al. 2019). Furthermore, mental health evaluations done on regular ayahuasca consumers compared to non-ayahuasca consumers showed that regular ayahuasca consumers experienced a preserved cognitive state, reduction of anxiety, an increased sense of well-being, and less depressive symptoms ((Bouso et al. 2012),(Grob et al. 2011), (Barbosa et al. 2016). The main limitation of these studies often include sample size, and the examination of only treatment-resistant depression. Another obstacle is trying to maintain complete double blindness throughout the entire trial as participants who have had ingested a psychedelic drug display very unique effects (Palhano-Fontes et al. 2019).

Psilocybin is also another promising psychedelic to treat depression. A 2016 small-scale study on participants who had treatment resistant major depression using the HAM-D and BDI scale showed that by the end of the first week, the response rate to psilocybin was 67% and seven out of the eight patients went into remission. At 3 months, 58% of the participants continued to maintain their alleviated symptoms and 42% remained in remission. Once again these are promising results, but a blind, randomized study is still lacking (Robin L Carhart-Harris, Bolstridge, et al. 2016).

Another study was done with psilocybin in 2017 where functional magnetic resonance imaging (fMRI) was used to measure cerebral blood flow (CBF) and blood oxygen-level dependent (BOLD) resting-state functional connectivity (RSFC). fMRIs were done pre and post treatment with psilocybin. Within the first week, all 19 participants showed decreased depressive

symptoms and by week five, almost half of the participants maintained this reduction in symptoms. The fMRIs from patient's post-treatment revealed a decrease in activity in the temporal cortex as well as in the amygdala which is correlated with decreased depressive symptoms. Increased RSFC was seen post treatment within the default-mode network (DMN). There was also an increased ventromedial prefrontal cortex-bilateral inferior lateral parietal cortex RSFC. The observations support the current theory is that psilocybin appears to have a "reset" effect on the brain, returning the state of the brain back to the equilibrium before the depressive symptoms began (Robin L. Carhart-Harris et al. 2017).

Another fascinating aspect of psilocybin therapy is the reduction of suicides in people who have consumed it even if it was only once in their entire lifetime. Thoughts of suicide, suicide attempts, and psychological distress were all found to be decreased after psilocybin use and psilocybin has been suggested as a "suicide prophylaxis" (Hendricks, Johnson, and Griffiths 2015).

#### Depression and Anxiety in Terminal Patients

Psychedelics have also been used to help ease the minds of patients who have gotten a life-altering or life-threatening diagnosis such as cancer. Depression affects 20% of cancer patients compared to around 6% in the general population. Traditional antidepressants can have negative interactions with chemotherapy medications and can worsen cancer symptoms like nausea, fatigue and weight-loss (Pitman et al. 2018). Because of this, researchers have been looking into alternatives to aide patients in such situations.

LSD was the very first psychedelic to be researched for this purpose in the 1960s. A group of researchers went to Spring Grove State Hospital in Maryland to conduct research on patients who were dying of cancer in 1963. Around two-thirds of the cancer patients treated with

LSD felt a sense of relief as well as an improved mood and reduced anxiety associated with the fear of death (Pahnke et al. 1970).

A double-blind placebo-controlled study with psilocybin on this patient population was conducted in 2011 with twelve participants with advanced-stage cancer who were experiencing reactive anxiety and subsequent depression. A baseline score of anxiety and depression were measured by Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI) before the psilocybin was administered as well as a Profile of Mood States (POMS). The participants were tracked for six months. The mean BDI score was lower than baseline after six months and the mean STAI was lower than baseline after only one month compared to the placebo. However, the mean POMS score was not significantly different than the baseline score taken before the administration of psilocybin (Grob et al. 2011).

Research continued and in 2014 was done with LSD with twelve patients that were diagnosed with life-threatening diseases. The study found positive trends with a State-Trait Anxiety Inventory (STAI) over the course of twelve months (Gasser et al. 2014). This study has proven LSD-assisted therapy can be extremely beneficial to patients who are experiencing life-threatening diseases.

Another similar double-blind and placebo-controlled trial was conducted in 2016, but this time with twenty-nine participants using psilocybin and psychotherapy combined (or placebo and psychotherapy combined). The study found that in addition to the rapid anti-depressant effects psilocybin had on the participants and increase in quality of life, these effects were sustained for several months. By the six and a half month follow up, between 60-80% of the participants in the study were continuing to experience significant reductions in depression and anxiety as well as improved attitudes towards death and dying (Ross et al. 2016).

Also in 2016, another trial was conducted (randomized, double-blind, cross-over) with fifty-one cancer patients. The cancer patients' immediate community (hospital staff workers such as nurses, therapists, doctors and family), rated the patient's mood, behavior and attitudes throughout the study. At the six-month mark after the study had begun, over 80% of the patients showed continued and sustained improved mood and anxiety as well as reported increased well-being and life satisfaction which matched the patient's immediate community's observations (R.R. Griffiths et al. 2016).

These trials with psilocybin were small and not always uniform throughout, so Johns Hopkins and New York University tried to overcome the limitations of previous studies (sample size, lack of standardization) and designed a randomized double-blind and placebo controlled clinical trial which is the gold-standard to properly assess the efficacy of a pharmacological treatment. They also used differing doses of psilocybin and found that high doses of psilocybin (22 to 30 mg) had a distinct and significant advantage over low doses of psilocybin (1 to 3 mg). The participants who received the high doses of psilocybin experienced sustained reductions in depressive symptoms and anxiety as well as a feeling a greater sense of personal meaning in their lives (R Griffiths 2015).

#### Substance Abuse and Nicotine Addiction Treatment

Alcohol use disorder affects nearly 15 million people in the United States over the age of 12, with 9 million being men. Alcohol poisoning accounts for over 18% of emergency room visits with 95,000 individuals dying for alcohol-related death every year, and 10,000 of those deaths were from driving while under the influence. Alcoholism has been known as one of the leading causes of premature death and liver disease as well as heart disease and stroke. Alcoholics are also at an increased risk for depression and sleep disorders. Alcoholism is

typically treated with group therapy, individual psychotherapy or in combination with drugs such as acamprosate, disulfiram and naltrexone which have been shown to have varied success rates (Alcohol Use in the United States 2020).

Cigarette smoking is the leading cause of preventable deaths in United States with around 435,000 people dying each year from smoking-related causes. Around 45 million Americans use tobacco products. Cigarettes can cause lung cancer, ulcers, infections, diabetes and reproductive disorders. Around 70% of smokers say that they want to quit smoking, but only 3% successfully quit (Benowitz 2010).

Since both alcoholism and nicotine addiction are difficult to treat, psychedelics have been studied as a possible therapy. In the middle of the 20<sup>th</sup> century, LSD was being explored as an effective option to help people who were alcoholics, particularly by Canadian psychiatrists Humphrey Osmond and Abram Hoffer. In 1971, researchers looked at 1100 patients who suffered from alcoholism in the period from 1953-1969 who were treated with LSD. They came to the conclusion that at 10 months following the LSD treatment, 75% of patients experienced decreased use of alcohol compared to 44% of the control population (Abuzzahab and Anderson 1971). While this data revelation was promising, research on psychedelics ceased for forty years until the 2010s due to tightened legislation.

Psilocybin has also been effective in helping long-time cigarette users quit smoking. In 2014, an open label study was conducted with fifteen participants who were nicotine-dependent cigarette smokers who wanted to quit smoking and had tried but failed. The study was a 15-week program combining CBT and psilocybin where CBT was done once a week and psilocybin administration took place at week 5, week 7 and an optional dose at week 13. At six months post-treatment, 80% (12 out of 15 participants) showed complete smoking cessation. This rate of

cessation is much higher than the average 35% other behavioral or drug therapies have to offer. Twelve months following this study, 67% of the participants maintained cessation of smoking (Garcia-Romeu, Griffiths, and Johnson 2014).

Interestingly, psilocybin has also been used to help treat alcoholism, as shown in a study done in 2014 at the University of New Mexico. A sample group of ten volunteers with a clinical diagnosis of alcoholism were admitted to the study. The study first did cognitive behavior therapy (CBT), then CBT coupled with psilocybin administration, then a follow up post-treatment. They found no decrease in alcohol abuse with just CBT alone, but found a dramatic decrease after the participants had received a dose of psilocybin. From these results they concluded that the more mystical the psilocybin experience, the stronger the improvement of behavior (Bogenschutz et al. 2014).

A meta-analysis revealed that a single dose of LSD administered to patients diagnosed with alcoholism showed a large decrease in the abuse of alcohol, coming to the conclusion that administration of LSD correlated with lower alcohol abuse. This analysis looked at 536 participants, 325 who received the single dose or 211 who received the control, from the years 1943 to 2010 (T. S. Krebs and Johansen 2012).

### Obsessive Compulsive Disorder

Obsessive Compulsive Disorder (OCD) is one of the most difficult mental illnesses to treat. Around 2.2 million Americans each year suffer from OCD each year, with over half of clinically diagnosed patients reporting severe impairment in daily life (NIMH 2019). OCD also has an incredibly high comorbidity rate with over 75% of patients with OCD having also been diagnosed with anxiety disorders such as panic attacks, phobias or PTSD; over 60% have been diagnosed with major depression or bipolar depression; 55% have been diagnosed with ADHD

and almost 40% have a substance abuse disorder (Psychiatry 2008). Typical treatment of serotonin reuptake inhibitors (SSRIs) has limited efficacy with improvement in roughly half of patients which has allowed the opportunity for new therapies to arise.

A case study with LSD done in 1977 was conducted on a thirty-year old man suffering from disabling OCD that prevented him from engaging in everyday activities. The treatment of this man was done over fifteen months solely with LSD. He was administered LSD at home and checked on by nurses and doctors over these fifteen months. At the three year mark, the man was completely symptom-free and continued to be symptom-free twelve years later (Brandrup and Vanggaard 1977).

Psilocybin has also been used to help treat OCD. In 1996, a twenty-seven-year old man with severe body dysmorphia who would spend hours looking in the mirror to inspect his appearance was given psilocybin mushrooms. After ingestion, his sense of body dysmorphia decreased and sense of well-being increased (Hanes 1996).

A pilot study of nine participants was done in 2006 with individuals clinically diagnosed with OCD. The participants were given four different doses of psilocybin, separated by one week. Their symptoms were measured at hours 4, 8, and 24 using the Yale-Brown Obsessive Compulsive Scale. Significant decreases in symptoms were observed in all participants with between a 23-100% reduction in symptoms. However, by the six month mark, only one participant was still in remission. Researchers suggest that this warrants future studies but instead with a blinded, randomized, placebo-controlled study for optimal results and data collection (F.A. Moreno et al. 2006).

While these short-term and small-scale studies provide promising results for those suffering from OCD, there is still need for extensive clinical trials in the future as current



treatments for OCD have less than ideal efficacy and LSD and psilocybin could hold a much-needed treatment to those who are suffering from it.

### Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a common illness seen in combat veterans who have witnessed death or experienced severe injury themselves but it also common in survivors of sexual assault, rape or domestic abuse. Around 8 million adults in the United States have had PTSD in the past year. The standard course of treatment is typically CBT alone or used in conjunction with anti-depressants but that doesn't always work for everyone (2019).

MDMA has been shown to help alleviate symptoms in those suffering from PTSD. MDMA significantly increases serotonin and dopamine levels which can elevate mood and improve behavior. The first study to look at the effect of MDMA-assisted psychotherapy on individuals experiencing PTSD was done in 2011 and this study found a dramatic decrease in symptoms; 83% of participants that received the MDMA dose during psychotherapy sessions experienced a decrease in symptoms compared to only 25% in the placebo + psychotherapy group (Mithoefer et al. 2011). This improvement was sustained 74 months after treatment in the majority of participants (Mithoefer et al. 2013).

A meta-analysis exploring the effects of MDMA on PTSD patients analyzed six different double-blind, controlled clinical trials at five separate study sites conducted between 2004 and 2017. It was found that 54.2% of the participants who received the active MDMA dose experienced a decrease in symptoms while only 22.6% of participants in the control group experienced a decrease in symptoms (Mithoefer et al. 2019).

## Cluster Headaches

While cluster headaches are very rare, affecting up to 0.1% of the population, they are extremely painful, uncomfortable and severely debilitating. Individuals with cluster headaches can experience these painful attacks lasting from 15 to 180 minutes a day up to 8 times a day. The standard course of treatment is usually high-flow oxygen inhalation therapy but this usually requires a visit to a doctor's office (Yi-Ting Wei, Jia Yuan Ong, and James Goadsby 2018).

In 2006, an online survey was conducted with 53 individuals who suffered from severe cluster headaches and found that 22 out of 26 individuals who used psilocybin found that it prevented the headaches from occurring while 25 out of 48 psilocybin users and 7 out of 8 LSD users found that the cluster headaches terminated. There was also a successful rate of remission of headache attacks for 18 of 19 psilocybin users and 4 of 5 LSD users (Sewell, Halpern, and Pope 2006).

There have also been reports of a non-hallucinogenic LSD derivative known as BOL-148, to be effective in treating cluster headaches as well. This specific derivative was given to five individuals experiencing repeated cluster headache attacks and with a single oral dose of BOL-148, the severity of the cluster headache was severely reduced or the vicious cluster headache section was broken. This indicates that the therapeutic effect for the reduction in headache symptoms does not have to do with the psychoactive effects of the hallucinogenic version of LSD. The research on why this occurs is limited but theories have stated that these headaches are eased through the 5-HT<sub>2A</sub> receptor. The differences in pharmacology have been examined between BOL and LSD but the information was inconclusive (Karst et al. 2010).

## Other Potential Therapeutic Uses

### Inflammation

Most treatments for inflammation are put into three categories: nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressant steroid drugs (glucocorticoids), and biologics. NSAIDs work by blocking the activity of cyclooxygenases which produces prostaglandins to signal an inflammatory response. NSAIDs can be exceptionally hard on the kidneys and liver, especially to those that suffer from kidney or liver disease. Glucocorticoids, such as prednisone modify gene expression to prevent cytokine production, among other effects. Because these drugs suppress the immune system, individuals who take the medication are more susceptible to infection. Biologics are antibodies or antibody-like molecules which block the activity proinflammatory cytokines. Biologics can also cause an increased risk of infection as they control the inflammatory disease which can alter the immune system's ability to fight infections. This has created the need for more therapies to treat and control inflammation that have less severe side effects.

However, there appears to be a fourth class of anti-inflammatories: activators of the serotonin 5-HT<sub>2A</sub> receptor. Scientists have known for ages that increased serotonin correlated with an increase in serotonin receptors in inflamed tissues (Baganz and Blakely 2013). The 5-HT<sub>2A</sub> receptor is the most widely expressed serotonin receptor in mammals, having a presence in essentially all tissues. A study on rats found that the activation of 5-HT<sub>2A</sub> receptor had an anti-inflammatory effect as it prevented the anti-inflammatory response induced by the tumor necrosis factor alpha (TNF-alpha) (Yu et al. 2008).

While this research is very promising, there haven't been any human trials examining this. The only current trials have been done on animals, primarily rats. The mechanism for the

anti-inflammatory properties to take place are still largely unknown and can only be hypothesized for the moment.

## Tissue Regeneration

Tissue regeneration is a very important field of medicine. The goal of tissue regeneration is to restore the function of tissue. This can help a variety of people who suffer from spinal cord injuries, liver or kidney disease, burn survivors, etc. The current experiments that have been done with tissue regeneration have been with pluripotent stem cells which can differentiate into different tissue types. According to recent research, psychedelics may have a role in regenerating tissue.

A study was conducted in 2006 on rats who received a staggered double hemi-section (DH) two days after they were born (P2) on the left hemi-cord at T11 and right hemi-cord at T12. Another group had a complete transection done at T11 (CT) and the last group was the control for the experiment. The rats were then treated with neurotrophin-2 (NT-3) and/or LSD. The drugs were administered just above the lesion site at post-natal days 4,6,8, and 10. The rats with the staggered double hemi-section and complete transection who received the NT-3 and LSD showed improved coordination and more kicks while swimming. By day 40, the kicking frequency was on par with the control group which suggests that NT-3 and LSD as a combination treatment might be an effective avenue for spinal cord injuries in humans as it appears to promote neuronal regrowth (Arvanian et al. 2006).

## Where Are We Now With Psychedelics? – Progress and Challenges

The current and main challenge with approving psychedelics for medical use is due to its classification as a Schedule I drug. For a Schedule I drug to be allowed for medical use requires several special licenses. To receive such special licenses, several security protocols must be in place to ensure it is only being used by approved individuals, who have had a background check, in the right context and environment. The trials with such drugs are closely monitored as well (Rucker, Iliff, and Nutt 2017).

To bypass what could be a long and tedious process, the FDA has made available several special regulatory pathways. There is the Fast-track designation applies to a drug that is being intended to treat a serious condition and preliminary data points to a potential solution. There is the breakthrough therapy designation where the drug is intended to treat a serious condition and preliminary clinical evidence supports significant improvements in the subject's condition. Another possibility is the accelerated approval pathway where the drug treats a serious condition and could potentially provide an advantage over current available therapies and possibly replace them as the leading way to treat that particular illness (Sellers and Leiderman 2017).

In 2019, the Food and Drug Administration (FDA), approved the beginning of Phase 3 clinical trials with MDMA for severe PTSD. These Phase 3 trials are going to be large, multi-center, and placebo-controlled for best possible results. These Phase 3 trials will be conducted at fifteen sites in the United States, Canada and Israel, with plans for expansion into the European Union. MDMA-assisted psychotherapy for the treatment of PTSD is anticipated to be approved by the FDA by the end of 2021 or the beginning of 2022 (Doblin et al. 2019).

Successful preliminary trials have led the FDA to approve two clinical trials for psilocybin in its treatment for depression. This process started in 2018 when the FDA proclaimed

Compass Pathways' psilocybin research a major breakthrough and moved on the clinical trials to Phase 2B which are currently underway in both Europe and North America respectively. By the end of 2019, the breakthrough therapy status was also designated to the Usona Institute for its Phase 2 clinical trial and is expected to be finished in late 2021 (Covas and Campbell 2021).

Ayahuasca has been approved for Phase I trials for the formulation of ayahuasca tea from the two plants *B. Caapi* and *P. viridis*. As of early 2021, DMT, the active ingredient in ayahuasca, has been moved to a Phase I trial initiated by a London-based pharmaceutical company for treatment in patients suffering from anxiety and depression. A Dublin-based pharmaceutical company has announced its successful completion of their Phase I clinical trial with DMT and will begin Phase 2 soon (Zipkin 2021).

In 2020, a New York-based company acquired rights to begin eight clinical trials with LSD after preclinical research indicated potential efficacy for treating those with anxiety and ADHD. While this is a very important and promising step, the timeline for completion and approval is still relatively unclear (Williams 2020).

### Conclusion

While all of these trials have revealed some very important and ground-breaking information, psychedelics are still a long way from becoming a mainstream treatment for several illnesses and ailments. Psychedelics are unique in that they must be used under the direct supervision of a physician, so it's called psychedelic-assisted therapy. Anti-depressants are prescribed and monitored by a physician in an indirect way in that you pick up the medication at a pharmacy and take it at home under the direction of a physician. Phase 3 and Phase 2 trials have just recently begun with different psychedelic drugs. Most other trials that have been done have been small-scale and poorly designed due to the legal aspects surrounding the acquisition of

such controlled substances. The recent designation of breakthrough therapy by the FDA for MDMA and psilocybin for PTSD and MDD, respectively, created an unprecedented opportunity for quality research that will provide much needed information to support the therapeutic use of psychedelics.

Another challenging obstacle is going to be changing the attitudes towards psychedelics. At the moment, psychedelics are clumped together with other illicit drugs such as cocaine and methamphetamine which are legitimately dangerous and pose severe health and societal concerns. Because of this, public opinion might associate psychedelics with dangerous drugs, even if they have widely different therapeutic and safety profiles. Public health initiatives from the National Institute of Health (NIH) and DEA are vital in changing this view. Without the support and trust from the general public, getting the approval of society and eliminating the taboo of psychedelics will make it hard for them to be integrated into society as a reliable form of medical treatment.





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