A REVIEW ON THE USE OF LSD AND PSILOCYBIN AS A FORM OF TREATMENT

by

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HONORS THESIS

Submitted to Texas State University
in partial fulfillment
of the requirements for
graduation in the Honors College
December 2021

Thesis Supervisor:

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DEDICATION

I am grateful to my loved ones for getting me this far in my academic career. For all the tears, stress, and hard work, I dedicate this thesis to my encouraging parents, loving partner, caring siblings, and kind friends without whose constant support this paper would not be possible.

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ABSTRACT

Interest surrounding the potential benefits of psychedelics has increased in recent years. This literature review will discuss the potential benefits of psychedelics and review research examining how they may be used to help those suffering from depression, substance abuse, obsessive-compulsive disorder, or end-of-life anxiety (a syndrome that usually occurs near the end of one's life in which an individual may experience anxiety, restlessness, and agitation). Thus far, psilocybin has been used to treat alcohol dependence with abstinence noted after psilocybin administration accompanied by some form of therapy (Bogenschutz et al., 2015). Additionally, abstinence from tobacco usage has been reported following psilocybin treatment up to six months after the first dosage (Johnson et al., 2014; Johnson et al., 2017). There have been promising effects of psychedelic (LSD and psilocybin) treatment on major depressive disorder and end-of-life anxiety with significant reductions of symptoms reported in multiple studies (Carhart-Harris et al., 2018; Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Current challenges in psychedelic research are present in the variance of dosage amount (micro-dosing- intaking small sub-behavioral doses in which the individual does not experience psychotropic effects, and what is considered a moderate, large, and mild dose), dosage schedule, and adverse effects reported in research studies. However, regardless of unanswered questions, psychedelics demonstrate potential in treating ailments of the mind and serotonin-related disorders.

I. INTRODUCTION

Mind-altering drugs have been used for religious purposes for thousands of years. Drug-induced states were thought to allow the individual to travel to different realms of consciousness and heal the state of disorder (Schultes and Hofmann, 1980). When LSD was discovered, it was used to treat anxiety, depression, addiction, and psychosomatic diseases (Abramson, 1967). After a 25-year hiatus in psychedelic research, findings reaffirm that psychedelics alleviate depression, anxiety, substance abuse, and other disorders.

The mechanisms regarding how psychedelics affect the brain are unknown. There are indications that the effect of psychedelics on serotonin is the root of their effectiveness, especially in studies of end-of-life anxiety. On the other hand, individuals felt facilitated access to anxieties and emotions under the influence of psychedelics, which is postulated to explain positive results in treating unfavorable mental states. This review focused on the effects of LSD and psilocybin; however, other psychedelics like mescaline (obtained from the peyote cactus) (Uthaug et al., 2021), DMT (Lancelotta & Davis, 2020), and MDMA (Barone et al., n.d.) are also studied for their effects and potential. This report will discuss the history of LSD and psilocybin, their effects on the brain both chemically and psychologically, and current research findings after the 25-year hiatus. Then, it will outline challenges in the field and discuss the potential use of LSD and psilocybin as a form of treatment for depression, anxiety, substance abuse, and obsessive-compulsive disorder.

II. HISTORY OF LSD AND PSILOCYBIN

Traditionally, psychedelics have been used in healing, divination, and spiritual

practices (Griffiths et al.,2006). The oldest recording of the use of psilocybin exists in the caves at Tassili n'Ajjer in Algeria. The 9,000-year-old cave paintings portray ritual practices associated with the use of psilocybin ("magic mushrooms") (McKenna, 1999). Psilocybin has documented use in various indigenous cultures. On the other hand, in 1938, researcher Albert Hofmann first developed lysergic acid diethylamide when working with ergot, a fungus found on rye and other grains. Hofmann accidentally ingested the substance and reported intense colors and shapes. Intrigued by these effects, he decided to dose himself three days later (History.com Editors, 2018). On April 19, 1943, Hofmann took a larger dose of this substance and, famously, rode his bicycle home while experiencing the first-ever LSD trip (Hisory.com Editors, 2018).

Not long after, in 1950, researchers wrote the first report on LSD in the English language detailing the effects of LSD (Carhart-Harris & Goodwin, 2017). In the early 1950s, LSD was used by psychologists and psychiatrists on tens of thousands of patients as a part of psychedelic psychotherapy that persisted over the span of fifteen years (Carhart-Harris & Goodwin, 2017; Grinspoon & Bakalar, 1997). This kind of experimentation was conducted with the goal of expanding clinical discoveries and research. In the early 1950s to early 1960s, researchers used psychedelics methodically to treat alcoholism, neurosis, schizophrenia, and psychopathy (Costandi, 2014). Specifically, researchers dosed patients with LSD to treat alcoholism, obsession, anxiety, and depression with considerable success rates (World Science Festival, 2019). In addition, researchers developed a deeper comprehension of receptors, neurotransmitters, and the development of other psychoactive drugs because of this initial research (World Science Festival, 2019).

Around this time, the U.S. military and CIA saw Hofmann's discovery as a possible weapon (mainly using LSD and electroshock) (Gross, 2019). In the 1970s, weaponization attempts conducted by the Army and the Central Intelligence Agency began to reach the public eye causing LSD and other psychedelics to be perceived as dangerous and a threat to society (Lattin, 2017). Additionally, LSD, other psychotropic drugs, including marijuana, were all associated with the antiwar, sex liberation counterculture present at the time (Lattin, 2017). The fear of LSD weaponization, along with the stigma surrounding psychotropic substances, created the perfect environment for what followed.

The Nixon administration targeted psychoactive drugs as part of their political reaction to the liberation movement (LoBianco, 2016). One of his political moves against drugs was the Controlled Substances Act in 1970. This act listed LSD and psilocybin as having no accepted medical use and a high potential for abuse, finally illegalizing the substances (World Science Festival, 2017). Unfortunately, by the early 70s, research on the potential of psychedelics became stagnant; this was due to safety concerns surrounding use, ethical usage, and lack of funding (Killion et al., 2021). Furthermore, as the negative publicity and government anti-drug advertising unraveled, federal funding was withdrawn for human psychedelic research (Johnson et al., 2008). A lack of funding along with the illegality of the drug hindered the progress of psychedelic research. The War on Drugs had successfully been waged against psychedelics, and research abruptly stopped.

Although LSD and psilocybin remain illegal, the research surrounding these substances is continuously expanding. Science suggests that there may be significant

potential in the use of LSD and psilocybin in a clinical setting for treatment of various mental illnesses. On a positive note, the hiatus in research caused by the War on Drugs led to more detailed and cautious guidelines for psychedelic research in modern psychology to create ethical and experimental data instead of the unstructured research in the early 60s. Not only are researchers taking an interest in LSD and psilocybin, but the general population has as well. According to the National Survey of Drug Use and Health, LSD and psilocybin use increased by 50% from 2015 to 2018 (Yockey et al., 2020). Additionally, a study conducted by Killion et al. (2021) found a 200% increase in LSD use over 2002-2018. Research on the benefits of LSD and psilocybin use has reignited; therefore, it is imperative now more than ever that we try to analyze the benefits, risks, and uses of these substances. This literature review will discuss the potential benefits of psychedelics, the possible mechanisms of function, current research about their benefits, and some challenges in psychedelic research.

III. HOW LSD AND PSILOCYBIN AFFECT THE BRAIN

LSD and psilocybin both have similar molecular structures and impact the brain in a similar style. First, this section will discuss the role of LSD and psilocybin in increasing connectivity and their agonistic behavior at 5-HT2A receptor sites. Then, the following area will report the psychological effects of LSD and psilocybin that contribute to alleviating negative thoughts. Even though all the effects of LSD and psilocybin on the brain are not known, in cases of depression, end-of-life anxiety, obsessive-compulsive disorder, and substance abuse disorder, a combination of increased serotonin levels, increase in prefrontal cortex activity (PFC), and default mode network (DMN) deactivation may indicate the therapeutic benefits of psychedelic administration.

The Mechanisms of LSD and Psilocybin on the brain.

To understand the effects of LSD and psilocybin on the brain, the role of serotonin must be discussed. Serotonin is perhaps the most well-known neurotransmitter correlated with major depressive disorder, mood disorders, schizophrenia, anxiety disorders, addiction, attention deficit hyperactivity disorders, and autism (Berger et al., 2009; Lin et al., 2014). Moreover, "the development of selective serotonin reuptake inhibitors (SSRIs) illustrates the importance of the serotonergic system with regard to the treatment of mental disorders" (Lin et al., 2014, p.196). This suggests that serotonin may have a significant role when treating some mental disorders like depression, and because psychedelics increase serotonin levels in the brain, they have therapeutic benefits in treating the same psychological disorders that are currently treated with SSRIs.

Researchers have discovered that psilocybin, LSD, and serotonin all have similar molecular structures and that LSD and psilocybin fit the brains' 5-HT2A receptors, making them serotonin agonists (Wacker et al., 2017). Interestingly, it seems that LSD fits this receptor site better than serotonin itself (Backstrom et al., 1999)! Furthermore, 5HT2A receptors are found in high concentrations in the prefrontal cortex, striatum, ventral tegmental area, and thalamus (Pazos & Palacios, 1985). This is relevant because of the relationship between serotonin and the default-mode network (DMN). This network consists of the medial prefrontal cortex, posterior cingulate cortex, and inferior parietal cortex (Buckner et al., 2008) and interacts with profound and older brain centers involved in emotion and memory like the thalamus (Lim et al., 2019). The DMN has high concentration of serotonin receptor sites, especially in the prefrontal cortex. Other brain areas not in the DMN, like the thalamus, contain high levels of serotonin receptors and

interact with the network. The DMN is responsible for self-reflection, mental time travel, the theory of mind (Molnar-Szakacs et al., 2013); it is most active when an individual is not focusing on the outside world and is engaging in introspective thoughts (Buckner et al., 2008).

A study by Schrantee et al. (2018) focused on the effects of SSRIs on the DMN and concluded that evidence indicates a significant role of serotonin in the function and connectivity of the DMN. In Helmbold's study (2016), the decreased synthesis of serotonin was significantly correlated with a reduction in baseline brain activity in areas of the DMN. Moreover, preliminary studies imply that 5-HT is involved in the function and connectivity of the DMN (Helmbold, 2016). Though it is unknown precisely what happens to the brain during an LSD or psilocybin experience, there is an established correlation between serotonin and the DMN. One significant finding has been the decreased activation of the default mode network discovered through fMRIs conducted on participants who had ingested psychedelics (Carhart-Harris et al., 2016). After studying fMRI images of individuals on LSD, Dr. Carhart-Harris concluded that as the DMN is deactivated, brain areas with no prior communication begin connecting, which contributes to the hallucinogenic experience (Carhart-Harris et al., 2016). Specifically, Muller et al. (2018) explain these consequences of LSD administration:

> "...significantly decreased functional connectivity within visual, sensorimotor, and auditory networks and the default mode network. While between-network connectivity was widely increased and all investigated networks were affected to some extent, seed to voxel analyses consistently indicated increased connectivity between networks and subcortical (thalamus, striatum) and cortical (precuneus,

anterior cingulate cortex) hub structures" (p. 2213).

The psychedelic caused deactivation of the DMN indicates the possible effectiveness of these substances in treating disorders involved with DMN abnormalities. For instance, Mulders et al. (2015) and Kaiser et al. (2015) have reported that an increase in activity of the DMN appears to be characteristic in mood disorders; moreover, psychedelic-assisted psychotherapy may be an effective treatment as its' inhibitory effects on the DMN counter the high activation present in patients with mood disorders (Ruban & Kolodiej, 2018). Expanding from the treatment of mood disorders, the role of the prefrontal cortex (PFC) in neuropsychiatric disorders and the reported impact of psychedelics on the PFC suggests that psychedelics may be beneficial in alleviating neuropsychiatric ailments. Depression and other neuropsychiatric diseases are usually categorized as stress-related disorders and can be worsened by chronic stress (Yang et al., 2015). Stress is reported to cause withering of the hippocampus, prefrontal cortex, and amygdala, causing functional impairment in the prefrontal cortex (PFC) (Lin et al., 2008; McEwen, 2007; Yuen et al., 2012). These stress-induced neural alterations to the PFC are thought to cause a decrease in learning, mood, motivation, and reward-seeking, all of which are features of depression, substance use disorder, and other maladies (Duman et al., 2016; Goldstein & Volkow, 2002; Goldstein & Volkow, 201; Koenigs & Grafman, 2009; Pittenger & Duman, 2007; Pahng et al., 2017; Volkow, 2002). Various neural circuits in the PFC seem to regulate behaviors connected to the treatment of depression, anxiety, and addiction (Lammel et al., 2013; Riga et al., 2014; Vargas et al., 2021). Significantly, the PFC has high levels of serotonin receptors that affect prefrontal functions (Lambe et al., 2011). When serotonin levels are increased in the brain, so is

activity in the PFC. The prefrontal cortex's role in neuropsychiatric disorders and the increase of activity caused by psychedelics implies the possible use of psychedelics for depression, anxiety, and substance abuse treatments. Meanwhile, the deactivation of the DMN and the experience of ego-dissolution may be significant to healing mental disarray.

Impact of Psychedelics on the Mind

If the ego were represented in the brain, it would be represented, at least in part, by the default mode network (DMN). When an individual is under the influence of psychedelics, because the DMN regulates regular brain activity, its' deactivation increases connectivity between parts of the brain that were previously separated (Letheby et al., 2017, Tagliazucchi et al., 2016). These findings are significant because the sensory hallucinations that subjects experience during a psychedelic encounter are thought to be due to the increase in functional connectivity. At the same time, occurrences of ego dissolution are linked to the decrease of activity in the DMN or ego center.

As described, an increase in functional connectivity and a decrease of activity in the DMN occur during a psychedelic experience; however, the decrease in DMN activity particularly correlates with reports of ego dissolution - a compromised sense of "self" where disruption of ego-boundaries occurs, commonly reported in a psychedelic trip (Nour et al., 2016; Tagliazucchi et al., 2016). The occurrence of ego dissolution is thought to contribute to the psychological benefits that may aid participants in reaching essential conclusions (such as coping with death, the realization of one’s mortality, or the realization that life is too short), especially in individuals troubled by end-of-life anxiety. Ego-dissolution is beneficial in the psychedelic experiences because of the disrupted

sense of self that is regularly experienced in various mental health conditions (Northoff, 2014). The deactivation of the DMN and possible experience of ego-dissolution may help break individuals out of harmful thinking habits. For example, in addiction disorders, the use of LSD and psilocybin can help break the cycle of addiction through assisted psychedelic psychotherapy by facilitating therapeutic conclusions that one may have been closed off to prior. There is not much research viewing psychedelics from this angle; however, Hartogsohn (2018) points out that assessing the degree to which psychedelics can enhance meaning would help us understand the therapeutic potential of psychedelics. Although researchers have not fully discovered the mechanisms of LSD and psilocybin, research has just recently reignited and reports positive results in treating depression, substance use disorder, end-of-life anxiety, obsessive-compulsive disorder, among other mental maladies.

IV. EXISTING RESEARCH

In the early 2000s, Johns Hopkins researchers were the first to acquire approval to continue psychedelics research in the U.S. In 2006, Griffith et al. (2006) produced a study titled "Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance" that would re-spark the interest in psychedelic research. In their study, they reported the mystical experiences that a high dose of psilocybin could cause participants' to have while providing a safe and comfortable environment. This study was conducted safely and sought to scientifically examine a mystical experience practiced in many cultures that little was known about. This encouraged researchers by demonstrating that psychedelics could be safely researched. Moreover, a paper titled "Human Hallucinogen research: Guidelines for

safety" by Johnson et al. (2008) was the first to establish safety guidelines concerning the study of psychedelics. Johnson et al. (2008) report about the history of psychedelics, the unstructured early research and recommend specific safety guidelines for psychedelic research; this report led researchers to implement these guidelines to ensure safe and ethical psychedelic research. In addition, this report discusses the concerns of physiological toxicity, abuse and dependence, distress, prolonged psychosis, and lasting perceptual abnormalities (Johnson et al., 2008). Discussing such effects is necessary, as it would be unethical to ignore any possible danger that may accompany psychedelic use. Johnson et al. (2008) concede that research precautions are necessary to continue research; however, they outline that the perceived dangers of psychedelics have been blown out of proportion and provide data to explain these substances in a new light. As the paper eloquently describes, "…. carefully conducted research that respects hallucinogens' unique and often powerful psychological effects may potentially inform the treatment of various psychiatric disorders, as well as lead to significant advances in our understanding of perception, cognition, behavior, the psychology of religion and the biological underpinnings of consciousness (Johnson et al., 2008, p.616)".

In 2019, John Hopkins established a research center with a $17 million dollar donation by a group of private donors. The center is the largest dedicated to psychedelic research and was a significant advancement due to the lack of federal funding in the area. Since the re-awakening of psychedelic research, Johns Hopkins has published more than 60-peer reviewed peer journal articles that demonstrated the benefits of psilocybin. Furthermore, these articles have discussed a range of topics, such as the therapeutic benefits for those who suffer from addictions, end-of-life anxiety, or depression (Johns Hopkins Launches

Center for Psychedelic Research, 2019).

It is necessary to note that most studies conducted on the effects of psychedelics focus on the use of psilocybin or the micro-dosing of LSD. Lysergic acid diethylamide is more difficult to study because of its' potency and the stigma surrounding substance use. Psilocybin, on the other hand, is less stigmatized, seen as natural, and has therefore been studied more extensively. The following sections will describe studies with psychedelics (either LSD or psilocybin, or both) and their effects on substance abuse, depression, end-of-life anxiety, and obsessive-compulsive disorder.

Substance Use Disorders.

In the 1950s, researchers in Canada treated a group of alcoholics with d-lysergic acid diethylamide (LSD) and discovered a significant increase in recovery rates among addicted individuals receiving LSD (Dyck, 2006). Furthermore, a study conducted by Krebs and Johansen (2012) found similar evidence pointing to the beneficial effects of LSD on alcohol misuse; however, this study does not test for long-term benefits in alcohol abuse treatment, although short-term benefits were observed. In 2015, a study conducted on individuals suffering from alcohol dependence received psilocybin in one or two supervised sessions in congruence with Motivational Enhancement Therapy (Bogenschutz et al., 2015). Bogenschutz et al. (2015) reported that alcohol abstinence did decrease among some participants in the first four weeks as individuals engaged in therapy sessions (before the administration of psilocybin doses), but results were not statistically significant, yet there was a statistically significant increase in alcohol abstinence following psilocybin administrations. Additionally, a self-report study found that out of three hundred and three respondents, after taking a moderate dose of LSD or

psilocybin, eighty-three percent no longer met alcohol use disorder criteria (Garcia-Romeu et al., 2019). These results attest to the potential of psychedelics in curbing substance use disorders.

Moreover, LSD and psilocybin can aid in decreasing tobacco use. For instance, Johnson et al. (2014) reported that after administering moderate (20 mg/70 kg) and high (30 mg/ 70 kg) doses of psilocybin to 15 participants over a structured period of 15-weeks, 12 out of 15 participants showed abstinence of tobacco use after six months. Similarly, a group of Johns Hopkins researchers reported that a few longtime smokers, who had previously failed to quit their habit, reported succeeding after a cognitive behavioral therapy treatment program that included the controlled and monitored use of psilocybin (Johnson et al., 2017). Such results further support the role of serotonin agonists, specifically psychedelics, in the use of addictive disorders.

It can be inferred that higher rates of success would be prominent if psychedelics are used in a proper and safe environment (where participants feel comfortable and can be helped by professionals if necessary) with some form of psychotherapy for the treatment of substance abuse. Ongoing research should decern what other substance abuse disorders LSD and psilocybin could alleviate.

Depression.

Perhaps the most investigated association is between psychedelics and depression. Psychedelics (LSD and psilocybin) have been most effective in reducing depressive symptoms among individuals with treatment-resistant depression; this may be because SSRI (serotonin reuptake inhibitors) focus on slowing the reuptake of serotonin, while psychedelics flood the system with serotonin. As noted by Dr. Robin Carhart-Harris,

psilocybin therapy is noted to improve depressive symptoms at a quicker rate than SSRIs do (Simon, 2021). Although SSRIs are the most used and prescribed antidepressants, it is not due to their effectiveness. Studies have proven that SSRIs have the weakest effect on depression (Cipriani et al., 2018). Regardless, SSRIs are the first choice of antidepression medication because they have fewer side effects than other medications (Overview- Selective serotonin reuptake inhibitors (SSRIs), 2018). Additionally, they are accompanied by common side effects like dizziness, low sex drive, agitated feelings, or blurred vision (Overview- Selective serotonin reuptake inhibitors (SSRIs), 2018). Meanwhile, psychedelic use has shown a decrease in depressive moods. Depression, also known as major depressive disorder, is characterized by at least five of the following present for two weeks:

> "…depressed or irritable mood for most of the day, diminished interest in previously pleasurable activities, significant unintentional weight loss or weight gain, insomnia or hypersomnia, physical agitation or slowness, loss of energy or fatigue, feelings of worthlessness or excessive guilt, indecisiveness or a diminished ability to concentrate, and recurrent thoughts of death" (Oyama, 2021, 1p).

In the following studies, individuals diagnosed with depression were treated with psychedelics to minimize and control symptoms and experienced a decrease in depression-related symptoms.

A study on the effects of psilocybin on treatment-resistant depression found a significant reduction of depressive moods six months after psilocybin administration (Carhart-Harris et al., 2018). In this study, twenty patients were given two oral doses of

psilocybin of 10 and 25 mg administered a week apart and reported reductions in depressive moods, which could be predicted by the quality of their psychedelic experiences (Carhart-Harris et al., 2018). Fauvel et al. (2021) report on the psychological mechanisms such as self-compassion and self-rumination that individuals experience on psychedelics as the possible cause of the reported decrease in depression, anxiety, and stress. Likewise, Spriggs et al. (2021) found overwhelming reports of improved depression symptoms and increased wellbeing scores relevant to a two-week psychedelic treatment. Another study focused on the micro-dosing of either LSD (100-200 mcg) or psilocybin (15 mg average) on depression (Kuypers, 2019). However, this study found a decrease in depressive moods, Kuypers (2019) contests that definitive statements about the effectiveness of micro-dosing LSD or psilocybin are difficult to make due to the limited number of studies. Overall, regardless of dosage, LSD and psilocybin are effective in reducing depressive moods and could be a possible legitimate treatment (Carhart-Harris et al., 2017; Kuypers, 2020).

Whether the effectiveness of psychedelics is due to neurochemical or psychological mechanisms is not clearly defined, but the overall conclusion is that LSD and psilocybin administered to individuals suffering from depression decreases depressive thoughts and moods and increases general wellbeing.

End-of-life Anxiety.

End-of-life anxiety is common among individuals diagnosed with a terminal illness. It is categorized by anxiety and depression about end-of-life matters. End-of-life anxiety is particularly interesting because of the role of ego dissolution in alleviating anxious and depressive thoughts. Not all studies include ego dissolution as there is no

guaranteed method of experiencing this phenomenon, yet studies are still able to find significant positive results in the decrease of anxiety and depression created by terminal illnesses. For example, one pilot study by Grob et al. (2011) reported mood improvement significantly up to six months after the administration of two moderate doses of psilocybin (0.2 mg/kg) in patients with advanced-stage cancer. Similarly, Ross et al. (2016) found that cognitive-behavioral therapy in conjunction with a single dose of psilocybin (3 mg/kg) had antidepressant effects in individuals with cancer. Numerous studies have uncovered a decrease in end-of-life anxiety in terminally ill patients after a controlled dose of LSD (lysergic acid diethylamide) or psilocybin (Gasser et al., 2014; Griffiths et al., 2016; Grob et al., 2011; Reiche et al., 2017). For instance, in 2016, a Johns Hopkins double-blind study found a decrease in end-of-life anxiety or depression in people who have cancer after a single large dose of psilocybin (Griffiths et al., 2016). After six months, patients continued to demonstrate a decreased level of depressed moods and anxiety (Griffiths et al., 2016). Likewise, a double-blind study by Gasser et al. (2014) analyzed the effects of LSD- assisted psychotherapy on the anxiety levels of 12 individuals with life-threatening diseases. The results found that when given in a safe, supervised, and medical setting, LSD reduced patients' end-of-life anxiety (Gasser et al., 2014). All these studies provide support to the idea that psychedelic treatments can ultimately decrease end-of-life anxiety and depression, although further studies are necessary to determine whether serotonin is the cause of these effects.

Obsessive-Compulsive Disorder.

New studies consider the increase of serotonin caused by psychedelics implies that their effectiveness has potential in the treatment of other disorders such as obsessive-

compulsive disorder, which is also associated with low levels of serotonin. Incidentally, positive preliminary results have been presented on the safety of psilocybin use to treat obsessive-compulsive disorder (Moreno et al., 2006). This study focused on the administration of four varying doses of psilocybin (low dose- 7mg/70kg- a medium-dose- 14mg/70kg- a high dose- 21mg/70kg and a randomly administered very low dose of 1.75mg/70kg) on individuals with obsessive-compulsive disorder. No studies on LSD were found, except initial testing on rats with OCD (Zghoul & Blier, 2003). Zghoul and Blier (2003) report theoretical implications of LSD administration to reduce OCD symptoms. The 5HT2A agonistic behavior of psilocybin and LSD decreased the threshold of emotional reactivity present by a reduction in amygdala responses that may interrupt the obsession-compulsion cycle (Jacobs, 2020).

These studies show potential, but the link between cause and effect is difficult to make as the neuro-mechanisms behind psychedelics are not fully understood. Further research should focus on the neuroscience of psychedelics to discover what other ailments they may effectively treat, such as the current studies testing psilocybin administration to aid with anorexia nervosa (Mennitto, 2021), type 2 bipolar depression (Aaronson, 2020), and chronic cluster headaches (Knudsen, 2020).

V. AREAS FOR GROWTH

As with any research, challenges arise as the field expands. Pointing out these areas is not to critique or discourage research but aids in correcting and addressing these predicaments. Psychedelic research has just recently reignited and has progressed from early research into a new era. In this section of the review, I will discuss the variation of dosage, substance and administration schedule, data collection methods, and the reporting

of adverse effects.

Dosage Issues: How much and of what?

One major inconsistency in psychedelic research is the dosage administered to patients. For instance, while some studies focus on the advantages of micro-dosing, others report the positive benefits of a full-dose experience. Additionally, the dosage amount of LSD or psilocybin varies among research, so the most effective treatment and substance are difficult to pinpoint, so calibrating dosages to achieve maximum benefit is a current challenge to this field.

To begin, in studies on the effects of psilocybin on end-of-life anxiety, a single dose (21mg/70kg) of psilocybin was given to participants along with cognitive-behavioral therapy (Ross et al., 2016). Meanwhile, other studies administered two doses of psilocybin (14mg/70kg) ingested in a controlled setting where participants were left undisturbed (Grob et al., 2011). Both resulted in a decrease in end-of-life anxiety symptoms achieved through different methods. Similarly, LSD also alleviates end-of-life anxiety with successful results when participants were given two doses of 200 mcg (Gasser et al., 2015). LSD and psilocybin alleviate end-of-life anxiety symptoms, but it is undetermined which substance is most effective and should be used.

Moreover, micro-dosing is when one administers a small dose of a psychedelic substance at a level where hallucinogenic effects are not experienced. Micro-dosing has been credited with improving mood, motivation, mental health, and easing depression symptoms (Anderson et al., 2018, Kuypers, 2019, Lea et al.,2019; Ona et al., 2020). On the other hand, Kaertner et al. (2021) found that although positive changes in depressive symptoms, wellbeing, anxiety and emotional stability were observed, positive

expectations were significantly predictive of improvements in mental health. Findings like those by Kaertner et al. (2021) highlight why proper dosage is highly contested in psychedelic research. Some studies find that micro-dosing is best, while others focus on moderate or high dosages, all of which have reported positive results. Nevertheless, there is no current standard protocol for the administration of psychedelics across studies for different disorders. Additionally, the practice of micro-dosing is scrutinized for having effects similar to those of a placebo. Kuypers et al. (2019) discussed the need for rigorous placebo clinical studies are necessary to determine whether a distinction can be made between the actual benefits of micro-dosing versus benefits derived from the expectations.

All in all, psychedelic treatment theories outline the need for a full dose to induce the serotonin flood theorized to be significant, in addition to targeted psychotherapy. On the other hand, micro-dosing seems to treat ailments while eliminating the psychedelic experience (accompanied by hallucinations, sensations, etc.). Current research does not answer whether a full dose, moderate dose, or micro-dose of psychedelics is more effective, nor does it determine what substance is best for treatment, and future studies are needed to determine the minimum effective dosages for these treatments.

Methods of Data Collection.

Another challenge in psychedelic research is the method by which data is collected. As mentioned, studies on LSD tend to be conducted on data gathered from past studies or self-surveys (Lea et al., 2020), while psilocybin studies collect their data from clinical studies (Bogenschutz et al., 2015; Carhart-Harris et al., 2017; Moreno et al., 2006). For this review, LSD studies were difficult to find in human trials as opposed to

psilocybin studies.

For instance, in the treatment of substance abuse, a study on psilocybin was conducted in the span of fifteen weeks; one session of therapy with a moderate dose of psilocybin (20mg/70kg) occurred five weeks into the program, followed by two high doses (30mg/70kg) given at seven and thirteen weeks (Johnson et al., 2017). On the other hand, Lea et al. (2020) discuss the perceived outcomes of LSD micro-dosing by analyzing online surveys. Although surveys are valid data collection methods, it is difficult to understand the full effects and implications of psychedelic use with this method. Reports, like those written by Anderson et al. (2018), Kuypers (2019), Lea et al. (2019), and Ona et al. (2020), analyze prior research or conduct self-surveys to report on micro-dosing. Unfortunately, there have been no empirically conducted research studies on micro-dosing thus far. Consequently, the long-term effects of micro-dosing psychedelics are unknown, and the actual benefits cannot be determined due to the data collection methods.

Current research should create a standard treatment dosage for a specific ailment. Research has just recently restarted on the effects of psychedelics on humans. Still, we cannot ignore their medical potential and should compare dosages and results to create a systematic treatment method.

Adverse Effects.

When researching psychedelics, studies must report any adverse effects that have occurred to remain ethical and safe. Notably, most studies report no occurrence of adverse effects and, the few that do, report the effects to be short-term (Bogenschutz et al., 2015). Adverse effects highlighted by Johnson et al. (2008) are considered in this

review, as their work outlines human safety in hallucinogen research. Johnson et al. (2008) explain that acute psychological destress, dangerous actions, abuse and dependence, prolonged psychosis, and physiological toxicity may be areas of concern but can be minimized by effective research procedures such as obtaining a safe environment for participants, pre-screening for psychosis, and ensuring professional help is present if necessary.

One effect discussed by Johnson et al. (2008) was the psychological distress an individual may face, known as having a bad trip, and the physical danger one may encounter because of their impaired status. A bad trip is categorized by fear, panic, anxiety, paranoia, and/or dysphoria (Johnson et al., 2008). These reactions may come about due to uncomfortable or unsafe environments that make participants feel uneasy, anxious, and paranoid while simultaneously placing them in physical danger (Johnson et al., 2008). For instance, a paper written by Family et al. (2019) found that a placebo group during an LSD study reported more adverse effects than the control group. This suggests that there may be a positive correlation between negative expectations and a negative psychedelic experience. A bad trip and the fear of dangerous physical situations can be avoided by controlling the participants' environment and ensuring a safe, comfortable, and guided trip.

On the other hand, some may argue that psychedelics cause prolonged psychosis and are too dangerous to research. However, guidelines mandate the pre-screening of participants and exclusion of those with susceptibility or history of psychosis. Aside from pre-screening patients, it should be noted that psychedelic induced psychosis is rare; for instance, in a survey of investigators who administered LSD or mescaline, only one case

of a psychotic reaction lasting more than 48 hours occurred in a total of one thousand two hundred participants (Cohen, 1960). Notably, the participant who experienced psychosis was an identical twin of a schizophrenic patient and would have been excluded due to current guidelines (Johnson et al., 2008).

A significant concern with psychedelic research is abuse and dependence. Yet, hallucinogenic substances are not considered drugs of habit and are not known to cause compulsive drug-seeking (National Institute on Drug Abuse, 2001; O'Brien, 2015). Besides, psychedelics have not been observed to cause withdrawal syndrome physically or psychologically (O'Brien, 2015). It is highly unlikely that participants become addicted or experience any withdrawal symptoms whatsoever.

The last concern regards the potential physiological toxicity of psychedelics, but there has been no evidence that LSD and psilocybin have potentially neurotoxic effects (Johnson et al., 2008). The bodily impact experienced under the influence of psychedelics may vary from individual to individual (such as dizziness, nausea, dilated pupils, tremors, increase in pulse, etc. caused by an increase of serotonin); nonetheless, the effects vary and are unimpressive even at potent psychedelic doses (Metzner et al.,1965; Metzner, 2006; Passie et al., 2002). Aakeroy et al. (2021) report on the possible toxic effects of LSD. Aakeroy et al. (2021) discuss the case of a young man who experienced a seizure while having LSD in his system. Although this instance is not impossible, it is essential to cautiously consider other factors that may have influenced the event besides LSD. More importantly, Aakeroy et al. (2021) urge others not to turn a blind eye to the possible adverse effects of LSD and use guidelines to ensure patient safety.

In clinical environments, the risk of severe complications is decreased by

ensuring that necessary safety guidelines are followed, such as screening of patients, creating adequate support for participants before the session, and producing a safe and reliable physical environment (Johnson et al., 2008; Reiche et al., 2018).

VI. DISCUSSION

Overall, the use of psychedelics has spanned over several years; however, their study is only beginning leaving many unanswered questions. As explained, LSD and psilocybin are 5HT2A receptor agonists (Backstrom et al., 1999; Wacker et al., 2017), which increase serotonin levels in the brain and cause deactivation across the DMN (Schrantee et al., 2018). Psychedelics cause an increase of serotonin levels in the brain, decrease activation in the DMN, and increase activity in the PFC; this suggests the possible effectiveness of treatments using serotonergic psychedelics for the reduction of depressive, anxious, or obsessive thoughts.

Even so, the effects of psychedelics on the brain are not entirely understood. Research findings report decreases in depressive symptoms, anxiety, end-of-life included anxiety and depression, and obsessive thoughts (Carhart-Harris et al., 2018; Grob et al., 2011; Reiche et al., 2018; Ross et al., 2016; Gassser et al., 2015; Moreno et al., 2006) but evidence to prove serotonin as the cause of these decreased moods is difficult to prove; however, a correlation is present.

LSD and psilocybin seem to facilitate access to emotions, traumatic memories, emotional and intellectual insights, and catharsis (Grof, 1980; Leuner, 1981). Therefore, their administration can produce more productive sessions of CBT or other psychotherapies for individuals. Using this viewpoint, a decrease in depressive thoughts, abuse disorders, and end-of-life anxiety result from the profound emotional impact that

guided psychedelic experiences provide.

As discussed in this review, many studies have shown the potential benefits of LSD and psilocybin on mental illnesses despite differences in dosage (amount and substance), dosage schedule, and whether they are taken in unity with a form of psychotherapy. However, as the field grows, it is the burden of researchers to decipher which substances, dosage, and administration techniques are best for treatment. Unfortunately, there is not much knowledge on the effects of psychedelics in psychotherapy for mental illnesses, especially at a neurobiological level. However, the discussed mechanisms, such as the role of the PFC, DMN, and serotonin, may point to why psychedelics may be a form of potential treatment.

Although there is uncertainty as to the long-term effectiveness of LSD and psilocybin treatments, we cannot overlook their reported potential. The benefits of LSD and psilocybin are consistently reported despite our lack of understanding. Thus far, LSD and psilocybin help decrease depressive moods, obsessive symptoms, end-of-life anxiety, substance abuse, among other ailments not included in this review. Hopefully, as technology advances, we can thoroughly study the mechanisms behind psychedelics to create standardized treatments that benefit the greatest number of people. Nevertheless, psychedelic research must continue to expand and unravel possible benefits.

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