Bipolar Disorder: Microdosing Psilocybin to Lessen Depressive Symptoms

A thesis submitted in partial fulfillment of the requirements

for the degree of

Master of Science in Psychology

Ashley Nichole Heath

Purdue University Global

2021

Author Note

Ashley Nichole Heath, Department of Graduate Psychology, Purdue University Global.

The author wishes to express appreciation to my thesis committee Dr. Gabrielle Blackman, Dr. Rupard, and Dr. Chung, and to my loving husband Michael Heath II and my children Kaileigh Ross, Gavin Ross, and Reese Coy whose patience, love, selflessness, and support have made this possible.

Correspondence concerning this thesis should be addressed to Ashley Heath, email address ashleyheath7@student.purdueglobal.edu.

Abstract

Research on microdosing psilocybin as a novel treatment option for bipolar depression is still in its infancy; however, new research studies show significant improvement in major depression and treatment-resistant depression after a one-time large dose of psilocybin. The purpose of this systematic literature review was to evaluate recent studies on psilocybin and the reduction of depressive symptoms in participants with treatment-resistant depression or major depression, as well as the benefits of microdosing psilocybin. A total of seven studies met the criteria for statistical data, population characteristics, and the use of psilocybin for depression. One study examined the benefits versus challenges of microdosing psilocybin recreationally along with depression screening via online self-reporting questionnaires and DAS-A-17 scale. The additional six studies evaluated the effects of psilocybin on depression, anxiety, and mood disturbances. Quantitative results indicate that psilocybin can significantly reduce depressive symptomatology in treatment-resistant depression, along with anxiety, neuroticism, anhedonia, anger and hostility, and impulsiveness. Results also found an increase in joy, awe, the feeling of love, and positive emotions. The researcher discussed the strengths, limitations, and suggestions for future research. Further studies with more rigorous analysis, larger and more inclusive sample sizes, and increased double-blind and controlled designs would be necessary to understand treatment options involving psilocybin for depression.

Keywords: psilocybin, bipolar II disorder, depression, microdosing, serotonin agonist

Table of Contents

Bipolar Disorder: Microdosing Psilocybin to Lessen Depressive Symptoms

Bipolar II disorder is a chronic mental health disorder that affects approximately 0.4% of the American population and equally affects men and women (Rowland & Marwaha, 2018). According to the American Psychiatric Association (2013), this disorder consists of periods of alternating chronic depressive and hypomanic episodes that can last for several days up to two or more weeks. Compared to men, women have more rapid cycling between episodes of mania and depressive states (American Psychiatric Association, 2013). Bipolar II disorder differs from bipolar I disorder as it features greater depressive symptoms rather than manic episodes. Many individuals with bipolar II disorder experience depressive symptoms or major depressive episodes throughout a considerable portion of their lives; this leads to an exhaustion of treatment options and leaving the individual prone to treatment-resistant bipolar depression (TRBD) (Hidalgo-Mazzei et al. 2019).

Psilocybin mushrooms (i.e., “magic mushrooms”) are from the genus psilocybe, which is best known for psychedelic properties (“Psilocybin,” 2006). Psilocybin mushrooms are considered a prodrug. When digested, psilocybin turns into psilocin, which acts as a 5-HT agonist. The psilocin agonist 5-HT2A resembles the serotonin inhibitor receptor naturally occurring in the human brain. Serotonin is a chemical imperative for many functions such as appetite, memory, mood, sexual desire, and sleep (Campbell, 2020). When depression is present, serotonin levels decrease, and psilocybin can help to increase these levels. The present study is a comparative meta-analysis research study that examines the benefits of psilocybin for the treatment of bipolar II depression. In America, 2.3 million people suffer from bipolar II disorder, with half of that population considered treatment-resistant (Hui Poon, Sim, & Baldessarini, 2015). This systematic

literature review is important for understanding bipolar II depression and treatment-resistant bipolar disorder and the use of psilocybin as an effective treatment.

Literature Review

Neurology and Neuropsychology of Bipolar Disorder

Rocca, Heuvel, Caetano, and Lafer (2009) completed a literature review of controlled studies on emotion recognition deficits in bipolar disorder. The review included studies with sample sizes exceeding 10 participants. The researchers evaluated studies in Medline, Lilacs, PubMed, and ISI journals. The results of this study found impairments in recognizing disgust and fear in individuals with bipolar disorder. Rocca et al. (2009) also found that those with bipolar I mania had difficulties recognizing fearful and sad faces. These findings concluded that those with bipolar disorder experience cognitive and affective deficits during various mood states within the disorder.

Rowland and Marwaha (2018) studied the epidemiology and risk factors for bipolar disorder. The researchers analyzed several studies and study types, including meta-analysis, cross-sectional, control studies, case-control, Prospective cohort, Retrospective cohort, Umbrella review, and systematic reviews. The studies chosen focused on areas of family genetics, polymorphism, Multiple SNPs (single nucleotide polymorphism), environment, childhood trauma, perinatal infections, and *T. gondii* infections. The results found that there are multiple risk factors in the development of bipolar disorder. Genetic and environmental factors played a role, but the lack of a clear biological mechanism and the vague nature of bipolar disorder leave an inability to assign causation to each case. Evidence pointed to the correlation between the level of severity of bipolar

disorder and relation to childhood emotional abuse and the use of cannabis for self-medicating (Rowland & Marwaha, 2018). Medical comorbidities, such as inflammatory disorders like irritable bowel syndrome and asthma, share a pathophysiological correlation with the disorder. Other psychiatric disorders can pose as a risk factor to the development of BPD. There is a substantial correlation between substance abuse and bipolar disorder, as well as shared genetic factors between the risk of developing substance misuse disorder and bipolar disorder. Child abuse is also a substantial risk factor for bipolar disorder (Rowland & Marwaha, 2018).

Lu et al. (2019) studied bipolar disorder and the brain's morphological abnormalities found within BD. The researchers comprised this study analyzing in-depth literature through web searches of PubMed, EBSCO, and BrainMap voxel-based morphometry (VBM) databases. They considered studies that examined gray matter anomalies of healthy and bipolar disorder subjects. The authors used an activation likelihood estimation (ALE) algorithm software to analyze the studies (Lu et al., 2019). The authors compared 46 studies containing 56 experiments, which included 1720 subjects. The results showed that 15 regions of the brain were remarkably different in gray matter volume within the subject groups. Pervasive gray matter deficiencies were present in the temporal cortex and prefrontal regions, along with increased gray matter in the precuneus, putamen, and cingulate cortex (Lu et al., 2019). It is conclusive that diminished gray matter in the prefrontal cortex with an expansion of gray matter in the cingulate cortex to offset the deficit in the prefrontal region's deficit is predominant in pathophysiology in bipolar disorder.

Bipolar Disorder: Medication, Therapies, Treatment-resistance

Hui Poon, Sim, and Baldessarini (2015) studied different Pharmacological Approaches for Treatment-resistant Bipolar Disorder. The researchers utilized digitized medical research literature on pharmacological treatments for treatment-resistant bipolar disorder. The researchers used literature published in MedLine and PubMed databases; used search terms such as bipolar, treatment, drug or medication-resistant, resistance, refractory, and difficult to treat; and limited the search to those articles published in the English language. The researchers sought meta-analyses, systematic reviews, randomized controlled trials, naturalistic and retrospective studies, case series, and case reports on bipolar disorder treatment. Two researchers reviewed all accepted studies' abstracts to ensure they met the criteria for the research. The criteria for this study included: participants with a clinical diagnosis of bipolar disorder via the DSM III, IV, or V, or the ICD 9 or 10 and medication therapy used during the trial. Medications reviewed in this study were: Atypical Antipsychotics such as *Clozapine, Aripiprazole, Olanzapine, and Quetiapine*; Anticonvulsants such as *Eslicarbazepine, Pregabalin, and Topiramate*, Antidepressants, Glutamatergic Agents such as *Memantine*, Anticholinesterases, Dopamine Agonists, Psychostimulants such as *Methylphenidate* and *amphetamines*, and *Modafinil*, Calcium Channel Antagonists such as *diltiazem*, and other agents such as *oxycodone*. The study did not require a certain number of subjects, randomization, or controls (Hui Poon, Sim, & Baldessarini, 2015). The study considered 100 articles and used 38, which met the criteria of the researchers. Results found that adding clozapine, aripiprazole, pregabalin, bupropion, ketamine, memantine, pramipexole, and possibly tri-iodothyronine to current treatment plans have been found to help decrease treatment-resistant bipolar disorder. The depressive components of bipolar disorder demand more extensive therapeutic trials with experimental therapeutic trials involving consistent sampling, randomization,

placebo controls, and transparent treatment schedules that last a minimum of a year (Hui Poon et al., 2015).

Hidalgo-Mazzei et al. (2019) studied treatment-resistant bipolar disorder and multi-therapy resistant bipolar depression to reach an agreement on criteria definitions for these disorders. The researchers utilized a modified Delphi method with a panel of bipolar disorder experts to agree on criteria for multi-therapy-resistant bipolar depression. The panel consisted of 18 UK experts representing all major specialty domains and relevant areas of expertise. The researchers administered surveys to the panel, which assessed unresolved diagnostic and therapeutic issues related to bipolar disorder. The results of this study showed that the experts defined the criteria for TRBD as the inability to reach continual symptomatic remission for eight weeks following two separate treatments at acceptable doses, in conjunction with two singular therapy treatments or combination treatment (Hidalgo-Mazzei et al. 2019). MTRBD is the same definition with the inclusion of a failed trial of one or more antidepressants, a failed psychological treatment, and electroconvulsive therapy.

Serotonin

Campbell (2020) defines serotonin as a chemical that acts as a neurotransmitter that carries signals from one nerve cell to another. The body produces serotonin to assist in mood balance. The majority of serotonin is produced in the gastrointestinal tract, but it may also appear in the central nervous system and platelets. The chemical makeup of serotonin is 5-hydroxytryptamine or 5-HT. The chemical develops when an amino acid called tryptophan combines with a chemical reactor called tryptophan hydroxylase. Serotonin cannot cross the blood-brain barrier, which means that all

serotonin produced in the brain must stay there. Research suggests that serotonin is essential in regulating functions such as appetite, memory, digestion, mood, social behavior, sexual functions, and sleep. Depression can cause a reduction in serotonin production and tryptophan levels, lack of receptor sites, inability for serotonin to reach receptor sites, and decreased brain cell regeneration (Campbell, 2020). Selective Serotonin Reuptake Inhibitors (SSRIs) can increase serotonin and decrease depression; higher serotonin levels can amplify transmission among brain cells, improving mood. Excessive amounts of serotonin, however, can cause unwanted health problems. Certain dietary supplements, medications, and illegal drugs can satiate the serotonin receptors causing unwanted side effects and even a deadly disease called serotonin syndrome. Campbell (2020) suggests ways to naturally increase serotonin in the body, such as foods with high levels of tryptophan, exercise, and direct sunlight.

Psilocybin

According to Psilocybin (2006), psilocybin is a species of mushroom from the genus Psilocybe. Psilocybin mushrooms are most noted for their mind-altering or psychedelic properties. These mind-altering effects can range from mood swings, feelings of time standing still, and visions of bright colors or tracers. Researchers in the 1950s and 1960s began studying the effects of psilocybin on psychiatric disorders such as schizophrenia and other serious mental disorders. The researchers were unable to yield any helpful results due to the unpredictable effects of psilocybin. The U.S. government has deemed psilocybin a schedule 1 controlled substance, which means that these mushrooms carry the maximum penalties for those who use and illegally sell this drug (Psilocybin, 2006). Psilocybin works as a serotonin agonist, which means that psilocybin

enters the central nervous system and increases the body's serotonin receptors. Serotonin regulates mood, anxiety, senses, digestion, blood flow, and other organ functions (Psilocybin, 2006).

Psilocybin and Mood disorders, Anxiety, Depression, and Bipolar Disorder

Kraehenmann et al. (2016) studied the effects of psilocybin on threat-induced modulation on the amygdala in the brain. The researchers suggested that psilocybin contributes to altering emotional tendency from negative to positive stimuli during serotonergic neurotransmission stimulation. Researchers recruited subjects from local universities via advertisements placed within the campuses. Participants consisted of 25 healthy, right-handed individuals 16 males and nine females, with 21-27 years. These participants must meet the criteria of having normal or corrected vision and were screened for DSM-IV mental and personality disorders via the Mini-International Neuropsychiatric Interview and the Structured Clinical Interview. The researchers excluded those who were pregnant or left-handed; did not speak German; had a personal and family history of mental illness or a drug and alcohol addiction; were under the influence of drugs, alcohol, or medications that alter cerebral metabolism and/or blood flow, cardiovascular disease, head trauma, other neurological disorders, claustrophobia (which would prohibit the use of MRI imaging); or had an adverse reaction to hallucinogenic drugs (Kraehenmann et al., 2016). The study was a randomized, double-blind, placebo-controlled, cross-over study where subjects were either administered a lactose placebo or .16 mg/kg of oral psilocybin in identical gelatin capsules during two sessions. They chose a .16 mg/kg dose due to its dependability in altering mood and consciousness without affecting behavior and task performance during testing. They immediately followed these sessions with MRI imaging sessions spaced out 14 days apart. The study's

assessments were the Positive, Negative Affect Schedule, the State–Trait Anxiety Inventory, and fMRI, where amygdala reactivity tasks were completed during the scan. The results showed that psilocybin decreases threat-induced modulation from the amygdala to the primary visual cortex when psilocybin is present. Kraehenmann et al. (2016) also found that threat sensitivity in the visual cortex shifts from negative to a positive disposition during emotion processing. The findings suggest that psilocybin has the potential to transfer emotional biases in those with anxiety and mood disorders and may help inhibit fear responses during exposure-based psychotherapy in those with post-traumatic stress disorder.

Carhart-Harris et al. (2017) studied the effects of the psychedelic substance psilocybin (i.e., magic mushrooms) on brain function and structure in people with depression. Psilocybin is a biologically inactive ingredient of psilocin, which becomes a psychedelic drug once broken down by the body. Psilocybin's chemical compound 4-OH-dimethyltryptamine comprises a non-selective serotonin 2A receptor- 5HT2AR that is a psychedelic agonist. The serotonin receptor occurs naturally in the psilocybe mushroom (Carhart-Harris et al., 2017). The compound structurally mirrors the endogenous neurotransmitter serotonin. As an agonist, dimethyltryptamine binds to serotonin molecules and can travel to brain sections that utilize serotonin for proper functioning. According to Carhart-Harris et al. (2017), practitioners can administer psilocybin for end-of-life anxiety and depression, alcohol and tobacco addictions, obsessive-compulsive disorder, and treatment-resistant major depression. The researchers recruited 19 female patients with a median age of 42.8 and diagnoses of treatment-resistant major depression. The researchers conducted before and after treatment fMRI brain scans to research the brain structure; three participants' scans were removed from the study due to movement or other artifact issues during the imaging process,

which left 16 participants' scans. The results show a rapid and substantial antidepressant effect on the brain, especially in cerebral blood flow (CBF). CBF was measured after treatment and showed a decrease in depressive symptoms in all subjects one-week post-treatment, and 47% met the criteria for response five weeks post-treatment in the areas of the left Heschl's gyrus, left precentral gyrus, left planum temporale, left superior temporal gyrus, left amygdala, right supramarginal gyrus, and right parietal operculum (Carhart-Harris et al., 2017). All 19 subjects showed signs of improved depressive symptoms within one week, and six subjects showed a treatment response of at least 50% reductions in their QIDS-SR16 scores at five weeks.

Barrett, Doss, Sepeda, Pekar, and Griffiths (2020) studied the effects of psilocybin and residual changes in emotion and brain function. Participants in this longitudinal pilot study consisted of 12 volunteers: seven females and five males with a mean age of 25-39. The researchers included participants who were between 18-45 years of age, physically and medically healthy, psychiatrically healthy per the DSM-IV, and right-handed. They excluded individuals with a previous history of head trauma claustrophobia, certain implants including ferrous metals, taking certain medications, had a family history of psychosis or bipolar disorder, moderate to severe substance abuse within the last five years, or were pregnant. The sample was 100% Caucasian, more than half were married, and 83% had a bachelor's degree or higher. They compensated volunteers $240 upon completion of the study. Participants ate a low-fat breakfast more than one hour before arriving at the Johns Hopkins Bayview Medical Center. Once they arrived, they took a capsule of psilocybin (25mg/70kg). The study staff monitored participants' vital signs and behaviors up to six hours post-ingestion by study staff (Barrett et al., 2020). The researchers administered a battery of questionnaires one day before, a week after, and one month after

participants took the psilocybin capsule. The battery consisted of the Positive and Negative Affect Scale - X (PANAS-X), the Profile of Mood States (POMS), Positive Emotions Scale (DPES), the Depression Anxiety Stress Scale (DASS), the State-Trait Anxiety Inventory (STAI), and the Big Five Inventory (BFI)5. The researchers also administered an MRI assessment one day before, a week after, and a month after participants took the psilocybin capsule. Participants completed various tasks, including a STROOP test for emotion discrimination, emotion recognition, and emotional conflict Stroop, while being assessed under MRI imaging. The study found that psilocybin reduced negative and increased positive moods and reduced the amygdala response to negative affective stimuli (Barrett et al., 2020). One week after administration of psilocybin, subjects experienced a reduction in amygdala response to facial affect stimuli and an increase of positive affect on the dorsal-lateral prefrontal and medial orbitofrontal cortex regarding emotionally-conflicting stimuli. One month after the administration of psilocybin, the amygdala response to facial affect stimuli returned to normal. However, levels of positive affect remained elevated and had a decrease in trait anxiety. The findings showed that psilocybin increases emotional and brain plasticity, and psilocybin may be a therapeutic option for negative affect (Barrett et al., 2020).

Stroud et al. (2018) studied the effects of psilocybin on facial recognition in individuals with bipolar disorder. The study examined whether psilocybin alters an individual’s emotional processing biases in those with treatment-resistant depression. Participants included 17 patients with treatment-resistant depression who completed the DEER-T assessment. These participants did not have success with past treatment of two antidepressants, and all scored moderate severity on the HAM-D assessment. The study’s participation criteria included normal or corrected vision, the

ability to complete computer tasks, aged between 18-60, and fluent in the English language. Those excluded were individuals with a clinical psychiatric illness and/or a learning disability. Participants were initially screened for drugs, pregnancy, psychiatric illness, administered urine screens, and ECGs. Participants took two doses of psilocybin one week apart. The first dosage of psilocybin was 10mg, while the second dose was 25mg. The second dosage was chosen for a week after the first dose to ensure efficacy compared to previous studies on ketamine in treatment-resistant depression (Stroud et al., 2018). One week after the second dose of psilocybin, participants returned to complete the DEER-T, the QIDS16, and SHAPS assessments. Researchers found that psilocybin, in conjunction with psychological assistance, can improve emotional face recognition in treatment-resistant depression. This evidence corresponds with a reduction in areas of inability to feel and experience pleasure.

Psilocybin: Psychopharmacology and Pharmacokinetics

Thomas, Malcolm, and Lastra (2017) studied psilocybin-assisted therapy and its role in treating psychiatric disorders. The researchers reviewed the literature regarding the role of psilocybin-assisted therapy for the treatment of psychiatric disorders. The researchers believe that psilocybin works as a serotonin agonist, disrupting dysfunctional neural network circuits in psychiatric disorders, thus making psilocybin a viable treatment option. The researchers studied articles that fell under the category of “Clinical Trial.” The research contained the topics of “psilocybin and psychiatry” and “psilocybin, pharmacodynamics, and pharmacokinetics," published through December 31, 2016 (Thomas et al., 2017). This study found that Pharmacokinetics Psilocybin is an appropriate substitute for indolealkylamine, which works as a

serotonin agonist. Psilocybin's organic compound was altered when exposed hydrolysis during metabolization in the intestines, where serotonin is primarily produced. They found that the psilocybin concentration may greatly decrease from the time of ingestion to peak plasma concentration or tmax (Thomas et al., 2017). Psilocybin administered intravenously had a mean terminal elimination half-life of 74 minutes, while oral administration doubled at 163 minutes. The results indicate a possible dose-dependent effect due to metabolization, which practitioners should consider when using psilocybin as a treatment option. Thomas et al. (2017) noted a study that yielded similar results with an oral half-life of 135 minutes and an elimination constant of 0.307/hour, and an absorption constant of 1.307/hour. The study determined that after 20-90 minutes, the bioavailability is at 52.7%; this should be considered when developing treatment dosages.

Adverse Reactions to Psilocybin

Bienemann et al. (2020) studied the self-reported negative effects of using psilocybin. The researchers obtained literature from the EROWID website, a self-reporting site dedicated to reporting and documenting psychoactive substance use. Criteria for this study included: description of the experience and previous mental state; details of predetermined dosages and the duration of time participants used psilocybin; other medications, including herbs and supplements; and a description of physical and mental effects that occurred during psilocybin use (Bienemann et al., 2020). Researchers selected reports under main categories of Magic Mushrooms and Psilocybin-containing Fungi, and subcategories of health problems, bad trips, and train wreck & trip disasters. The researchers did not include reports if the individual consumed mushrooms with

substances, and the main active ingredient was not psilocybin, such as Amanita Muscaria (Bienemann et al., 2020). The researchers considered other substances participants used, the dosages, administration route, how participants consumed psilocybin (e.g., tea, dried, fresh), and gender. The results showed that thought distortion was the primary causation for bad trips. They found that bad trips correlated with higher levels of psilocybin consumed.

Meta-Analysis Research

Lee (2019) studied the strengths and weaknesses of meta-analysis in research. Meta-analysis integrates multiple studies' results and methods to produce precise data on a topic that would otherwise be difficult to study without such information (Lee, 2019). In the thesis research on Psilocybin and the effects on Bipolar II disorder, a controlled study where a researcher is to observe an individual dosing psilocybin while monitoring the effects via assessments, imaging, therapy, etc., would be a lengthy and costly process. For this thesis proposal, it makes sense to conduct a meta-analysis study without struggling with time constraints, funding, government approvals, and so on. Lee (2019) found that results from a meta-analysis are typically more objective and transparent than narrative reviews, and they allow researchers to overcome biases by comparing several studies at once. As with all study types, meta-analysis does have limitations, such as lack of heterogeneity, publication bias, disagreement with findings in randomized trials, and incomparable variables (Lee, 2019). However, for the proposed thesis study, the strengths outweigh the weaknesses. Lee's (2019) outlined strengths such as increasing the generalizability, larger population size, increased sample size, and clinically significant effects by

comparing data from several studies. These strengths allowed me to increase the sample size and data by combining several studies.

Summary and Research Question

Rocca et al. (2009) studied bipolar disorder and found that individuals experience cognitive and affective deficits during various mood states within the disorder. Rowland and Marwaha (2018) studied the epidemiology and risk factors for bipolar disorder. Due to a lack of clear biological mechanisms and the vague nature of bipolar disorder, there is an inability to assign causation to each case. Lu et al. (2019) studied bipolar disorder and the morphological abnormalities of the brain. A decreased amount of gray matter in the prefrontal cortex was evident in the images with an expansion of gray matter in the cingulate cortex. A research study centered around the pharmacological approaches to bipolar disorder by Hui Poon et al. (2015) show components of bipolar disorder demand more extensive therapeutic trials with experimental therapeutic trials involving consistent sampling, randomization, placebo controls, and transparent treatment schedules that last a minimum a year. Hidalgo-Mazzei et al. (2019) developed a panel of specialists to define the criteria of treatment-resistant bipolar disorder and multi-therapy resistant bipolar depression; their suggested criteria include that the individual has not achieved continual symptomatic remission for eight weeks following two separate treatments at acceptable doses in conjunction with singular therapy treatments or a combination of treatments.

Campbell (2020) defines serotonin as a chemical that acts as a neurotransmitter with the chemical makeup 5-hydroxytryptamine (5-HT). Campbell (2020) also found that Selective Serotonin Reuptake Inhibitors (SSRIs) can increase serotonin, decrease depression, and amplify

mood. According to Psilocybin (2006), psilocybin is a fungus from the genus Psilocybe, which has psychedelic properties and acts as a serotonin agonist that increases serotonin receptors in the body. A study on psilocybin and the brain conducted by Kraehenmann et al. (2016) identified that psilocybin may have the ability to transfer emotional biases in those with anxiety and mood disorders and may help inhibit fear-responses during exposure-based psychotherapy in those with post-traumatic stress disorder. Carhart-Harris et al. (2017) studied the effects of psilocybin and the brain and found a decrease in depressive symptoms in all subjects one week post-treatment. Psilocybin was also found to increase emotional and brain plasticity and may be a therapeutic option for negative affect (Barrett et al. 2020). In another study by Stroud et al. (2018), psilocybin was found to improve the processing of emotional face recognition in treatment-resistant depression when used in conjunction with psychological assistance. Thomas et al. (2017) studied psilocybin-assisted therapy for psychiatric disorders and found that oral psilocybin has an oral half-life of 135 minutes, while intravenous has 74 minutes, and has a total bioavailability of 52.7%. In treatment, larger doses of psilocybin can lead to bad trips, which mainly resulted in thought distortion (Bienemann et al. 2020). Lee (2019) studied the strengths and weaknesses of meta-analysis in research and found that meta-analysis increases the generalizability and provides a larger population size, increased sample size, and clinically significant effects by comparing data from several studies.

The literature reviewed suggests that microdosing psilocybin is a viable treatment option for bipolar depression and treatment-resistant major depression. Psilocybin acts as a serotonin agonist, which mirrors serotonin in the brain and promotes an increase in serotonin receptors. Serotonin has been linked to improving depression, including treatment-resistant depression and bipolar disorder,

by decreasing anxiety, mood cycling, and facial recognition. These findings are missing information on microdosing psilocybin as the studies are short term, contain small sample sizes, and measure high doses of psilocybin because effects can be easily measured. The current research aims to address this concern. Therefore, the current study's research question asks: Does microdosing psilocybin decrease depressive symptoms in individuals with bipolar and treatment-resistant depression?

Method

Systematic Literature Review Method

The researcher initially applied Field and Gillett's (2010) six-step process for conducting a meta-analysis to ensure validity in this study. The first step outlined is to complete a literature review of articles relevant to the research question. In the present study, the researcher searched for articles using backward-searching and forward-searching to find both published and unpublished articles relating to the study. Step two is to decide on inclusion criteria. This step ensures the quality of the study and removes methodological issues that could potentially harm the research. Next is to calculate the effect size across the studies chosen for the meta-analysis. Different studies measure different variables and different scales of measurement; it is important to calculate the relationship between variables then combine them into a single analysis. When conducting a meta-analysis, after the researchers calculate the effect size, they would then perform a basic meta-analysis. The statistical analyses would provide an estimation of the effects on the population from the collection of articles. After the researchers complete the basic meta-analysis, they may apply more extensive

statistics to address moderators and publication biases. The final step is to write the study. This step includes all sections of the meta-analysis including the abstract, introduction, method section, discussion, plots, graphs, and other statistical information (Field & Gillett, 2010). Due to the many different types of statistical data provided in the chosen studies, the researcher of the present study found that completing a multitude of statistical computations weakened the statistical power of the meta-analysis. Therefore, this research study transitioned to a systematic literature review.

Sample of Studies

Databases to Search: Studies utilized in the systematic literature review were retrieved from the Purdue University Global library and other sources as needed. The researcher used the online research platform EBSCOhost, which contains psychology research databases for peer-reviewed articles, journals, books, and other texts. To obtain research studies with relevant information, the researcher used a specific set of keywords that restrict insignificant and extraneous data. The databases that were used are PubMed (National Library of Medicine), PubMed Central, Medline Complete, Cochrane Library, Google Scholar, APA PsycArticles, Directory of Open Access Journals, PLOS ONE, and ResearchGate. The researcher obtained a list of all databases within the Purdue University Global library and searched for databases in the fields of psychology, medicine, and pharmacology, then applied the keywords to find relevant articles. Due to the lack of studies on psilocybin and bipolar disorder, these databases provided useful articles for the study. Titles and abstracts of the chosen articles were initially screened, and articles of considerable importance were analyzed in detail. The defined inclusion criteria were studies of patients with a clinical diagnosis of bipolar I or II disorder using psilocybin as a treatment option, patients diagnosed with treatment-resistant bipolar disorder or depression using psilocybin as a treatment

option, and patients with depression using psilocybin as a treatment option. Field and Gillett (2010) mentioned the importance of including additional articles that are not found in either published or unpublished databases. The researcher contacted other researchers in the field to inquire about unpublished studies or other articles that will benefit the study.

Keywords to Search: Keywords used in the database search are: Psilocybin, Psilocybin treatment, Psilocybin and depression, Psilocybin and bipolar disorder, Psilocybin and treatment-resistant depression, microdosing psychedelics, microdosing psilocybin, serotonergic hallucinogens, serotonin 2A receptor, serotonin, psilocybin assisted therapy, clinical trials, double-blind study, placebo, placebo-controlled study, microdose, hallucinogen

Figure 1.

Keyword Search Terms

Microdosing Psilocybin	Related Terms	Narrower Terms	Broader Terms	Additional Terms
Microdosing Psilocybin to Lessen Depressive Symptoms in Bipolar Disorder	Psilocybin and depression, Psilocybin and bipolar disorder, Psilocybin and treatment resistant depression, Psilocybin treatment	Psilocybin, microdosing psychedelics, microdosing psilocybin, microdose, hallucinogen	serotonergic hallucinogens, serotonin 2A receptor, serotonin	clinical trials, double-blind study, placebo, placebo-controlled study

Selection Criteria

The researcher did not recruit participants in this study directly but retrieved data from a systematic review of peer-reviewed, scholarly articles pulled from the Purdue University Global library, PubMed, PMC PubMed Central, Medline Complete, Cochrane Library, Google Scholar, APA PsycArticles, Directory of Open Access Journals, PLOS ONE, and ResearchGate. Unpublished studies collected from authors who publish in the area of psilocybin treatments were also considered. These studies included participants with a clinical diagnosis of bipolar I or II disorder with depressive symptoms from the DSM-5 and those diagnosed with treatment-resistant bipolar depression or major depression. Studies were not excluded based on participants' race, ethnicity, gender, sexual orientation, religion, and cultural background. Participants excluded were those under the age of 18 years old or a major medical condition diagnosis.

Participants ranged in age from 18 to 65 years of age with a clinical diagnosis of bipolar I or II disorder with depressive symptoms. The participants may or may not have treatment-resistant bipolar depression or major depression. These participants included females, males, and non-binary/non-conforming genders. Participants came from all ethnicity, racial, and cultural backgrounds and were not excluded due to educational background to promote the study's validity and reliability.

Moderators

Moderator variables that were found to be important to document and examine were comorbidities to bipolar disorder. The DSM-5 includes the following comorbidities for bipolar I and II disorder: anxiety disorders, ADHD, disruptive, impulse-control, or conduct disorder, any substance use disorder, a lifetime eating disorder, metabolic syndrome, and migraines (American Psychiatric Association, 2013). These comorbidities could affect the correlation between

psilocybin and bipolar disorder as the results may differ due to these factors. Anxiety disorders are a common comorbidity for bipolar disorder I and II. Psilocybin has been found to decrease anxiety symptoms after a single dose of psilocybin which can last up to 6 months post-ingestion (Johnson, Griffiths, Johnson, & Griffiths, 2017). Substance Use Disorders are another common comorbidity of Bipolar Disorder. Bogenschutz (2017) researched the effects of psilocybin on substance use disorder and found a notable decrease in drinking that was maintained at the 9-month follow-up. Smoking cessation also occurred in 80% of subjects at the 6-month follow-up. Other comorbidities such as ADHD, conduct disorders, and metabolic disorders were taken into consideration throughout the study. The researcher also documented the setting of each research study as results may differ depending on the setting.

Systematic Literature Review Procedures

A literature search/review was conducted utilizing several available studies and articles relating to the study of microdosing psilocybin for the treatment of bipolar depression. These articles provided scientific evidence backing the need for additional research into psilocybin for the treatment of the depressive symptoms of bipolar disorder. Inclusion criteria are essential features of the target population that were researched during the study. For a systematic literature review, inclusion criteria are characteristics of the population of several different studies. Age, race, ethnicity, gender, sexual orientation, religion, and cultural background was examined closely within each article. Exclusion criteria included those under the age of 18 or diagnosed with a major medical condition. After the inclusion and exclusion criteria were determined, a systematic search of articles related to the topic being studied was completed. This step included searching through

several literature databases using specific keywords, contacting authors of studies focusing on the same area of research, and ensuring the quality of each study.

Once the researcher obtained the studies, the researcher reviewed each study and extracted the effect sizes. The effect size is the relationship between the two variables being tested (e.g., psilocybin and bipolar depression). Pearson's correlation coefficient, *r* and Cohen's d, were used to measure the correlation coefficient or relationship between psilocybin and bipolar depression. The researcher utilized Microsoft Excel software to organize and evaluate the findings and study characteristics across the research articles.

Data Management

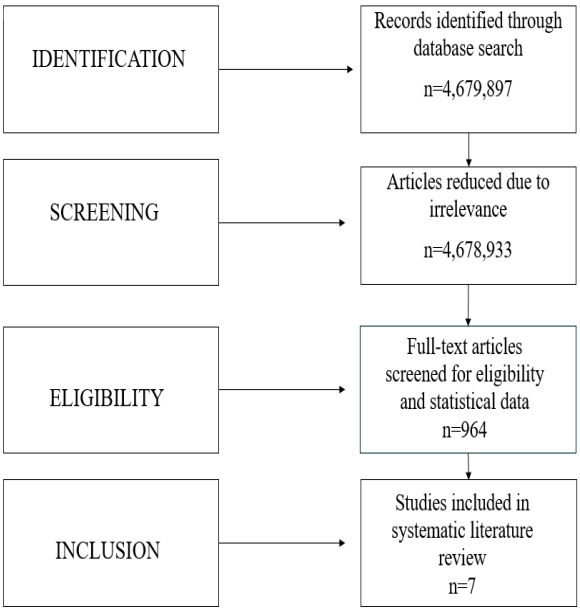
The researcher has saved and will maintain copies of the research studies, spreadsheets, and statistical databases for five years for the request and replication of research by other researchers. Data has been stored using a password protected flash drive that will be kept in a locked cabinet. Only the researcher has access to the locked cabinet and flash drive. File transfers of confidential data will be compressed and encrypted prior to being transferred if transferred via email or other digital media. These steps help to minimize the chance of the transfer failing due to the file being too large. A password encryption is used and will allow for only the receiver to view the data as they will have a specific password given in advance. Data destruction after 5 years will consist of flash drives being permanently deleted and wiped clean.

Results

Selection of Studies

The researcher briefly reviewed results from each keyword search, then reduced each keyword search result down to those articles that pertained to specific details that included articles on psilocybin, psilocybin treatment for depression, psilocybin treatment for bipolar disorder, etc, as outlined in table 2. Total search results for all keywords used in the identification process were 4,679,897, with 99% of these results not relevant to the effects of psilocybin on bipolar depression. The researcher screened keyword search results by title and eliminated 4,678,933 that were unrelated to psilocybin and bipolar disorder. A title and abstract review was completed of the remaining 964 articles. The review consisted of identifying statistical data, results, and method processes of the articles. If data was not consistent with the systematic review, such as lack of statistical data, irrelevant material, or did not pertain to psilocybin and depression, the articles were further reduced. Eight of the 964 articles were found compatible with statistical data consistent with the systematic literature review.

Figure 2. Flowchart of t the inclusion process



Main Effects for Psilocybin on Bipolar Disorder II

The researcher briefly reviewed the studies' results in Table 1 below, which includes each study's author(s), participants, sex, study design, control and experimental group, dosage, assessment times, outcome measures, and results. The dosages, results, and data were examined further and placed into a spreadsheet where the researcher compared effect sizes, population means, and correlation coefficients if provided in the study. Seven studies had relevant data and measurable outcomes that were included in this systematic literature review. Of the studies, 86% were experimental, with 14% observational or self-reporting. A total of 1,032 participants were examined within the seven studies, and participants ranged from healthy subjects, those who have been diagnosed with major depression and/or treatment-resistant depression, current microdosers, or those who have never microdosed before the study. All of the psilocybin studies were published recently, with 100% of the studies published between 2017 and 2020. Of the seven studies, 86%

were experimental, with one being observational. Six of the seven studies examined the use of psilocybin on major depression or treatment-resistant depression. In contrast, one study examined the effects of microdosing psilocybin versus not using or microdosing psilocybin.

Participant Characteristics

A total of 1,032 participants ranging in age from 20-65 were examined within the seven studies. Participants included healthy subjects, those who have a clinical diagnosis of major depression and/or treatment-resistant depression, current microdosers, or those who have never microdosed before the study. Of the 1,032 participants, 9% were diagnosed with treatment-resistant depression. Nine hundred and nine participants made up subjects that were current/previous microdosers or had never microdosed before. Less than 1% were healthy volunteers used in control groups. Males made up the majority of the participants, while only 19% were female, and 63% of the participants were mentioned to be Caucasian.

Measures

Within the studies that were evaluated by the researcher, self-reporting scales and assessments were the primary preference of the researchers conducting the studies. Eighty-six percent of the studies evaluated used self-reporting scales, while 1 study used a clinician-administered depression scale. The ‘Profile of Mood States’ (POMS) scale is a 65 item, self-report psychological instrument intended to assess short-term mood states which are transient and frequently fluctuating (Shacham, 1983). The Beck Depression Inventory is also a self-rating scale used to measure the severity of depressive symptomatology and treatment progression (Stark, 2019). The Snaith-Hamilton Pleasure Scale (SHAPS) is a rapid screening battery designed for assessing anhedonia or the inability to experience pleasure (Martino et al., 2018). The SHAPS

battery includes the Beck Depression Inventory (BDI), which was also used as an assessment tool in two of the seven studies. The QIDS-SR16 is a 30-question scale that measures the severity of depressive symptomatology (Rush, 2003). The Hamilton Depression Rating Scale (HAM-D) is a 17-item clinician-administered depression scale (Hamilton, 1967). The HAM-D is the only clinician-administered assessment that was utilized within the studies evaluated. One study (Carhart-Harris et al., 2017) utilized this assessment in their 6-month follow-up study on the effects of psilocybin and depression. Self-report assessments are more common in research studies as they can be quickly administered and are more cost-efficient. In this study, self-reporting tools were most commonly used as they could be given quickly and at several time intervals during the study. It has been found that self-report scores are more predictable of clinician-rated instruments; while clinician assessments are less predicting of result outcomes on self-reported scales. It is suggested that self-reporting measures be used instead of a clinician's rating if a choice has to be made (Uher et al., 2012).

Results of the Studies

The 'Profile of Mood States (POMS) scale is a questionnaire that measures six dimensions of mood swings; tension or anxiety, anger or hostility, vigor or activity, fatigue or inertia, depression or dejection, confusion or bewilderment, which occur over a period of time (Heuchert & McNair, 2012). Barrett et al. (2020) utilized this tool after administration of 25 mg of oral psilocybin and found that PANAS negative affect, STAI state anxiety, POMS tension, depression, and total mood disturbance scale scores were significantly lowered 1-week post psilocybin administration. At one week, all symptoms were lowered significantly but returned toward baseline one month after psilocybin administration. Depression was significantly higher at the one month

mark compared to one week after psilocybin administration; Trait anxiety results were reduced 1-month post-psilocybin compared to baseline: POMS tension (F[2,20] = 6.37, p = 0.007, η2 p= 0.376), depression (F[2,20] = 5.46, p=0.013, η2 p=0.316), and total mood disturbance (F[2,20]=5.66, p=0.011, η2 p=0.352).

The Beck Depression Inventory (BDI) is a 21-item, self-report rating scale that measures characteristic attitudes and symptoms of depression (Beck et al., 1961). Carhart-Harris et al. (2017) utilized the BDI scale for a follow-up study 6 months after the initial administration of 25mg oral psilocybin. The researchers found that BDI scores were significantly reduced at 1 week (mean reduction = − 22.7, 95% CI = − 17.6 to − 27.8, $p < 0.001$), 3 months (mean reduction = − 15.3, 95% CI = − 8.7 to − 21.9, $p < 0.001$) and 6 months post-treatment (mean reduction = − 14.9, 95% CI = − 8.7 to − 21.1, $p < 0.001$). Mertens et al. (2020) also administered the BDI scale to study psilocybin and treatment-resistant depression. The researchers administered 25mg of oral psilocybin to 19 participants with diagnosed TRD. The researchers followed up with assessments at baseline, one day, one week, two weeks, three weeks, five weeks, three months, and six months after treatment; the results showed that BDI scores were significantly reduced at one week (M reduction = 22.26, SD = 11.37, with 57.9% meeting criteria for remission (BDI < 9)). Both studies had similar results for their subjects with TRD showing that a significant reduction in BDI score at one week was present with a mean reduction of 22.26 and 22.7.

The Snaith-Hamilton Pleasure Scale (SHAPS) is a screening battery designed for assessing the presence of anhedonia or the inability to experience pleasure (Martino et al., 2018). Carhart-Harris et al. (2017) utilized the SHAPS assessment in their 6-month follow-up study after administering 25mg of oral psilocybin. The researchers found that SHAPS anhedonia scores were

significantly reduced at 1 week (*M* reduction = − 4.6, 95% CI = − 2.6 to − 6.6, $p < 0.001$) and 3 months post-treatment (*M* reduction = − 3.3, 95% CI = − 1.1 to − 5.5, $p = 0.005$). Stroud et al. (2017) also administered the SHAPS battery during their study on treatment-resistant depression. The researchers administered 25mg of oral psilocybin to 17 participants with treatment-resistant depression and 16 healthy participants and found that SHAPS scores were significantly reduced at the post-treatment assessment compared to the 'pre' treatment assessment, which showed an improved capacity for experiencing pleasure after the psilocybin-based treatment ($F(1, 16) = 37.14$, $p < .001$, ηp 2 = .699).

The HDRS (also known as the Ham-D) is the most frequently used clinician-administered depression assessment scale. The HAM-D is a 17 item assessment that gauges depression symptoms over the past week's duration (Hamilton, 1967). Carhart-Harris et al. (2017) used the HAM-D assessment in their six-month follow-up study on psilocybin and treatment-resistant depression. The researchers administered 25mg of oral psilocybin to 20 adults with TRD and measured depressive symptoms at one week and six months post-treatment. The results showed HAM-D scores were significantly reduced at 1-week post-treatment (mean reduction = − 14.8, 95% CI = − 11 to − 18.6, $p < 0.001$).

The QIDS-SR16 is a 30-item, self-reporting depression scale that measures the severity of depressive symptomatology (Rush, 2003). Carhart-Harris et al. (2017) completed a study on psilocybin and treatment-resistant depression and used the QIDS-SR16 assessment scale to measure depression symptoms in those participants. The researchers administered 25mg of oral psilocybin to 19 participants with TRD, the results found that all 19 patients showed a decrease in depressive symptoms at one week, 12 participants meeting criteria for response (change=−10.2 ±

5.3, t =−6.4, $p < 0.001$), and 18/19 participants had decreased QIDS-SR16 scores at week 5. Mertens et al. (2020) also found a decrease in depression symptoms in participants with treatment-resistant depression using the QIDS-SR16 after a 25mg dose of psilocybin. QIDS-16 scores for patients were significantly lower ($p < .001$) at the 'post' time point (M = 7.65, SD = 5.34) as compared to the 'pre' time point (M = 18.88, SD = 2.23), reflecting a reduction in depressive symptoms after receiving the psilocybin-based treatment.

A study by Anderson et al. (2018), investigated whether microdosing psychedelics is related to differences in personality, mental health, and creativity. This study found that microdosing psilocybin concluded lower negative emotionality (b = − 5.78, 95% CI [− 10.13 − 1.43], z(396) = − 2.60, p = 0.009, r = − 0.85). Controlling for gender also showed a significant predictor (higher negative emotionality in females, b = 10.49, 95% CI [5.33 15.65], z(396) = 3.99, $p < 0.001$, r = 0.95). This study also suggested that microdosing concluded lower scores on dysfunctional attitudes (b = − 8.69, 95% CI [− 12.48 − 4.89], z(364) = − 4.49, p < 0.001, r = − 0.92). Controlling for a history of mental illness showed significant results (b = 5.74, 95% CI [2.45 9.03], z(364) = 3.42, p < 0.001, r = 0.85).

Table 1

Summary of Study Characteristics for Bipolar Disorder: Microdosing Psilocybin to Lessen Depressive Symptoms

Author(s)	Participants	Sex	Study design	Experimental group	Control group	Dosage	Assessment times	Outcome measures
Anderson et al. (2018)	909 participants (microdosers: n = 594, 65%) (non-microdosers: n = 315, 35%) (median age = 26) 70% white	82% males 18% female	Observational study	Participants with experience and participants without experience microdosing psychedelics	Non-microdosers	Varied (0-100) microdoses	N/A	Online, computer-based questionnaires, DAS-A-17
Barrett et al. (2020)	Twelve healthy volunteers n=12	7F, 5M	Open-label pilot study/open trial	Twelve healthy, Caucasian volunteers	Uncontrolled	25mg/70kg	1-day before, 1-week after, and 1-month	POMS 46, STAI 47, PANAS-X 48, DASS 49, DPES 5, BFI 51 TAS
Carhart-Harris et al. (2017)	19 participants diagnosed with treatment-resistant major depression n=19	4F, 15M	Open label clinical trial	19 participants with diagnosed treatment-resistant major depression	Uncontrolled	Week 1- 10mg Week 2- 25mg	1 week and 5 weeks	fMRI, ALS, BOLD, QIDS-SR16, RSFC
Carhart-Harris et al. (2017)	20 adults with treatment-resistant depression n=20	6F, 14M	Open-label feasibility study/ open trial	Twenty patients (six females) with (mostly) severe, unipolar, treatment-resistant major depression	Uncontrolled	2 oral doses, 10mg and 25mg (7 days apart); 5mg psilocybin in size 0 capsule	6 months post treatment	BDI-depression STAI-anxiety SHAPS-anhedonia HAM-D-depression, clinician-administered GAF-clinician administered
Erritzoe et al. (2018)	20 adults with treatment-resistant depression n=20	6F, 14M	Open-label feasibility study/ open trial	Twenty patients (six females) with (mostly) severe, unipolar, treatment-resistant major depression	Uncontrolled	2 oral doses, 10mg and 25mg (7 days apart); 5mg psilocybin in size 0 capsule	Baseline and 3 months	Revised (NEO-PI-R), subjective psilocybin experience with Altered State of Consciousness (ASC) scale, depressive

Table 1 cont.

Summary of Study Characteristics for Bipolar Disorder: Microdosing Psilocybin to Lessen Depressive Symptoms

Author(s)	Participants	Sex	Study design	Experimental group	Control group	Dosage	Assessment times	Outcome measures
Mertens et al. (2020)	19 Participants with treatment-resistant depression	6F, 13M	Open label study	19 Participants with treatment-resistant depression	Uncontrolled	Week 1-10mg Week 2-25mg	Baseline, one day, one week, two weeks, three weeks, five weeks, three months and six months after treatment	Self-rated Beck Depression Inventory (BDI), QIDS-SR16, RRS, fMRI
Stroud et al. (2017)	33 participants (17 with treatment-resistant depression n=17) (16 without treatment-resistant depression n=16)	Control: 11M, 5F Experimental: 11M, 6F	Pilot study	17 participants with treatment-resistant depression who were given psilocybin	16 participants without treatment-resistant depression who were not given psilocybin	Week 1-10mg Week 2-25mg	Baseline, one week, and one month	DEER-T, the QIDS16 and SHAPS

Note: F=Female, M=Male, DAS-A-17=Differential Ability Scales, POMS=Profile of Mood States, PANAS-X=Positive and Negative Affect Schedule, DASS=Depression, Anxiety, Stress Scales, STAI=State and Trait Anxiety Inventory, DPES=Dispositional Positive Emotion Scale, BFI=Big Five Inventory, TAS=Toronto Alexithymia Scale, fMRI=Functional Magnetic Resonance Imaging, BOLD=Blood-oxygen-level-dependent imaging, QIDS-SR=The Quick Inventory of Depressive Symptomatology, RSFC=resting-state functional connectivity, BDI=Beck Depression Inventory, SHAPS=Snaith-Hamilton Pleasure Scale, HAM-D=The Hamilton Depression Rating Scale, GAF=Global Assessment of Functioning, NEO-PI-R=The Revised NEO Personality Inventory, ASC=Altered State of Consciousness, RRS=Rumination Response Scale, DEER-T=Dynamic Emotional Expression Recognition Task, ALS=The short Affective Lability Scales

Table 2. *Summary of Study Results*

https://docs.google.com/document/d/1qUW203ESydo_L0sOVA0ZicNvy7dj5gYCSD0rh9qkSeo/edit

Moderator Analysis

The DSM-5 lists comorbidities for both bipolar I and II disorder as anxiety disorders, ADHD, disruptive, impulse-control, or conduct disorder, any substance use disorder, a lifetime eating disorder, metabolic syndrome, and migraines (American Psychiatric Association, 2013). Anxiety disorders are a common comorbidity for bipolar disorder I and II and a moderator analysis from Carhart-Harris et al. (2017) and Barrett et al. (2020), utilizing the STAI- State and Trait Anxiety Inventory found a significant reduction in anxiety scores in both studies: Barrett: STAI state (F[2,20]=3.91, p = 0.037, η2 p = 0.27) and trait (F[2,20]=3.96, p = 0.036, η2 p = 0.277). Carhart-harris: STAI-T anxiety scores were significantly reduced at 1 week (mean reduction = − 23.8, 95% CI = − 16.5 to − 31.1, p < 0.001), 3 months (mean reduction = − 12.2, 95% CI = − 6.1 to − 18.3, p < 0.001) and 6 months post-treatment (mean reduction = − 14.8, 95% CI = − 8.1 to − 21.6, p < 0.001).

Psilocybin has also been found to increase positive emotions in participants when evaluated with the DPES scales. The Dispositional Positive Emotions Scales (DPES) are seven scales that measure joy, awe, amusement, pride, contentment, compassion, and love (Dixson, Anderson, & Keltner, 2019). Barrett et al. (2020) found that psilocybin caused significant changes from baseline to one month post psilocybin administration in the domains of joy, content, pride, compassion, and amusement: DPES joy (F[2,20]=6.03, p = 0.009, η2 p =0.36), content (F[2,20]=5.11, p = 0.016,

η2 p = 0.314), pride (F[2,20] = 5.85, p = 0.011, η2 p = 0.343), compassion (F[2,20]=7.69, p = 0.004, η2 p = 0.44), and amusement (F[2,20]=7.66, p = 0.004, η2 p = 0.435) scales.

Discussion

The researcher evaluated the effects of microdosing with the psychoactive drug psilocybin from the mushroom family Psilocybe (magic mushrooms) for treating bipolar II disorder depression. Findings indicate a lack of research into lose-dose treatments using psilocybin. However, a large, one-time dose of at least 25mg/70kg of psilocybin has been found to significantly decrease depression symptoms in those with treatment-resistant depression and major depression. Many individuals with bipolar II disorder experience depressive symptoms or major depressive episodes throughout a considerable portion of their lives; this leads to an exhaustion of treatment options and leaving the individual prone to treatment-resistant bipolar depression (TRBD) (Hidalgo-Mazzei et al. 2019). The evidence that psilocybin is a viable treatment option for treatment-resistant depression indicates that psilocybin would be a treatment option for bipolar II depression.

Implications

Evidence suggests that psilocybin, a serotonin agonist, has successfully decreased depressive symptomatology within the treatment-resistant depression population. Bipolar II disorder has been found to leave individuals with treatment-resistant depression as many have exhausted several treatment options with no success. Serotonin produced in the central nervous system cannot cross the blood-brain barrier, indicating that all serotonin in the brain must stay there. The amount of serotonin dispersed within the central nervous system is limited (Campbell, 2020). As an agonist, dimethyltryptamine binds to serotonin molecules and can

travel to brain sections that utilize serotonin for proper functioning (Carhart-Harris, 2017). Serotonin is thought to regulate emotional responses by lowering depression and increasing joy, compassion, and love. Barrett et al. (2020) found that depression significantly decreased while joy, compassion, and love increased after a 25mg dose of psilocybin. Carhart-Harris et al. (2017) found that not only depression scores decreased on the Beck Depression Inventory, but Suicidality scores on the QIDS-SR16 were significantly reduced 1 and 2 weeks post-treatment. Stroud et al. (2017) concurred that there was an improved capacity for experiencing pleasure after the psilocybin-based treatment.

Limitations

The studies that the researcher reviewed relied on small sample sizes that limit statistical strength and efficacy of using psilocybin as a viable treatment option for psychological disorders. The statistical data is limited due to research into psychedelics for treating psychological disorders being a relatively new and budding field. More rigorously controlled studies would be vital for developing an accurate dosage for the type of disorder it will be treating. Demographics of the study sample would need to be more inclusive. Of the studies reviewed, most of the participants were White, young males, which is not always an indicative precursor to certain mental health disorders. Studies should also be equal in the amount of controlled versus uncontrolled study designs. Controlled studies would allow researchers to manipulate variables to be more suitable for the psychological disorders they are studying (e.g., dosage, assessment intervals, and measures). There should also be more adequate studies on adverse side effects psychedelics have on disorders with psychotic traits and rapid cycling, such as Bipolar I disorder. The lack of double-blind studies is also a limitation that could contribute to biased results. Participants with the knowledge that they

are given a psychoactive drug may unintentionally present with positive results as opposed to someone unaware of what drug they were given, such as an active placebo. Researchers and participants alike would benefit from double-blind studies, especially when the disorder being tested involves grandiosity, euphoria, and mania like in bipolar disorder.

Conclusion

Psilocybin is a psychoactive derivative from the mushroom genus Psilocybe. When digested, psilocybin turns into psilocin, which acts as a 5-HT agonist. The psilocin agonist 5-HT2A resembles the serotonin inhibitor receptor naturally occurring in the human brain. Serotonin made within the central nervous system cannot cross the blood-brain barrier, so the serotonin needed for the proper functioning of appetite, memory, mood, sexual desire, and sleep would need to come directly from diet, which increases serotonin in the gut. In individuals with depression, serotonin levels in the CNS are decreased, thus needing large amounts from foods high in tryptophan, which is converted to tryptamine, Selective Serotonin Reuptake Inhibitors (SSRIs), or Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs). Psilocybin works as a serotonin agonist, which means that psilocybin enters the central nervous system and increases the body's serotonin receptors. In this systematic literature review, the researcher found substantiated evidence that serotonin decreases depressive symptomatology and increases feelings of joy, love, peace, contentment, and compassion. Mertens et al. (2020) found that 57.9% of their treatment-resistant depressive participants met the remission criteria one week after a 25mg dose of psilocybin. Psilocybin constitutes a novel treatment for bipolar II depression as BPD II and TRD have similar failed treatment outcomes due to exhausting many treatment interventions. Due to the study design and analysis's methodological

limitations, future studies with more integrated and vigorous analysis, larger and more inclusive sample sizes, and increased double-blind and controlled study designs would be necessary to better understand treatment options using psilocybin for depression.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington DC: American. *Psychiatric Association*

Anderson, T., Petranker, R., Rosenbaum, D., Weissman, C. R., Dinh-Williams, L.-A., Hui, K., Hapke, E., & Farb, N. A. S. (2019). Microdosing psychedelics: personality, mental health, and creativity differences in microdosers. *Psychopharmacology*, *236*(2), 731–740. https://doi.org/10.1007/s00213-018-5106-2

Barrett, F. S., Doss, M. K., Sepeda, N. D., Pekar, J. J., & Griffiths, R. R. (2020). Emotions and brain function are altered up to one month after a single high dose of psilocybin. *Scientific Reports, 10*(1), 1. Retrieved from https://www-ncbi-nlm-nihgov.libauth.purdueglobal.edu/pmc/articles/PMC7010702/pdf/41598_2020_Article_59282 .pdf

Beck, A.T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961) An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561-571.

Bienemann, B., Ruschel, N. S., Campos, M. L., Negreiros, M. A., & Mograbi, D. C. (2020). Self-reported negative outcomes of psilocybin users: A quantitative textual analysis. *PloS One, 15*(2), e0229067. https://doi.org/10.1371/journal.pone.0229067

Bogenschutz, M. P. (2017). It's time to take psilocybin seriously as a possible treatment for substance use disorders. *The American Journal of Drug and Alcohol Abuse, 43*(1), 4–6. https://doi.org/10.1080/00952990.2016.1200060

Campbell, J. (2020). Serotonin. *Salem Press Encyclopedia of Health*.

Carhart-Harris, R. L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J. N., Wall, M. B., Tanner, M., Kaelen, M., McGonigle, J., Murphy, K., Leech, R., Curran, H. V., & Nutt, D. J. (2017). Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific Reports, 7*(1), 13187. https://doi.org/10.1038/s41598-017-13282-7

Carhart-Harris, R. L., Bolstridge, M., Day, C. M. J., Rucker, J., Watts, R., Erritzoe, D. E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Curran, H. V., & Nutt, D. J. (2018). Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology, 235*(2), 399–408. https://doi.org/10.1007/s00213-017-4771-x

Dixson, D. D., Anderson, C. L., & Keltner, D. (2019). Measuring Positive Emotions: and Examination of the Reliability and Structural Validity of Scores on the Seven Dispositional Positive Emotions Scales. *Journal of Well-Being Assessment 2*(115–133). https://doi.org/10.1007/s41543-019-00015-y

Erritzoe, D., Roseman, L., Nour, M. M., MacLean, K., Kaelen, M., Nutt, D. J., & Carhart-Harris, R. L. (2018). Effects of psilocybin therapy on personality structure. *Acta Psychiatrica Scandinavica, 138*(5), 368–378. https://doi.org/10.1111/acps.12904

Fielding, A. P., & Gillett, R. (2010). How to do a meta-analysis. *British Journal of Mathematical and Statistical Psychology. 63*(3), 665-694. https://doi.org/10.1348/000711010X502733

Hamilton M. (1967). Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol 6*(4):278–96. https://dcf.psychiatry.ufl.edu/files/2011/05/HAMILTON-DEPRESSION.pdf

Heuchert, J. P., & McNair, D. M. (2012). The Profile of Mood States 2nd Edition (POMS 2). *Journal of Psychoeducational assessment, 32*(3) 273-277. https://doi.org/10.1177/0734282913505995

Hidalgo-Mazzei, D., Berk, M., Cipriani, A., Cleare, A. J., Florio, A. D., Dietch, D., Geddes, R. J., Goodwin, G. M., Grunze, H., Hayes, J. F., Jones, I., Kasper, S., Macritchie, K., McAllister-Williams, R. H., Morriss, R., Nayrouz, S., Pappa, S., Soares, J. C., Smith, D. J., Suppes, T., Talbot, P., Vieta, E., Watson, S., Yatham, L. N., Young, A. H., Stokes, P. R. A. (2019). Treatment-resistant and multi-therapy-resistant criteria for bipolar depression: Consensus definition. *The British Journal of Psychiatry, 214*(1), 27-35. doi:http://dx.doi.org.libauth.purdueglobal.edu/10.1192/bjp.2018.257

Hui Poon, S., Sim, K., & Baldessarini, R. J. (2015). Pharmacological approaches for treatment-resistant bipolar disorder. *Current Neuropharmacology*, *13*(5), 592–604. https://doi.org/10.2174/1570159x13666150630171954

Johnson, M., Griffiths, R., Johnson, M. W., & Griffiths, R. R. (2017). Potential therapeutic effects of psilocybin. *Neurotherapeutics, 14*(3), 734–740. https://doi.org/10.1007/s13311-017-0542-y

Kraehenmann, R., Schmidt, A., Friston, K., Preller, K. H., Seifritz, E., & Vollenweider, F. X. (2016). The mixed serotonin receptor agonist psilocybin reduces threat-induced modulation of amygdala connectivity. *NeuroImage: Clinical, 11*, 53–60. https://doi.org/10.1016/j.nicl.2015.08.009

Lee, Y. H. (2019).Strengths and limitations of meta-analysis. *The Korean Journal of Medicine 94*(5):391-395. https://doi.org/10.3904/kjm.2019.94.5.391

Lu, X., Zhong, Y., Ma, Z., Wu, Y., Fox, P. T., Zhang, N., & Wang, C. (2019). Structural imaging biomarkers for bipolar disorder: Meta-analyses of whole-brain voxel-based morphometry studies. *Depression and Anxiety, 36*(4), 353–364. https://doi.org/10.1002/da.22866

Martino, I., Santangelo, G., Moschella, D., Marino, L., Servidio, R., Augimeri, A., Costabile, A., Capoderose, G., Cerasa, A. (2018). Assessment of Snaith-Hamilton Pleasure Scale (SHAPS): the dimension of anhedonia in Italian healthy sample. *Neurol Sci. 39*(4):657-661. doi: 10.1007/s10072-018-3260-2.

Mertens, L.J., Wall, M. B., Roseman, L., Demetrious, L., Nutt, D., & Carhart-Harris, R. L. (2020). Therapeutic mechanisms of psilocybin: Changes in amygdala and prefrontal functional connectivity during emotional processing after psilocybin for treatment-resistant depression. *Journal of Psychopharmacology 1*(14). https://doi.org/10.1177/0269881119895520

Psilocybin. (2006). In B. C. Bigelow (Ed.), UXL Encyclopedia of Drugs and Addictive Substances (Vol. 5, pp. 791-806). UXL. https://link.gale.com/apps/doc/CX3448100102/GVRL?u=chic13451&sid=GVRL&xid=7b118e34

Rocca, C. C. de A., Heuvel, E. van den, Caetano, S. C., & Lafer, B. (2009). Facial emotion recognition in bipolar disorder: a critical review. *Revista Brasileira de Psiquiatria*, *31*(2), 171–180.

Rowland, T. A., & Marwaha, S. (2018). Epidemiology and risk factors for bipolar disorder. *Therapeutic Advances in Psychopharmacology*, *8*(9), 251–269.

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., Markowitz, J. C., Ninan, P. T., Kornstein, S., Manber, R., Thase, M. E., Kocsis, J. H., Keller, M. B. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry. 54*(5):573-83. doi: 10.1016/s0006-3223(02)01866-8

Shacham, S. (1983). A Shortened Version of the Profile of Mood States. *Journal of Personality Assessment*, *47*(3), 305. https://doi.org/10.1207/s15327752jpa4703_14

Stark, S. W. (2019). Beck Depression Inventory (BDI). Salem Press Encyclopedia of Health.

Stroud, J. B., Freeman, T. P., Leech, R., Hindocha, C., Lawn, W., Nutt, D. J., Curran, H., & Carhart-Harris, R. L. (2018). Psilocybin with psychological support improves emotional

face recognition in treatment-resistant depression. *Psychopharmacology*, *235*(2), 459–466. https://doi.org/10.1007/s00213-017-4754-y

Thomas, K., Malcolm, B., & Lastra, D. (2017). Psilocybin-assisted therapy: A review of a novel treatment for psychiatric disorders. *Journal of Psychoactive Drugs*, *49*(5), 446–455. https://doi.org/10.1080/02791072.2017.132

Uher, R., Perlis, R. H., Placentino, A., Dernovšek, M. Z., Henigsberg, N., Mors, O., Maier, W., McGuffin, P., & Farmer, A. (2012). Self-report and clinician-rated measures of depression severity: can one replace the other?. *Depression and anxiety*, *29*(12), 1043–1049. https://doi.org/10.1002/da.21993