

Psilocybin Induced Psychedelic Experiences: their Neural Mechanisms and Efficacy for Treating Depressive Disorders

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Abstract

The aim of this systematic review is to present the current literature on the therapeutic potential of the classic psychedelic compound psilocybin for depressive disorders and the neurocognitive mechanisms involved recorded with functional magnetic resonance imaging (fMRI). A comprehensive literature search was conducted in the electronic databases Web of Science, Scopus and Medline EBSCO using a Boolean search string containing the keywords psilocybin, depression, fMRI, MRI and PET. Our inclusion criteria require original neuroimaging research articles published in scientific peer-reviewed journals involving participants diagnosed with depression receiving psilocybin in conjunction with psychological support. Five articles were identified including a total of 104 participants with depression and 75 who received treatment, resulting in significant reduction of depressive symptoms associated with observable changes in neural activity. Specifically reduced cerebral blood flow (CBF) in amygdala, decreased brain modularity along with functional changes in default mode network (DMN), executive network (EN), salience network (SN), decrease in functional connectivity (FC) between ventromedial prefrontal cortex (vmPFC) to amygdala and increased amygdala reactivity to fearful faces. Limitations of our systematic review include a currently limited amount of articles published and thus lack of control groups in most studies. The current evidence indicates that the therapeutic potential of psilocybin-assisted therapy may provide fast acting and efficient amelioration of depressive symptoms and the effects may be mediated by neurocognitive changes acute and post-treatment. The preliminary results warrants further research in order to optimize treatment and establish safety and efficacy long term.

Keywords: psilocybin, depression, fMRI, systematic review, DMN

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Depression

The World health organization (WHO) predicts that by 2030 depression will be the leading cause of disease in the world (WHO, 2011). Depression is ranked as the most economically burdensome disease globally both for the individual and society. The direct cost of healthcare usage for treatment is high and the indirect cost for increased risk of mortality in suicide and other related risk factors is substantial (Richards, 2011). Depression affects the individual's ability to manage their relationships, daily responsibilities and the individual's ability to work. It is the leading cause of absence in the workplace (Jesulola et al., 2018). Depression has a high lifetime prevalence, up to 21% of the population is estimated to experience at least one depressive episode during their lifetime (Gutiérrez-Rojas et al., 2020). Of patients with major depression disorder, up to 15% die from suicide (Gonda et al., 2007). Studies point to several aspects when it comes to risk factors of developing depression. Sociodemographic factors play a part in the likelihood of developing depression, women are for example twice as likely to have depression as men. Physical disease and chronic pain are also risk factors. Heredity is estimated to be up to 45% for depression. Despite this no specific gene has been found to be involved, there seems to be a combination of several genes identified. What seems to be the greatest risk factors are adverse childhood experiences (ACE), the occurrence of emotional, physical and sexual abuse as well as neglect during childhood. Though ACE is usually assessed in retrospect which makes it difficult to determine a causal relationship (Dagnino et al., 2020).

Classification and Symptoms

Depression is described by WHO's International Classification for Disease and Related Disorders (ICD-10) as loss of interest in activities, lack of emotional reactions, sleep

disturbance, loss of appetite, loss of libido, weight loss and slow movement as well as loss of facial expression and lack of energy (WHO, 1993). If four of these symptoms are present for a duration of two weeks it is classified as depression (Richards, 2011). The American psychological association's Diagnostic and statistical manual of mental disorders (DSM-5) describes depression similarly (APA, 2013). The symptoms have to be present for a duration of two weeks with at least five of the listed symptoms present. Symptoms include anhedonia, loss of interest or pleasure, loss of appetite and sleep disturbance. Feelings of guilt, worthlessness and suicidal thoughts are also symptoms included in the diagnosis. DSM differs between major depression disorders (MDD) and chronic depressive disorder in that the latter is milder with longer duration (Richards, 2011). The majority of patients diagnosed with a depressive episode normally recover within a year post treatment but a significant number do not experience remission and may show no signs of recovery even after several years. The definition of treatment resistant depression (TRD) is non-responsiveness to two different treatments of medical antidepressants. Treatment resistance can be as common as up to 55% and patients with a longer duration of depression have only 40% chance of recovery within ten years (Nedic Erjavec et al., 2021). Relapse is common, after a year of remission as many as up to 25% experience relapse. After two years the number is 30% and after five years up to 42% (Richards, 2011). For patients diagnosed with major depression about 80% of patients will experience several recurring episodes during their lifetime (Fava et al., 2003).

Over the span of a hundred years several attempts have been made to measure depression in patients and other populations such as students. Depression is a complex disorder with differential biomarkers typically assessed by the descriptions of symptoms (Fava et al., 2003). The Beck Depression Inventory (BDI) is one of many self-report questionnaires used by both researchers and clinicians to evaluate the severity of depression. It was first developed in 1961 by Aaron T Beck and his colleagues. The theory of depressive cognitive distortions is the basis for the 21 items rated on a four point scale, a higher score indicate more severe depression. It has since undergone several revisions and the latest BDI-II has a high

validity as a tool to assess depression (Jackson-Koku et al., 2016). Another questionnaire to assess depression is the 30-item Inventory of Depressive Symptomatology (IDS). The items are scored on a scale from zero to three and a higher score indicates more severe symptoms. A short 16 item form has also been developed. The Quick Inventory of Depressive Symptomatology (QIDS) has been evaluated and has good validity and internal consistency (Rush et al., 2003). The items in both of the inventories are well matched to the DSM diagnostic criterion. The Hamilton depression rating scale (HAMD) was first developed by Max Hamilton in the 60s. Since then there have been several revisions and there are several versions of the scale that can be used in both structured interviews and as self-report measurements. The scale measures for example mood and somatic symptoms and a higher score than 20 indicate depression with a more severe depression the higher the score. The GRID HAMD differentiate frequency of symptoms from intensity of the symptoms (Williams et al., 2008).

Neural Correlates

As of yet there has not been identified a single biomarker for depression (Nedic Erjavec et al., 2021). Differential evidence exists on the biology of depression and they are often contradictory, likely due to heterogeneous patient groups (Singh & Gotlib, 2014).

In patients with depression there is a disruption in emotional functioning and regulation. Researchers have noted both structural and functional abnormalities in brain regions such as amygdala and hippocampus as well as anterior cingulate cortex (ACC), dorsolateral prefrontal cortex (dlPFC) and ventral striatum in patients with MDD (Singh & Gotlib, 2014). Hippocampus is involved with the generation of emotion and regulation of stress by inhibiting other subcortical structures. Reduced volume in hippocampal areas is associated with longer duration and recurrent depressive episodes. Reductions in PFC, ACC and orbitofrontal cortex (OFC) are associated with disrupted reasoning, attention and poorer executive functioning. Rumination is a symptom of depression correlated with less cortical volume in ACC and right inferior frontal gyrus (Singh & Gotlib, 2014). Researchers have also

found that some regions are underactive in MDD while others are overactive compared to healthy controls. Clusters in the anterior insula and right ACC have been found to be underactive, this is associated with biased affective information processing and disrupted cognitive control. Abnormal activation of medial prefrontal cortex (mPFC) and the right ACC are involved in self-referential processing and are believed to be related to bias toward negative emotional processing as well as an increased self-focus. Overactivity in dorsolateral prefrontal cortex (dlPFC) in response to negative emotional stimuli but underactivity of the DLPFC response to positive emotional stimuli support the hypothesis of a negativity bias (Singh & Gotlib, 2014). The ventral mPFC, the dorsal mPFC, the posterior cingulate cortex (PCC), the precuneus and the lateral parietal cortex are part of the default mode network (DMN) (Raichle, 2015). The DMN is active when we think about nothing in particular, it is considered as the brain at rest. It is usually involved in self-referential processes. The network of activity in a resting state task seems to be altered in those with depression. The research has indicated both an increase in the DMN as well as decrease in MDD patients compared to healthy controls (Yan et al., 2019). The DMN normally has a reduced activity when performing attention demanding goal directed tasks however in people with depression the DMN fails to deactivate (Raichle, 2015). The DMN is also involved in rumination, a symptom of depression where the patient gives excessive attention to their distress by constantly thinking of negative feelings, events and aspects of self (Zhou et al., 2020).

Treatment

Treatment aim to alleviate the acute symptoms of depression as well as aid in recovery from the disease. Pharmacotherapy with antidepressants is the first line of treatment for depression with serotonin synaptic reuptake inhibitors (SSRI) as the most commonly used medications (Karrouri et al., 2021). Research suggests that psychotherapies can enhance the long term outcome of antidepressants on depression and treatment with pharmacotherapy is often offered in combination with psychotherapy (Petersen, 2006).

Antidepressants

Although several types of antidepressants exist, most operate from the hypothesis of chemical imbalance in the brain. Chemical imbalance in the brain, especially with lowered levels of neurotransmitters such as serotonin, dopamine and norepinephrine is believed to be linked to depression. Antidepressant medications are believed to restore the levels of monoamine neurotransmitters to a normal level (Nedic Erjavec et al., 2021). However, a recent systematic review found that the data derived from the hypothesis that low serotonin causes depression are inconclusive. The research on serotonin does not show a relationship between depression and serotonin (Moncrieff et. al., 2022). According to a review by Kirsch (2019) the effect of antidepressants can also be due to the placebo response. The placebo effect is the effect a non-active treatment has on the participants due to expectancy or belief. The response to treatment with the antidepressant substance or placebo treatment in the control group can depend on what the participants are told about the study. If the patients are told they participate in a placebo controlled study it has been shown that patients and their doctors easily can identify whether they are given the active substance or placebo even in double blind studies. In those studies the placebo effect is usually lower than if the participants believe they are given an active substance. Antidepressants also have side effects that can be identified when the participant has taken a similar substance before. Even subtle adverse effects can be recognized (Kirsch, 2019). Treatment with antidepressants do however seem to normalize activity in some areas affected by depression such as inferior frontal gyrus (IFG), ventrolateral prefrontal cortex (vlPFC) and the left ventral anterior cingulate gyrus. Patients taking medication also have higher volumes in the hippocampus than in unmedicated patients. There is also an increase in functional connectivity between areas related to emotion processing such as prefrontal areas, the caudate and thalamus (Singh & Gotlib, 2014). The research on antidepressants have also indicated neurotrophic factors such as brain derived neurotrophic

factor (BDNF) as associated with depression. BDNF is involved in neuronal maintenance as well as neural plasticity especially in the hippocampal area. BDNF is impaired in people suffering from depression. Treatment with antidepressants such as SSRIs seem to regulate the neurotrophic factors to normal levels (Nedic Erjavec et al., 2021). Treatment with antidepressant medication has a delayed onset, it can take weeks for them to have the wanted effect and with high risk of adverse side effects (Nedic Erjavec et al., 2021). Antidepressants are more effective than placebo but as Kirsch (2019) pointed out, the effectiveness can be due to the placebo response. Medication can for some patients be a lifelong necessity though many experience adverse effects and the risk of relapse in long term usage of antidepressants can occur in as many as one third of patients (Fava et al., 2003). Relapse prevention usually includes maintenance pharmacotherapy. The research on long term effectiveness of antidepressants seem to have promising results but they are also susceptible to bias. Some research suggests that the risk of relapse after discontinuation of antidepressants is the same regardless of the duration of the treatment, whether the treatment is months or years does not seem to make a difference (Fava et al., 2003).

Psychotherapy

While antidepressants seem to affect grey matter plasticity in depressed patients to normal volumes and activity it affects white matter to a much lesser degree. Psychotherapy or talk-therapy is when the patient discusses their issues with a therapist and receives coping tools and support with managing and alleviating symptoms. Psychotherapy affects white matter remodelling and creates new pathways through voluntary action (Singh & Gotlib, 2014). Psychotherapy's mechanism of action is not yet fully understood, but research in neuroplasticity and the brain's ability to change the neural pathways through learning and experience is considered a key to understanding the phenomena (Singh & Gotlib, 2014). Depressed patients have a pattern of overactivity in limbic areas and an underactivity in prefrontal areas that reverse with psychotherapy intervention suggesting better emotion

regulation (Singh & Gotlib, 2014). There are varying types of psychotherapeutic approaches that are suitable for different types of problems and patient profiles (Karrouri et al., 2021). Two common approaches are Cognitive behaviour therapy (CBT) and Interpersonal therapy (IPT). CBT has been well researched and there is abundant evidence of its effectiveness in treating depressive symptoms. The idea is to identify and challenge dysfunctional behaviours, beliefs and thoughts (Karrouri et al., 2021). The purpose of IPT is helping the patient build social skills and resources as well as recognize and regulate emotion (Karrouri et al., 2021). Among the most common approaches are also psychodynamic therapy. This form of therapy, with its beginnings in psychodynamic theory, focuses on self-esteem and shame as well as early childhood problems that can affect the patient (Karrouri et al., 2021). According to a review by Kirsch (2019) the relapse rate is higher in antidepressant groups than in placebo groups and psychotherapy groups. Psychotherapy has a significantly better long term outcome for patients than antidepressant medication even though the short term outcome is about the same (Kirsch, 2019).

Somatic Treatments

Somatic treatments (or neuromodulation) is an option usually offered in the treatment of severe cases of depression or when antidepressant medication is not an option. Among them are electroconvulsive therapy (ECT) and repetitive magnetic transcranial stimulation (rTMS). With somatic treatment parts of the brain are physically stimulated. In ECT, under anaesthesia an electrical current is used to induce a controlled seizure while with rTMS magnetic pulses are used to affect neuronal activity in specific areas of the brain. ECT is a relatively safe, effective treatment for depression. It is considered as the first line treatment in severe cases of depression. Stimulation with rTMS to improve depressive symptoms have been used in research where preliminary results are promising. Though more research is needed with larger sample sizes (Karrouri et al., 2021). The effect is comparable to antidepressants but with fewer side effects (Brunoni et al., 2010 as cited in Singh & Gotlib, 2014).

Rapid Acting Antidepressants

Operating on the neuroplasticity hypothesis of depression research on rapid acting antidepressants is growing in interest. Research on the drug Ketamine shows that the anaesthetic seems to have fast acting antidepressant effects. Ketamine affects BDNF and the mammalian target of rapamycin (mTOR) involved in the synaptic protein synthesis and growth. For traditional antidepressants such as SSRI it takes weeks to affect BDNF and brain plasticity while it takes mere hours for Ketamine. Though ketamine is rapid acting it is short lived since patients show signs of relapse already two weeks after a single dose (Nedic Erjavec et al., 2021).

Classical serotonergic psychedelics have also recently been considered as potential rapid acting antidepressants with a growing interest in research on treatment for depressive disorders (Nedic Erjavec et al., 2021).

Classic Psychedelics

The classic psychedelic substances are a class of drugs known for their ability to induce mind altering effects. Hallucinogenic drugs such as psilocybin, lysergic acid diethylamide (LSD), mescaline and N, N-dimethyltryptamine (DMT) have recently been investigated. The hallucinogenic effects as well as the potential antidepressant effects are due to the activation of 5HT-2A receptors in the brain. A single dose of psilocybin or LSD has the potential of inducing long lasting behavioural changes (Nedic Erjavec et al., 2021). Recreational use of these substances is a controversial topic, yet frequently prevalent. Through documentaries, social media and scientific studies the psychedelic experiences induced by these drugs are reported and discussed, coinciding with increased public awareness of the potential therapeutic benefits and adverse events associated with consumption. When ingested these drugs can produce tangible psychedelic effects which may influence mood, thought processes

and perceptual alterations lasting for several hours. These compounds are potent and the intensity of the psychedelic experience is dosage dependent (Griffiths et al., 2011).

Psilocybin

The naturally occurring and most common of these drugs is psilocybin which is derived from various species of mushrooms, regularly referred to as “magic mushrooms”. Psilocybin metabolizes to psilocin which interacts with the serotonin 2A (5-HT_{2a}) receptors when it crosses the blood brain barrier (Carhart-Harris et al., 2014). Research suggests that the psychoactive effects induced by psilocybin are by modulation of brain connectivity, activity and neurotransmitter release of serotonin (Carhart-Harris et al., 2017a). The effects of psilocybin often begin within 30-60 minutes of ingestion and can last up to four to six hours. Throughout the duration the individual may experience alterations in sensory perception causing visual and auditory hallucinations, as well as alterations in their mood, thoughts, and sense of self (Carhart-Harris et al., 2016).

Psilocybin also affects the connectivity and activity of the brain regions involved in emotions, attention, and self-reflection, which in turn can lead to a sense of heightened introspection and emotional openness (Carhart-Harris et al., 2014). These effects can be perceived as both positive and negative, influencing factors such as the individual's mental state, the setting in which the drug is experienced, and the dose dependent intensity (Carhart-Harris et al., 2017a).

Background

Modern science discovered psilocybin in the late 1950s but the substance has been used for over a millennia for its medicinal and therapeutic properties (Carhart-Harris et al., 2017a). Research of psilocybin significantly decreased when the Comprehensive Drug Abuse Prevention and Control Act of 1970 was legislated and subsequently the compound received schedule 1 classification leading to difficulties in conducting regulatory approved clinical

experiments. In late 1990s studies resumed on the therapeutic potential for depression and anxiety along with various conditions, showing early promising results for post-traumatic stress disorders (PTSD), obsessive-compulsive disorder (OCD) and addiction (Griffiths et al., 2008). Studies have suggested that psilocybin-assisted therapy might have long lasting effects on mood and behaviour along with providing severe relief for depression in non-responding individuals of prescribed antidepressants and even for treatment-resistant depression (Carhart-Harris et al., 2016; Griffiths et al., 2011). Barrett et al. (2020) conclude that one of the potential healing aspects of psilocybin is due to a decrease in negative affect accompanied with an increase in positive affect in twelve healthy individuals, and this shift is associated with a reduction in ruminative thoughts or behaviours which may be a precursor to different mood disorders.

Psilocybin as Treatment

Psilocybin-assisted therapy is a form of psychotherapy often conducted in a supportive setting where participants receive psychological support before, during and after two treatments of psilocybin several weeks apart. In the first session a small dose is administered to introduce the compound and assess safety, followed up by a high dose treatment. The aim of this therapy is to facilitate psychological and emotional breakthroughs and provide relief of depressive disorders by interpreting the psychedelic experience with psychological support (Carhart-Harris et al., 2016). To assess the efficacy for the treatment participants are screened and provided self-evaluating questionnaires regarding individual depressive severity which generate clear calculable data points throughout the treatment window. A six week trial by Carhart-Harris et al. (2021) compared psilocybin with escitalopram for depression resulting in no significant difference in symptom reduction six weeks after high dose session. Side effects reported in the escitalopram group were dry mouth, sexual dysfunction and anxiety while a few participants in the psilocybin group reported nausea, confusion, and anxiety during the onset and headaches the day after treatment. Similar results on side effects were observed by

Carhart-Harris et al. (2016) through a feasibility trial involving 12 individuals suffering from mild/moderate to severe treatment resistant depression. Psilocybin was generally well tolerated by all participants besides expected mild headaches, anxiety, nausea, confusion and thought disorder. Depression severity was assessed at baseline by QIDS=19.2 and BDI=33.7, there were significant improvements at one week QIDS=7.4 and BDI=8.7 which to some degree sustained for three months in all participants. Eight participants even achieved complete remission one week post-treatment. Seven continued to meet remission at the three month assessment and five participants continued in complete remission at the time (Carhart-Harris et al., 2016). The volunteers later participated in a six-month follow-up study where symptom reduction of depression was still significant (Carhart-Harris et al., 2018). The heterogeneous nature of depressive disorders and the extensive adverse consequences for society warrants further and extensive research of psilocybin assisted therapy. Through increased knowledge of both cognitive and biological correlates of depression and the mechanisms of actions associated with treatment, advancements could be made in the fields of neuroscience and healthcare. As previously mentioned, traditional antidepressants such as escitalopram are taken daily with varying results, while psilocybin is administered one or a few times with preliminary promising results (Carhart-Harris et al., 2021). This signifies the need for reliable fast acting antidepressants.

Ethical Considerations

As psilocybin remains a controlled schedule 1 substance in many countries, usage is prohibited by law outside of approved clinical trials. Therefore continued rigorous research of the compound might be necessary in order to assess the true risk-benefit profile along with a re-evaluation of the current classification. The ethical implications of limiting access to the compound is that scientific progress might be stifled as the current classification makes it difficult to obtain research permission along with funding. Criminalizing psilocybin can lead to stigmatization and discrimination towards individuals who seek it for treatment purposes.

Additionally, limiting development of safe treatment protocols, along with exploration of alternatives to first in line treatments, which will restrict individuals from accessing the potential therapeutic benefits of psilocybin (Garcia-Romeu et al., 2016). Illegalizing substances that are in demand will also move production and distribution to black markets that lack regulation and oversight, which can cause great harm to individuals in absence of proper guidance and supervision of psychedelic drug experiences (Johnson et al., 2008).

The Aim

In conclusion, the aim of our systematic review is to provide evidence based on the existing literature on treatment efficacy in humans diagnosed with depression and the underlying neurocognitive mechanisms of psilocybin use in clinical settings assessed by brain imaging. Additionally we will discuss the limitations and challenges of using psilocybin as a treatment for depression.

Methods

Search Strategy

Searches were conducted on the 17th of February 2023 in the electronic databases Web of Science, Scopus and Medline EBSCO. Using the Boolean search string (psilocybin AND depression AND (fMRI OR MRI OR PET OR brain imaging OR neuroimaging OR functional magnetic resonance imaging OR magnetic resonance imaging OR positron emission tomography)) resulted in a total of 374 articles from Web of science (N=77), Medline EBSCO (N=53) and Scopus (N=244). All of the results were exported and uploaded in the online systematic review software Covidence. Duplicates were removed (N=54) and after an initial screening of titles and abstracts the articles deemed irrelevant were removed (N=294). A full

text review was made of the remaining articles (N=26). Articles were excluded if they had the wrong study design (N=9) (e.g. not having pre and post measurements, not using brain imaging measurements). Articles were excluded if they were not original studies (N=8) (e.g. review articles), articles were excluded if having the wrong patient population (N=3) (e.g. depression scores and wellbeing measurements in healthy subjects) and one article were excluded for only measuring a single symptom of depression (anhedonia). Five articles were ultimately included.

Inclusion and Exclusion Criteria

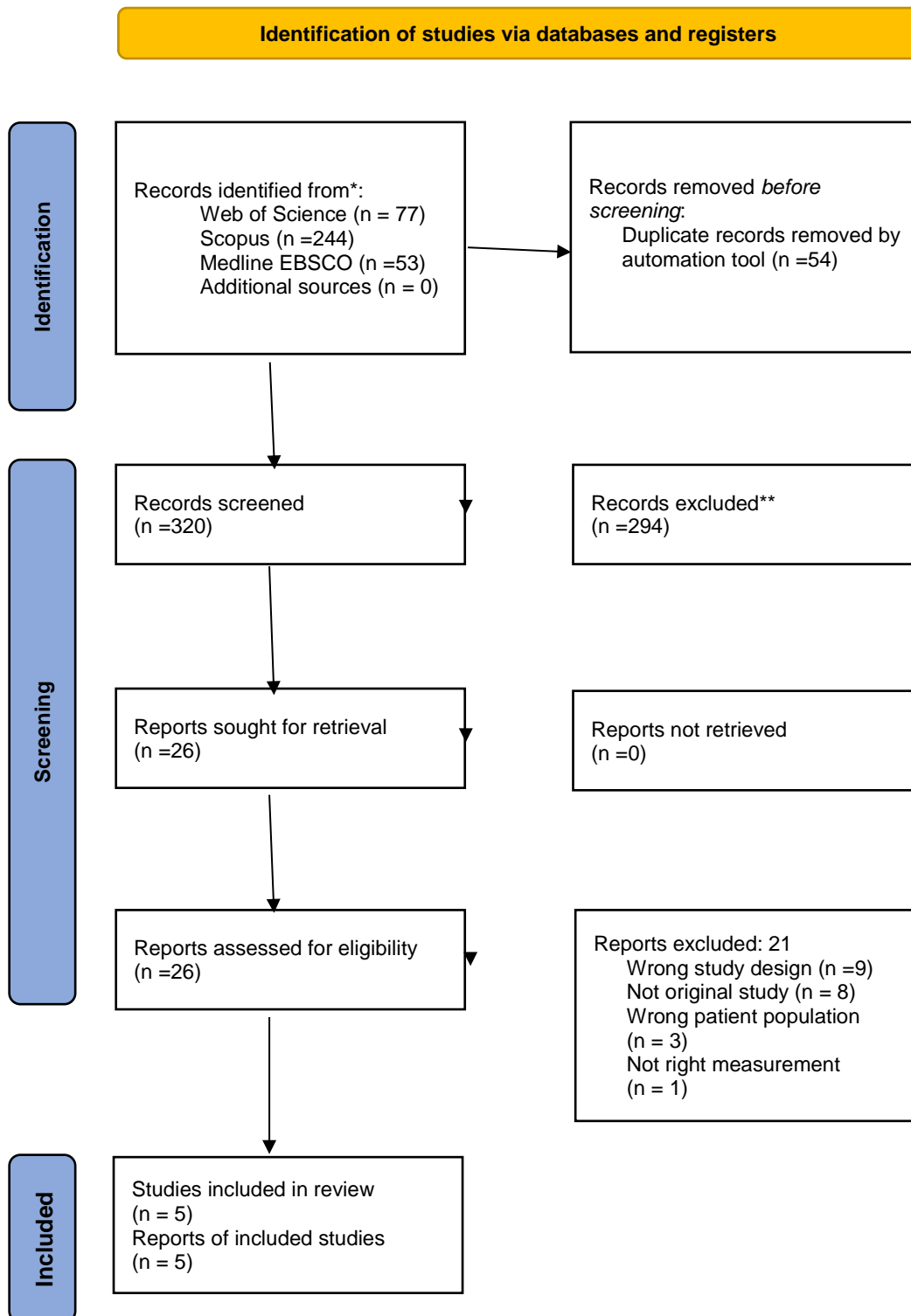
Eligibility criteria for the inclusion of articles were that they should be original research articles published in scientific peer-reviewed journals. Articles had to be written in English. Any study design (e.g. open-label, placebo controlled, cross sectional etc.) assessing the therapeutic effect of psilocybin in participants with diagnosed depressive disorders was included. Following the PICO model the population were human subjects diagnosed with depression, either MDD or TRD (Eriksen & Frandsen, 2018). The intervention was treatment with psilocybin. Although comparison of effectivity of treatment against placebo or other treatment would be preferable, we also included studies without control groups. The studies had to have both subjective outcome measures of depression (self-report and/or observation) and objective measures of brain function and/or structure changes using brain imaging measurements (fMRI, MRI or PET) pre and post-treatment.

Data Extraction

Data extraction was made regarding our eligibility criteria, 1) study design, 2) sample size, 3) sample characteristics, 4) administration dose and comparison to possible control, 5) pre-and post - brain imaging measurements and 6) pre- and post - depression measurements (QIDS and BDI). Primary outcomes (structural and functional brain imaging and measurements of depression) will be reviewed, as well as possible secondary outcomes.

Figure 1

PRISMA flow chart



Note: Flow diagram for reporting systematic reviews from Haddaway et al., (2022)

Results

Five articles were ultimately included in this systematic review. Four studies were performed at the Center for Psychedelic Research at the Imperial College in London (Carhart-Harris et al., 2017, Daws et al., 2022, Mertens et al., 2020 & Roseman et al., 2018) and one from Johns Hopkins Center for Psychedelic & Consciousness Research in Baltimore (Doss et al., 2021). The five independent reports derive their data from three different samples. Sample characteristics, treatment procedure and clinical outcome were first reported by Carhart-Harris et al. in 2016 and 2021 and by Davis et al. in 2020. Some of the sample characteristics and the clinical outcome are not reported in the articles included in this systematic review but will be taken from the original reports. The five reports presented in our systematic review report findings from the neuroimaging measurements.

Table 1.*Summary of data extracted from included studies*

Author/year (country)	Study design	Sample size (sex)	Sample characteristics (age range)	Control group	Administration dose	Measurements	Outcome
Carhart-Harris et al. (2017)	Open-label, within subjects design	N=19 (6 females)	TRD (27-64)	No	10 mg followed by 25 mg, one-week apart	fMRI, QIDS-SR16, BDI	Sig. reduced QIDS, BDI Reduced CBF in amg. sig. corr. w. reduced depression
Daws et al. (2022)	Open-label, within subjects design	N=19 (4 females)	TRD (27-64)	No	10 mg followed by 25 mg, one-week apart	fMRI, BDI	Sig. reduced, BDI decreased brain modularity
	Double-blind phase II randomized control	N=59 (30 experiment, 29 control)(20 females)	MDD (21-64)	Yes, escitalopram 10–20 mg	2 × 25 mg three weeks apart, plus six weeks of daily placebo	fMRI, BDI-1a	Sig. reduced, BDI-1a Decrease in brain modularity. functional changes in DMN, EN, SN
Doss et al. (2021)	Open-label, randomized, delayed treatment.	N=24 (13 experiment, 11 delayed treatment) (8 male)	MDD (24-59)	Yes, delayed treatment	20 mg/kg followed by 30 mg/70 kg	fMRI, QIDS-SR, GRID-HAMD	Sig. reduced, GRID-HAMD, QIDS-SR Sig. increase in cog. flexibility non sig. corr. w. changes in depression
Mertens et al. (2020)	Open-label, within-subjects design	N=19 (6 females)	TRD (27-64)	No	10 mg followed by 25 mg, one-week apart	fMRI, BDI, QIDS-SR16	Sig. reduced BDI Sig. reduced QIDS-SR16 Decrease in FC vmPFC to amg. sig. corr. w. decreased rumination
Roseman et al. (2018)	Open-label, within-subjects design	N=19 (6 females)	TRD (27-64)	No	10 mg followed by 25 mg, one-week apart	fMRI, BDI, QIDS	Sig. reduced BDI Sig. reduced QIDS Increased amg. reactivity to fearful faces sig. corr w. reduced depression

Note: TRD = treatment resistant depression, MDD = major depressive disorder, Sig. = significant, Amg. = amygdala, Corr. = correlation, W. = with, Cog. = cognitive, FC = functional connectivity,

CBF = cerebral blood flow, EN = executive network, SN = salience network

Study Characteristics

The five reports have a sample number of a total of 104 participants (42 females) in the age range of 21 to 64. Four trials (Carhart-Harris et al., 2017; Daws et al., 2022; Mertens et al., 2020; Roseman et al., 2018) obtain their data from the same sample of 19 participants (6 female), one trial has a control group (29 escitalopram, Daws et al., 2022) resulting in data from psilocybin treatment from a total of 75 participants. Some were excluded in the analyses of neuroimaging data due to head motion, Covid lockdown or adverse reactions to escitalopram.

Three reports have participants with TRD (Carhart-Harris et al., 2017; Mertens et al., 2020; Roseman et al., 2018) and one with MDD (Doss et al. 2021), one report presents data from each group in two different trials (Daws et al., 2022).

All studies use both neural measurements (fMRI) and self-assessment questionnaires pre-and post-treatment with psilocybin. For some of the studies the clinical outcome measurements are published in the original reports (Carhart-Harris et al., 2016, 2021; Davis et al., 2020). All studies provide the participants with therapeutic support before, during and after treatment.

The participants received a psilocybin dose ranging from 10 mg to 30mg/70kg. All but one trial had a lower dose session followed by a higher therapeutic dose one week later. One trial consisted of two high dose (25mg) sessions three weeks apart and six weeks daily placebo or two low dose (1mg) sessions with six weeks antidepressant medication escitalopram (Daws et al., 2022).

One trial tested cognitive and neural flexibility with a set-shifting task (Doss et al., 2021). Two trials test amygdala responsiveness and functional connectivity when viewing emotional faces (Mertens et al., 2020; Roseman et al., 2018). Neutral, fearful and happy faces were presented in a classic face/emotion perception task. One trial measures functional

connectivity during resting state (Carhart-Harris et al., 2017). One trial measured brain network modularity in an open label trial as well as in a trial comparing with an active control group receiving escitalopram (Daws et al., 2022). One trial had a waitlist/delayed treatment control (Doss et al., 2021) and four trials had no control group (Carhart-Harris et al., 2017; Daws et al., 2022; Mertens et al., 2020; Roseman et al., 2018).

Outcome

Treatment Efficacy

All studies found a relationship between psilocybin treatment and lowered depression scores. One trial compared with the antidepressant escitalopram and found a moderate advantage of psilocybin over escitalopram (Daws et al., 2022). All studies found psilocybin to be well tolerated with moderate transient adverse effects for a few of the participants. The values in Table 2 represent mean value changes for whole samples across the different studies with a single high dose treatment with psilocybin. Follow up reports shown in Table 2 demonstrate that psilocybin has sustainable antidepressant properties (Carhart-Harris et al., 2018; Gukasyan et al., 2022).

Table 2*Summary of data on treatment efficacy*

Author/year (country)	Measurement	Baseline measurement (standard deviation)	Post-treatment measurement <one week	Four weeks	Five weeks	Six weeks	Three months	Six months	12 months
Carhart-Harris et al. (2017b) ¹	BDI	34.5 (7.3)	11.8 (11.1)				19.2 (13.9)	19.5 (13.9) ²	
	QIDS-SR16	18.9 (3)	8.8 (6.2)		10.9 (4.8)				
Doss et al. (2021) data retrieved from Davis et al. (2021)	GRID-HAMD	22.8 (3.9)	8.7 (7.6)	8.9 (7.4)			9.3 (8.8) ³	7.0 (7.7) ³	7.7 (7.9) ³
	QIDS-SR	16.7 (3.5)	6.3 (4.4)	6.0 (5.7)					
Daws et al. (2022) ¹	BDI	34.81 (7.38)	Mean change - 21.0						
Daws et al. (2022) data retrieved from Carhart-Harris et al. (2021)	QIDS-16	14.5 (3.9)	Mean change - 5.7 (0.9)			Mean change - 8.0 (1.0)			
	BDI-1a	29.1 (6.8)				Mean change - 18.4			
	HAMD-17	19.2 (2.3)				Mean change - 10.5 (1.0)			

¹ Same sample of total 19 patients in Carhart-Harris et al. (2017b), Daws et al. (2022), Mertens et al. (2020) and Roseman et al. (2018)

² Data retrieved from Carhart-Harris et al. (2018)

³ Data retrieved from Gukasyan et al. (2022)

Neurocognitive Mechanisms

Carhart-Harris et al. (2017b) measured changes in cerebral blood flow (CBF) and functional connectivity during resting state before and the day after treatment with psilocybin. Measuring CBF they found changes between pre-and post-sessions in decreased blood flow in the amygdala with a significant correlation with reduced depressive symptoms ($r=0.59$; $p=0.01$). Measuring resting state functional connectivity (RSFC) they found an increased RSFC within the default mode network (DMN) post treatment. RSFC in the ventromedial prefrontal cortex (vmPFC) and bilateral inferior-lateral parietal cortex (ilPC) did not correlate with decreased depressive symptoms in the one day post-treatment scan ($r=-0.26$; $p=0.17$) but did predict decreased depressive symptoms at five weeks post-treatment ($t=2.1$; $p=0.03$). Another find that was nonsignificant the day after ($r=0.08$; $p=0.38$) but significant at five weeks ($t=-1.9$, $p=0.04$) was the correlation of decrease in bilateral parahippocampal (PH) and prefrontal cortex (PFC) resting state functional connectivity with reduced depressive symptoms. With a post-hoc analysis they suggest that a “peak” or “mystical type” experience during treatment with psilocybin is predictive of changes in PH RSFC amygdala and with DMN-related cortical regions.

Roseman et al. (2018) investigated amygdala response to emotional faces pre- and one day post-treatment with psilocybin. They found an increase in activity in response to viewing emotional faces in the right amygdala for fearful ($p=.001$) and happy faces ($p=.022$). An increase in amygdala response to fearful faces were correlated with a decrease in depressive symptoms one week post-treatment. More activity in the right amygdala was related to a larger decrease in depressive symptoms. Participants who responded to treatment and achieved remission had increased amygdala reactivity to fearful vs neutral faces while those who did not respond to treatment with psilocybin had a decrease in amygdala reactivity. Additionally no significant results were observed within the left amygdala.

Based on the findings of Roseman et al. (2018) Mertens et al. (2020) tested the functional connectivity on two regions of interest (ROI), the amygdala and vmPFC during an emotional face processing task. They found that decreased functional connectivity of the vmPFC and right amygdala during face processing post treatment were significantly correlated with rumination one week after treatment ($r=0.54$, $p=0.018$), with lower connectivity associated with less rumination. However it was not significantly correlated with lower levels of depression at one week ($r=0.28$, $p=0.253$). An increase in functional connectivity between vmPFC to the visual cortices, the occipital and parietal areas was significantly correlated with lower BDI scores at one week ($r=-0.46$, $p=0.048$).

Doss et al. (2021) investigated cognitive flexibility, neural flexibility as well as neuro-metabolite concentrations after psilocybin treatment. Cognitive flexibility increased for up to four weeks, however the changes were not correlated with lowered depression. With the use of fMRI and connectome-based predictive models they found a positive correlation of increase in dynamics (variance in FC over time) of functional connectivity (dFC) between ACC and posterior cingulate cortex (PCC) and less decrease in preservative errors on a set-shift task ($r(16) = 0.48$, $p = 0.043$) at one week post-treatment. This indicates a relationship between an increase in neural flexibility and less improvement in cognitive flexibility. They argue that those patients with lower baseline neural flexibility might have a greater benefit from psilocybin treatment whereas larger increases may be of less benefit. Decreases in neuro-metabolite concentrations were also found via magnetic resonance spectroscopy in the ACC, a region associated with cognitive flexibility. Glutamate and N-acetylaspartate (NAA) were decreased one week post-psilocybin. They found no significant changes in the hippocampus, a region associated with mood disorders and there was no significant correlation with depression or cognitive flexibility.

Daws et al. (2022) assessed the subacute impact and efficacy of psilocybin across two clinical trials of depression. Findings imply that decrease of brain modularity was correlated with symptom reduction in both studies on participants with diagnosed TRD and MDD.

Functional changes were observed in DMN, executive network (EN) and salience network (SN) dynamics which have been shown to be involved in neurobiological models of depression (Wang et al., 2016). These networks contain the highest density of 5-HT_{2A} receptors which are affected by serotonergic psychedelics. Daws et al. (2022) observation concludes that a global increase in functional connectivity between the brain's main intrinsic networks occurs when measured day one post-treatment. The global changes in network organization may be caused by a certain decrease in within-DMN connectivity and increase in DMN connectivity with higher-order networks which include the EN and SN. Pre and post-treatment changes in modularity correlated significantly with clinical assessment of BDI six months after administration. Additionally, significant reductions in DMN network recruitment and increases in integration between DMN and EN was observed.

Discussion

Psilocybin have been shown to have rapid and sustainable antidepressant properties. The results of this review exemplify significant brain changes between pre- and post-treatment with psilocybin for MDD or TRD that correlate with reduced symptoms of depression assessed with BDI, QIDS and HAMD.

Treatment Efficacy

Effectiveness of treatment displayed in Table 2 shows the significant reduction of depressive symptoms when comparing baseline and post-treatment values assessed from day one up to 12 months later on self-report scales. A notable characteristic of the summarized result is the fast acting and reliable efficacy in all reports from a single high dose treatment combined with predictable but transient adverse reactions in conjunction with administration of psilocybin. Griffiths et al., (2011) conducted a study on the immediate and persisting dose-related effects of psilocybin in psychedelic-naïve participants where 39% experienced extreme fear, fear of insanity or the sense of feeling trapped, 44% reported feelings of delusion and

paranoid thinking throughout the session. All negative effects were well managed due to a highly supportive setting with staff dedicated to reassure participants through psychological distress. Absence of safety measures can lead to prolonged negative experiences and result in dangerous behaviour which signify the importance of safe set and setting to minimize the adverse reactions of treatment (Griffiths et al., 2011). Currently the first-line treatment option for depression is daily administration of SSRIs where patients on average wait between two to four weeks for symptom reduction and chronic daily dosing is required to maintain the effects (Reid & Barbui, 2010) which modestly outperform placebo treatment (Kirsch, 2019). A meta-analysis of the effectiveness and safety of psilocybin found a significant moderate-to-large effect size of the antidepressant effect already on day one. They also found that the antidepressant effect lasted from one week to six months after treatment with a large effect size. The greatest benefit on depressive symptoms the patients had from receiving a higher dose of psilocybin (Yu et al., 2022).

Underlying Neurocognitive Mechanisms

Carhart-Harris et al. (2017b) found a decrease in cerebral blood flow (CBF) in the amygdala correlating with reduced depressive symptoms. This is in line with research indicating a higher risk for depression in those with increased CBF in amygdala and with a family history of depression. Even though the participants themselves have not had depression previously an increased CBF in especially the right amygdala predicted vulnerability to develop depression (Zhang et al., 2020a). Carhart-Harris et al. (2017b) found decreased resting state blood flow in bilateral amygdala but it was especially pronounced in the left amygdala. In healthy humans there is increased CBF in the amygdala when viewing fearful faces but in mood disorders such as depression there is an elevated resting state CBF in amygdala (Drevets, 2003).

Prefrontal functional connectivity to amygdala is increased in MDD compared to healthy controls and is decreased with antidepressants (Zhang et al., 2020b). Traditional antidepressants mute amygdala activation in response to negative emotional stimuli (Harmer et al., 2017). Activation in PFC increases inhibition of amygdala that in turn increases negative emotions (Zhang et al., 2020b). Psilocybin seems to decrease PFC, specifically vmPFC functional connectivity to the right amygdala in an emotion processing task leading to less rumination, a common symptom of depression (Mertens et al., 2020). Psilocybin in contrast to SSRI has the post-treatment effect of increased activity in the right amygdala when viewing emotional faces, especially fearful faces after psilocybin. This increased activity in amygdala has a correlation with decreased depressive symptoms. Greater activity in the right amygdala was related to a larger decrease in depressive symptoms (Roseman et al., 2018). The right amygdala is believed to be involved in detecting and processing emotionally salient stimuli, especially negative emotions such as fear while the left amygdala is believed to play a part in the reward system (Palomero-Gallagher & Amunts, 2022). Roseman et al. (2018) found a significant activation in the right amygdala but not the left amygdala that can indicate a greater willingness to deal with negative emotions. Psilocybin has been shown to increase mindfulness both with and without mindfulness training (Madsen et al., 2020; Smigielski et al., 2019). In a six month follow up study with interviews with the same sample of 19 patients with TRD as Carhart-Harris et al. (2017b), Daws et al. (2022), Mertens et al. (2020) and Roseman et al. (2018) two themes emerged. The participants reported greater connectedness with self, others and the world as well as less avoidance and more acceptance of emotions and an expanding emotional repertoire (Watts et al., 2017). Roseman et al. (2018) discuss a generalized emotional muting that patients experience during SSRI but though SSRI have a muting of amygdala activity to negative emotional faces an increased response to happy faces is shown on SSRI (Harmer et al., 2017).

The vmPFC is also believed to be involved in emotion regulation as in cognitive control of emotions. The vmPFC activity is impaired in people with early life trauma such as ACE thus

asserting less cognitive control over amygdala experiencing more negative emotions (Wang et al., 2013). The researchers do not control for ACE in the studies reviewed here but patients from one of the samples (Carhart-Harris et al. 2017b; Daws et al. 2022; Mertens et al. 2020; Roseman et al. 2018) report processing early traumas during treatment (Watt et al., 2017). As mentioned in the introduction, depression is a highly heterogeneous disorder, no single biomarker has been found and although vmPFC connectivity is increased in patients with depression there is also evidence that decreased connectivity has a relationship with depression (Wang et al., 2013). The vmPFC is a part of the DMN and Carhart-Harris et al. (2017b) found an increase within DMN resting state functional connectivity post treatment with psilocybin. RSFC specifically in the vmPFC and bilateral inferior-lateral parietal cortex predicted response to treatment at five weeks post-treatment but did correlate with decreased depressive symptoms in the one day post-treatment scan. They suggest a “reset mechanism” where DMN integrity is markedly decreased during treatment with psilocybin to increase or normalize after treatment (Carhart-Harris et al., 2017b). Improvements of depressive symptoms was observed by Daws et al. (2022) to correlate with decreased brain modularity, the finding is consistent between both trials presented in the article where functional changes were observed in DMN, EN and SN. Previous studies on depression have found that heightened network modularity correlates with symptom severity where within-DMN FC and increased FC between amygdala and high-level cortical regions are associated with the underlying rumination present in depression (Feurer et al., 2021). This finding may support the conclusion by Daws et al. (2022) where post-treatment reductions of modularity were observed as a result of the accompanying decrease in within-DMN connectivity and increase in DMN connectivity with high-order networks such as the EN and SN.

Carhart-Harris et al. (2017b) found that decreased RSFC between bilateral PH and PFC was predictive of treatment response at five weeks. A post-hoc exploratory analysis indicated that acute mystical type or peak experiences induced by psilocybin may be the underlying cause for the decrease in PH RSFC post-treatment. The association between mystical type

experiences induced by psychedelics and positive therapeutic outcomes is a recurring finding across several studies for individuals with life threatening cancers (Ross et al., 2016; Griffiths et al., 2016) alcohol misuse and dependence (Rothberg et al., 2021; Bogenschutz et al., 2015) and in treatment of tobacco addiction (Garcia-Romeu et al., 2014). The intensity of a mystical type experience also has a correlation with increased trait mindfulness (Søndergaard et al., 2022).

Doss et al. (2021) found an increase in cognitive flexibility though it did not correlate with decreased depression. They reason that the lack of correlation can be that they used the GRID-HAMD to assess depression that does not measure cognitive impairments. They do speculate, however, that an increase in cognitive and neural flexibility, albeit temporary, may open a “window of plasticity” where the patient, with psychotherapy, can have greater opportunity to make improvement (Doss et al., 2021). There is some evidence that serotonergic psychedelics promote neurogenesis and increasing synaptic growth through increasing blood BDNF as well as mTOR that support their speculations (Ly et al., 2018).

Further Research

Limitations of this systematic review besides the inherent difficulties of conducting experiments on schedule one controlled substances include a limited number of articles for our search string. Lack of viable control groups for these studies obscures the independent efficacy of psilocybin for this therapy. Additionally as mentioned in (Carhart-Harris et al., 2016) some participants may be subject to expectancy bias which further problematizes the placebo effect of treatment. Despite preliminary promising results of treatment about half of participants tend to relapse after six months post-treatment which supports the fact that depression can become a persistent and difficult problem that lingers indefinitely for some individuals (Nutt, et al., 2020). The legal classification of psilocybin places the compound in the most restricted class of drugs, indicating a high potential for abuse and no current accepted medical use or accepted safety under medical supervision (Garcia-Romeu et al., 2016). The preliminary data

presented in our systematic review indicate that psilocybin-assisted therapy under appropriate conditions can be conducted safely with significant efficacy, thereby challenging the current schedule 1 classification.

Further research conducted on larger samples could provide greater statistical reliability of the results and aid in the development of ethical guidelines and treatment protocols. Inclusion of long-term follow-up screenings of neural mechanisms is needed combined with further clinical assessments to evaluate treatment outcome. Additionally control groups need to be included to isolate the impact of psilocybin from the therapeutic setting.

Conclusion

This systematic review shows that current research on the serotonergic psychedelic compound psilocybin found in mushrooms along with therapeutic support show promising antidepressant effect for patients with major depression and treatment resistant depression. The substance has the potential to produce fast acting and lingering antidepressant effects with rapid changes in brain activity and functional connectivity. It is a safe treatment with moderate transient adverse effects for a few individuals. Although more research is needed, the treatment has the potential to come into use in clinical practice for the benefit of the individual and for society.

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