Degree Project

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Investigating the Potential of Psilocybin as a Treatment for Major Depressive Disorder: A Systematic Review

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Abstract

Major depression disorder is increasing globally, causing great personal suffering and economic burdens to society. Current antidepressant medications are not sufficiently able to treat all cases of depression and are often associated with troubling side effects. There is a great need for the development of novel treatments, and classic psychedelic drugs are currently being investigated with new interest. The legal status has hindered research, but promising results from pioneering studies on the antidepressant effect of psilocybin have recently given psilocybin breakthrough therapy status, allowing further research to occur more freely. This systematic review aims to investigate the literature available on psilocybin's effect on major depressive disorder. Five studies were selected according to set inclusion and exclusion criteria. Results are suggesting that psilocybin combined with psychological support is a fast-acting antidepressant agent, able to produce a sustained decrease in symptoms of depression with minimal side effects. However, current studies come with several limitations and further research is needed before the antidepressant effect of psilocybin can be stated as a fact.

Keywords: psilocybin, major depressive disorder, depression, psychedelics, 5-HT2A

Investigating the Potential of Psilocybin as a Treatment for Major Depressive Disorder: A Systematic Review

Major Depressive Disorder

Major depressive disorder (MDD) is a common yet serious mood disorder, affecting approximately 280 million people worldwide. MDD is the number-one cause of disability and a major contributor to the global disease burden. One in five people is expected to suffer from MDD at some time in their life (World Health Organization, 2021). The number of people being diagnosed with major depressive disorder has rapidly increased in the last decade. In the United States, the number of adults diagnosed with MDD increased by 12.9% from 2010 to 2018 (Greenberg et al., 2021). The global pandemic of COVID-19 has caused an estimated increase of 25% in depression and anxiety worldwide (World Health Organization, 2022).

A diagnosis requires that a patient, during a period of at least two weeks, meets five of the nine criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5TR; American Psychiatric Association, 2013). These criteria are "depressed mood…", "markedly diminished interest or pleasure in activities…", "weight loss . . . or weight gain, or decrease or increase in appetite", "insomnia or hypersomnia", "a slowing down of thought and a reduction of physical movement… ", "fatigue or loss of energy…", "feelings of worthlessness…", "diminished ability to think or concentrate, or indecisiveness…", and "recurrent thoughts of death…" (pp. 160-161).

The root cause of major depressive disorder is a complex matter, and most likely it differs from case to case. While MDD can be triggered by external factors and stressful life events, it also occurs without reasons that can be properly explained by the current framework. Genetic factors play a significant role, but the significance is not high enough to consider major depressive disorder a genetic disease (Chiriţă et al., 2015). MDD can also be a symptom of another disease, often neurological or endocrinological (Filatova et al., 2021).

MDD is a physically and mentally debilitating illness that causes great personal suffering and is highly linked to suicide. Approximately 1 million people commit suicide every year (Orsolini et al., 2020) and many more are injured due to attempted suicide. Even though not every suicide is due to depression, the suicide risk for MDD is fairly high and estimated to be 15% (Orsolini et al., 2020).

Apart from causing great suffering to those affected, MDD also causes vast economic burdens to society. Due to factors such as loss of productivity and burden to the health care system, it was estimated that the yearly cost of US adults with major depressive disorder in 2010 was $US236.6 billion. Eight years later, the estimated number had exceeded $US326.2 billion (2020 year's values; Greenberg et al., 2021).

Neural Correlates of MDD

Brain areas commonly associated with depression pathology are the prefrontal cortex (responsible for complex cognitive processes such as planning, decision-making and social adaptation), amygdala (our emotional centre) and hippocampus (an area that plays a significant role in the consolidation of memories; Trifu et al., 2020).

Structural alterations: i.e., visible changes in cortical thickness and decreased volume of grey matter have been found in various sub-areas of the frontal lobe; striatum (a critical component of the motor and reward systems), thalamus (a nucleus responsible for processing and relaying sensory information), parietal lobe (a major interpreter of sensory information), and hippocampus (Zhang et al., 2018). However, studies on amygdala volume in individuals with major depressive disorder are showing ambiguous results. Some studies show a significant increase in amygdala volume compared to healthy individuals, while other studies find a significant decrease (Trifu et al., 2020).

Functional neuroimaging studies on the amygdala have shown an overall increased activity in the amygdala of the depressed patient (Drevets et al., 1992), as well as a heightened amygdala responsivity to negative stimuli (Hamilton et al., 2008).

Neural circuits are a cluster of neurons, responsible for processing certain information and carrying out a specific function when activated (the myotatic spinal reflex or "knee-jerk" is an example). Several neural circuits have been shown to be impaired in the MDD brain. The role of the prefrontal-subcortical circuits is to enable motor activity and to process cognitive and emotional information. The function of these circuits is believed to be disrupted in the brain of the MDD patient. This may be the cause of the executive dysfunction and apathy commonly seen in patients diagnosed with MDD (Zhang et al., 2018).

Major depressive disorder impacts brain plasticity and synaptic functions. Dysfunction has been found in the brain's ability to support the growth and survival of neurons. MDD also correlates with oxidative stress (a toxic imbalance of free radicals and antioxidants), similarly to what is seen in neurodegenerative disorders such as Alzheimer's and Parkinson's disease (Trifu et al., 2020).

Treatment for MDD

The most commonly prescribed antidepressant medications are selective serotonin reuptake inhibitors (SSRIs). The use of these pharmacotherapies is based on the monoamine hypothesis, which theorizes that the cause of depression is imbalances of neurotransmitters in the brain. SSRIs' mechanism in the brain is to block the reuptake of serotonin that is released from synapses in the central nervous system. The same mechanism is involved with other pharmacotherapies used for treating depression, SNRIs (selective noradrenaline reuptake inhibitor) and NDRIs (norephedrine-dopamine reuptake inhibitor). However,

some studies reveal that an abrupt decrease in the synthesis of serotonin and dopamine is not sufficient to cause depression in healthy individuals (Filatova et al., 2021). This has led to questioning the validity of the monoamine hypothesis.

SSRIs are helping many alleviate their symptoms of depression, but many remain depressed. A meta-analysis (Kolovos et al. (2017) revealed that only a third of the patients experienced an improvement in their depression from SSRIs. A meta-analysis by Kirsch et al. (2008), suggests that SSRIs are no more efficient in treating depression than placebo.

Even though monoamine-targeting pharmacotherapies are better tolerated than their predecessors: tricyclic antidepressants (which carry a high risk of toxicity in the case of overdose and if combined with alcohol), SSRIs are still associated with a lot of side effects (Joshi, 2018). Common side effects are worsening of depressive symptoms (Kolovos et al., 2017), headache, nausea, and sexual dysfunction. Side effects are often a cause of patient adherence problems: the tendency for patients to discontinue the treatment (Nemeroff, 2003).

Many patients with MDD are considered to suffer from treatment-resistant depression (TRD). This is a widely used concept without adequate definition. A common suggestion for diagnosis is “an unsatisfactory response to two adequate trials of two different classes of antidepressants at optimum dosage for sufficient duration” (Pandarakalam, 2018, p. 274).

Measuring Depression

To measure the severity of depression, different scale instruments are often assessed. Three common instruments are the Beck Depression Inventory (BDI), the 16-Item Quick Inventory of Depressive Symptomatology (QIDS), and the Hamilton Rating Scale for Depression (HAM-D).

The BDI was introduced in 1961 (Beck et al., 1961) and is a 21-item, self-rated scale evaluating key symptoms of depression. Questions regarding current emotional state, cognition, and mood are answered. Depending on the answer, a score from 0-3 is set and then summarized to achieve a total score, estimating the severity of depression. BDI exists in three versions, BDI, BDI-1A, and BDI-II, where BDI-II is the most recent.

QIDS is a 16-item scoring inventory available both for self-report (QIDS-SR-16) and for rating by a clinician (QIDS-C-16; Rush et al., 2003). It consists of sixteen questions about sleep habits, thoughts, and feelings the patient has had during the last seven days.

HAM-D (also known as HDRS) was first introduced in 1960 and has since then been revised multiple times by its creator (Hamilton, 1960). It was originally created for hospitalized patients but has become widely used by clinicians and in medical research. The scale consists of 21 items, by which the last 4 items are intended to subtype the depression. HAM-D is a rating scale for the use of clinicians and is not available for self-report. The

GRID-HAMD is a version of the HAM-D which was designed to take into account the dimensions of depression intensity and frequency of symptoms.

Psychedelic Research

There is evident need for developing strategies to tackle the challenges of increasing mental illnesses. Recently, the therapeutic potential of classic psychedelics is being investigated with renewed interest. Classic psychedelics include psilocybin, lysergic acid diethylamide (LSD), N,N-Dimethyltryptamine (DMT), and mescaline. Classic psychedelics share the trait that they are full or partial agonists (a compound that can bind to a receptor and cause activation) to the serotonin 2A receptor (5-HT2A). It is hypothesized that they also may interact to a lesser extent with serotonin 2C receptors (Galvão-Coelho et al., 2021).

Psilocybin, mescaline, and DMT are naturally occurring compounds that have a long history of medicinal and ceremonial use in native societies (Lowe et al., 2021). LSD is a semi-synthetic substance, produced in 1938 when Albert Hofman was aiming for obtaining a respiratory and circulatory stimulant. Five years later, Hofman unintentionally discovered the psychedelic properties of LSD by ingesting the substance through the skin of his hand, and it became evident that LSD was a potent drug with the ability to produce powerful shifts in consciousness. LSD became the main focus of the research on psychedelics occurring in the mid-20'th century. In 1947, LSD was distributed by Sandoz Pharmaceuticals as Delysid™, as an experimental tool for researchers (Passie et al., 2008). LSD was investigated as a therapeutic tool for various psychiatric disorders, and more than a thousand articles were published on LSD in the upcoming 15 years (Dyck, 2015).

Psilocybin found its way into Western science in 1958 when it was synthesized, again by Hofman. Similarly to LSD, psilocybin was in 1960 manufactured and distributed as the psychotherapeutic drug Indocybin™ and used by clinicians as an aid in psychedelic psychotherapy (Lowe et al., 2021).

Due to bad publicity and widespread recreational use of psychedelic substances among countercultural groups in the late '60s, the United States Drug Enforcement Agency came to prohibit psilocybin along with other psychoactive drugs. Research on these substances became stigmatized and their therapeutic potential dismissed (Lowe et al., 2021). In the 1990s, after a campaign of lawsuits by psychedelic advocates, a revived interest spurred the renewal of psychedelic research (Carhart-Harris & Goodwin, 2017).

In a pilot study, Berman et al. (2000) demonstrated the fast antidepressant action of another psychedelic: ketamine, a dissociative psychedelic drug commonly used as an anaesthetic. Since then, many studies have proved the antidepressant effect of ketamine. However, ketamine carries a high risk of abuse due to its activation of the reward pathway (Liu et al., 2016) and can have toxic effects. Recreational use of ketamine is linked to ulcerative cystitis (inflammation of the bladder lining; Vu et al., 2021). The antidepressant effect of

ketamine is short-lived and typically lasts for a few days to two weeks (Davis et al., 2021).

By contrast, classic psychedelics have a low abuse potential and a high safety profile due to their low or non-existent physiological toxicity. The antidepressant effects are lasting. A large population study found that lifetime use of psychedelics could not be linked to mental health problems and suicidal behaviour (Johansen & Krebs, 2015), and there is research suggesting that lifetime use of psilocybin and MDMA is associated with reduced odds of major depressive episodes (Jones & Nock, 2022). That said, restrictions on the use of psychedelic drugs are advised for individuals with a personal or family history of psychosis, and individuals with severe cardiac disease (Galvão-Coelho et al., 2021).

In the 21st Century, psychedelic research has shown that ayahuasca (a traditional Amazonian brew containing DMT) has the potential to significantly reduce symptoms of depression (Osório et al., 2015). Psychedelics have been shown to promote dendritic spine growth and stimulate synapse formation in mice (Ly et al., 2018), and LSD has demonstrated its effectiveness in treating anxiety associated with life-threatening diseases (Gasser et al., 2014).

Psilocybin

A promising candidate among the psychedelics in the treatment of depression is psilocybin. A dramatic rise in publications on psilocybin in the last five years can be seen in PubMed (see Figure 1). Psilocybin is commonly preferred in research over LSD, since the effect of psilocybin typically lasts 6-8 hours, compared to LSD, which effects can last up to 12 hours.

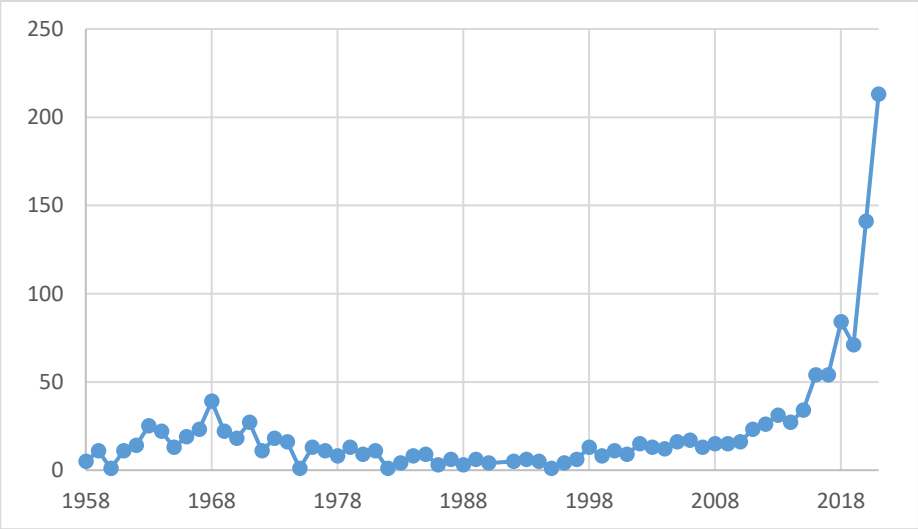
Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a naturally occurring alkaloid found in more than 100 species of mushrooms (Mithoefer et al., 2016), distributed all over the world (Lowe et al., 2021). Written records reveal that psilocybin mushrooms have been used by indigenous societies for centuries (Lowe et al., 2021), while cave murals reveal a culture of mushroom worshipping dating back thousands of years (Samorini, 1992). The Azteks in Mesoamerica referred to the psilocybin mushrooms as *teonanacatl*, meaning “God’s flesh” (Nichols, 2020). Research in modern times confirms that psilocybin can induce experiences of spiritual significance (Griffiths et al., 2006).

Recent studies are showing that psilocybin is effective in significantly reducing anxiety and improving the quality of life in advanced-stage cancer patients, with immediate and long-lasting effects (Griffiths et al., 2016; Ross et al., 2016).

Psilocybin has shown promising results in treating alcohol and nicotine addiction (Bogenschutz & Johnson, 2016) and obsessive-compulsive disorder (Moreno et al., 2006).

Figure 1.

Number of articles published on psilocybin in PubMed between years 1958 and 2021



Note: This diagram was created by the author of this review using data from PubMed.

Due to promising results from studies on psilocybin for treatment-resistant depression, the United States Food and Drug Administration has granted psilocybin "breakthrough therapy" status since 2018 (Galvão-Coelho et al., 2021).

Neural Correlates of Psilocybin

Significant changes in brain activity have been found in neuroimaging studies on psilocybin. Psilocybin has been shown to decrease activity in the medial prefrontal cortex (mPFC; Carhart-Harris et al., 2012), an interesting finding since increased activity in this region is found in patients with major depressive disorder.

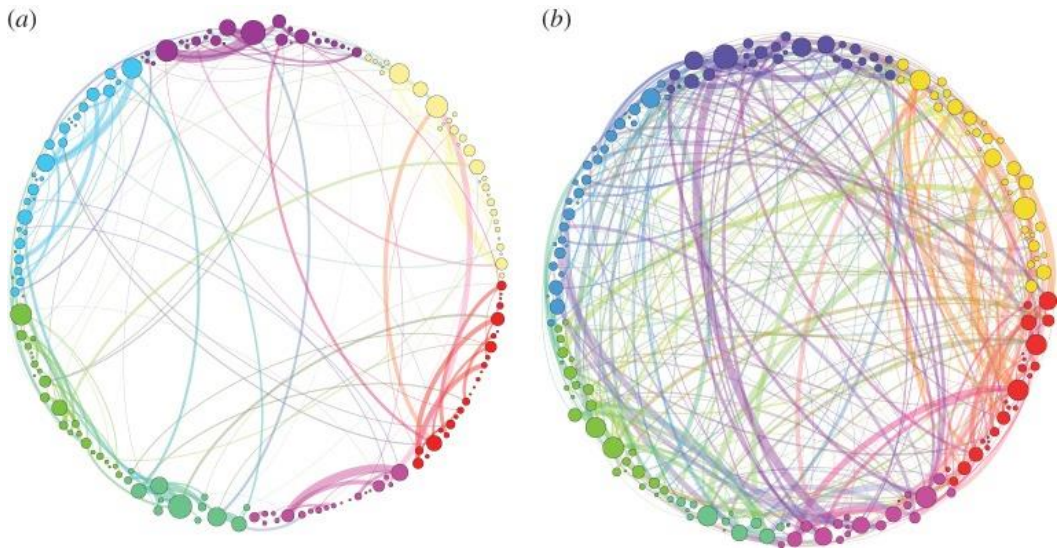
A positron emission tomography (PET) study (Vollenweider et al., 1997) shows that psilocybin increases the cerebral metabolic rate of glucose (CMRglu) in all regions of the brain, particularly in the frontomedial and frontolateral cortex (involved in numerous sensorimotor, cognitive, and affective processes) including the anterior cingulate (associated with several complex cognitive functions, such as empathy, impulse control, emotion, and decision-making), and temporomedial cortex (responsible for episodic and spatial memory). This suggests that the ingestion of psilocybin leads to overall heightened cortical activation.

Results from a functional magnetic resonance imaging (fMRI) study by Carhart-Harris et al. (2012) showed significant decreases in brain activity, but only in regions such as the thalamus and the anterior and posterior cingulate cortices (ACC and PCC). These are regions that are known to act as hubs of information: receiving input, processing it, and then

sending it forward. Activity decreases in these areas are thought to enable a state of unconstrained cognition, that allows different parts of the brain that don't normally interact to communicate directly (Nichols, 2020). Figure 2 illustrates this phenomenon by showing a simplified visualization from a study examining the functional connectivity (synchrony or correlation of brain activity between two or more regions of the brain) in the brain pre- and post-psilocybin (Petri et al., 2014).

Figure 2.

Simplified visual representation of the functional connectivity in the brain on a) placebo and b) psilocybin



Note: From Petri et al. (2014). Reproduced by permission of G. Petri.

Ethical Considerations

Along with the progress made within psychedelic research, there is a great need for an ethical framework to assure harm reduction. Psychedelics produce intense experiences, and without proper knowledge on how to integrate these experiences, they can do more harm than good. The Multidisciplinary Association for Psychedelic Studies (MAPS) has developed a five-principle framework for application to psychedelic research to ensure maximal risk reduction, including guidelines concerning informed consent, harm/benefit analysis, and transparency in research (Hans, 2021).

Despite the legal status of psychedelic drugs, there is a strong subculture of psychedelic users, with an estimated number of 32 million recreational users in the USA alone (Krebs & Johansen, 2013). While there already exists an established community of psychedelic practitioners, there is a potential danger with research pointing to the therapeutic benefits of

psychedelic drugs. Promising results can influence people to self-medicate, risking legal consequences and psychological harm. Pilecki et al. (2021) propose that therapists have an ethical duty to try to reduce the risk of harm among clients who are interested in exploring psychedelics. They suggest a model where therapists provide psychotherapy before and after a patient has a psychedelic experience. The authors emphasize the importance for a therapist to provide the patient with sufficient information to make an educated decision on whether to seek out psychedelic experience or not.

There is also a considerable risk of the lines between recreational use and medical use being blurred. However, since psychedelics seem to carry a low abuse potential in comparison to many other prescription drugs that are available on the market (e.g., opioids and benzodiazepines, which are highly addictive), the risk-benefit ratio is speaking in favor of psychedelics.

The Aim of this Review

There is an urgent need to develop new strategies in the treatment of mental illness to save lives and reduce human suffering, and society as a whole can only benefit from decreased depression rates. The fast antidepressant action of psychedelic agents is of great promise for developing new treatments.

Several systematic reviews have been made by gathering data from studies on psychedelic drugs, but to the author's knowledge, no systematic review has been made focusing solely on psilocybin's effect on major depressive disorder. This review aims to answer the following question:

> What does the accumulated evidence have to say about psilocybin's effectiveness in treating major depressive disorder?

With the results of previous research on psilocybin's effect on depressive states in consideration, it is hypothesized that psilocybin will prove to be effective in treating MDD.

Methods

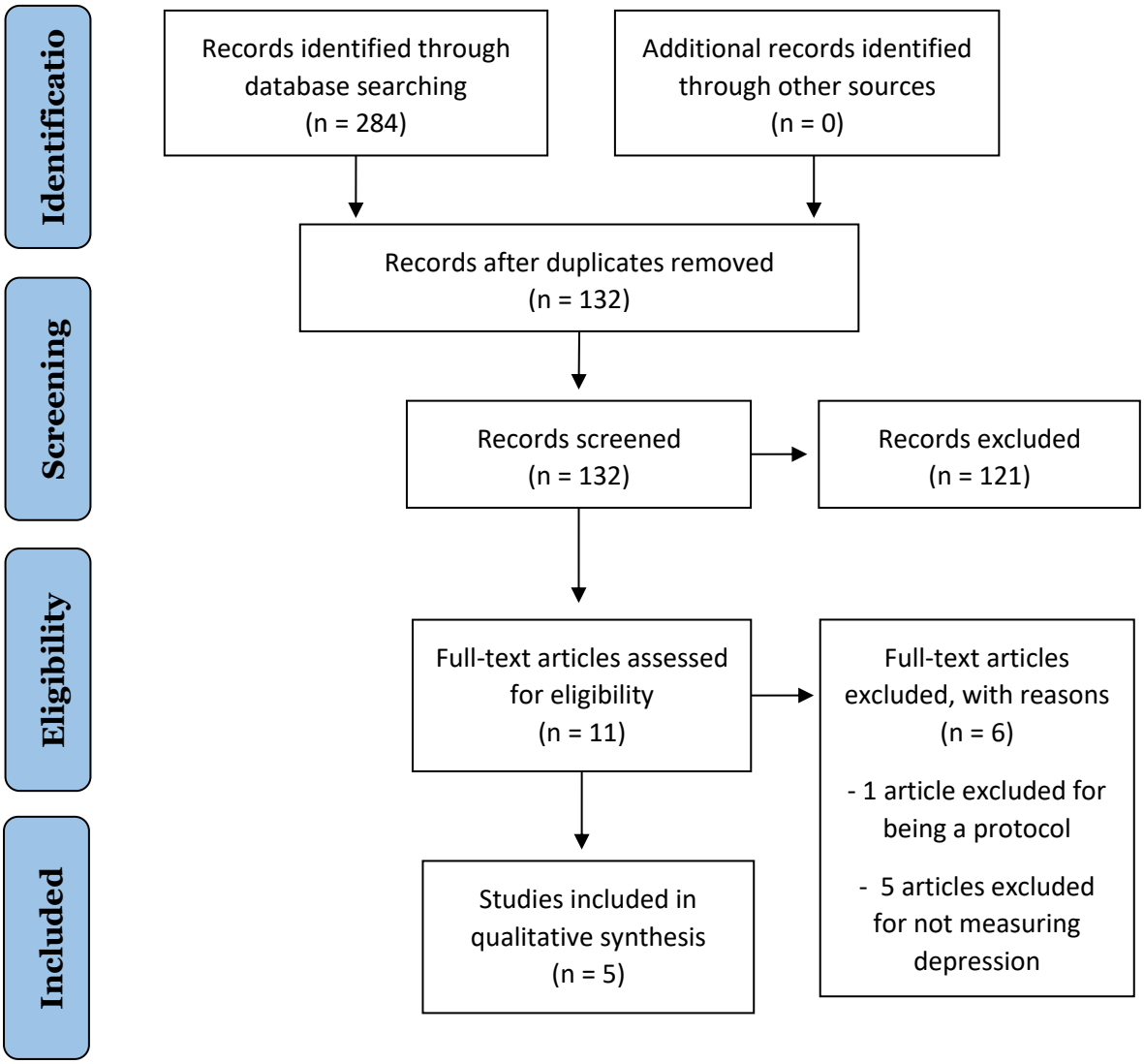
Search Strategy

The literature search was performed by following the PRISMA 2009 flow diagram (Moher et al., 2009). See Figure 3. The search was conducted on the 20th of February 2022 using PubMed, Medline EBSCO, and Web of Science. The following search string was used: (psilocybin OR 4-phosphoryloxy-N,N-dimethyltryptamine) AND ("major depressive disorder" OR "major depression disorder" OR "treatment-resistant depression" OR MDD OR TRD) AND (treatment OR therapy).

The search resulted in 284 articles (PubMed n=104, Medline EBSCO n=75, Web of Science n=105). All results were exported and uploaded to Rayyan, an online software for systematic reviews. Duplicates were discarded (n=152). Based on title and abstract, articles were removed if found to be irrelevant (n=121). The remaining articles were reviewed in full length (n=11) and included if meeting the inclusion criteria previously presented (n=5). One article was excluded for being merely a protocol and not presenting any results. Five articles were excluded for not measuring depression.

Figure 3.

PRISMA 2009 Flow Diagram



Note: Standard flow diagram used to document the literature search process. From Moher et al. (2009).

Inclusion and Exclusion Criteria

Eligibility criteria for articles to be included were that they should be original research articles in peer-reviewed journals. Articles should be written in English and published within the last ten years. Any design (e.g., placebo-controlled, open-label, observational, cross-sectional, longitudinal) investigating psilocybin's effect on depression was included. Following the PICO model; the population should be human subjects diagnosed with major depressive disorder and treatment-resistant depression; the intervention should be psilocybin therapy; a comparison should be made between the effectiveness of treatment for psilocybin relative to placebo or regular antidepressants; the outcome should be measured in terms of the effect on depression inventory instruments.

Studies regarding depression in cancer patients were excluded since this review aims to investigate the effectiveness of psilocybin in treating MDD exclusively.

Data Extraction

Data were extracted regarding 1) study design, 2) sample size, 3) other sample characteristics, 4) administration dose, and 5) pre-and post-administration depression scores. Primary outcomes (measurement of depression according to HAM-D, QIDS, and BDI) will be reviewed, as well as potential secondary outcomes.

Results

Study characteristics

An overview of the study characteristics can be seen in Table 1. Three of five studies were randomized, controlled studies, of which one was double-blind. Two of the five studies were open-label studies, where both patients and researchers were aware that the subjects were given psilocybin.

The sample size ranged from 12 to 59 subjects, with a total of 122 subjects. 58 subjects were female and 64 were male. Age ranged from 21 to 75 years.

All the studies administrated two separate doses of psilocybin. In two of the studies, the first dose was 10 mg of psilocybin (low dose), and the second was 25 mg (high dose; Carhart-Harris et al., 2016; Carhart-Harris et al., 2017). In one study, both administration doses were 25 mg, which were compared to 6 weeks of daily escitalopram administration (20 mg; Carhart-Harris et al., 2021). In two of the studies, psilocybin was administered with regards to body weight (David et al., 2021; Gukasyan et al., 2022). In the first session, 20 mg of psilocybin per 70 kg of body weight was administered (a moderately high dose). The second session was 30 mg per 70 kg of body weight (high dose). In all of the studies, participants received psychotherapy before and after psilocybin sessions.

A variety of measurement tools were used, measuring not only depression but anxiety, anhedonia, and global functioning. Three studies (Carhart-Harris et al., 2016; Carhart-Harris et al. 2017; Carhart-Harris et al. (2021) utilized QIDS-SR-16, BDI, and HAM-D, In Davis et al. (2021), the primary measurement tool was GRID-HAMD, which was assessed by blinded clinicians. QIDS-SR (self-report) was used as a secondary tool. Gukasyan et al. (2022), used GRID-HAMD, QIDS and BDI.

Table 1.

Summary of data extracted from included studies

Lead author/year	Country	Study design	Sample size	Other sample characteristics	Administration dose	Measurement	Outcome
Carhart-Harris et al. (2016)	United Kingdom	Open-label	12	Age range: 30–64, sex (f/m): 6/6	First session 10 mg; second session 25 mg	QIDS, BDI, STAI-T, SHAPS, HAM-D, MADRS, GAF	Mean QIDS at baseline: 19.2; one week: 7.4; three weeks: 6.4; three months: 10.1
Carhart-Harris et al. (2017)	United Kingdom	Open-label	20	Age range: 30–64, sex (f/m): 6/14	First session 10 mg; second session 25 mg	QIDS, BDI, STAI-T, SHAPS, HAM-D, GAF	Mean BDI at baseline: 34.5; one week: 11.8, three months: 19.2, six months: 19.5
Carhart-Harris et al. (2021)	United Kingdom	Double-blind, randomized, controlled	59	Age range: 21–64, sex (f/m): 20/39	First session 25 mg; second session 25 mg respectively 6 weeks of daily oral escitalopram (SSRI group)	QIDS-SR-16, HAM-D-17, BDI-1A	Mean QIDS at baseline: 14.5 (PG), 16.4 (EG); at six weeks: 6.5 (PG), 10.4 (EG)
Davis et al. (2021)	United States	Randomized waitlist-controlled	24	Age range: 21-75, sex (f/m): 16/8	First session 20mg/70 kg; second session 30mg/70 kg	GRID-HAMD	Mean GRID-HAMD at baseline: 22.9 (PG), 22.5 (DTG); at eight weeks: 8.5 (PG), 23.5 (DTG)
Gukasyan et al. (2022)	United States	Randomized waitlist-controlled	24	Age range: 21-75, sex (f/m): 16/8	First session 20mg/70 kg; second session 30mg/70 kg	GRID-HAMD, QIDS, BDI	Mean GRID-HAMD at baseline: 22.8; three months: 9.3; six months: 7.0; twelve months: 7.7

Note: PG = psilocybin group, EG = escitalopram group, DTG = delayed treatment group

Outcomes

In Carhart-Harris et al. (2016), all patients showed some reduction in depression severity after one week. The reduction was sustained three months post-treatment. The maximum effect was achieved after two weeks. Total remission of depression (a score of ≤9 on the BDI scale) was attained in 67% of the patient after one week. Three months after treatment, 42% remained in complete remission.

The 2017 study by Carhart-Harris et al. was a follow-up study, measuring depression scores six months after psilocybin administration. The mean BDI score at baseline was 34.5, after six months the mean BDI was 19.5. At the three-month check-in, six patients had begun new courses of regular antidepressant medication, and five patients had received or planned to receive psychotherapy. Five patients independently obtained and consumed psilocybin between the three-month and six-month check-in. When removing these five from the analysis, no substantial alterations to the main results were seen.

In the study by Carhart-Harris et al. (2021), psilocybin was compared to the regular SSRI escitalopram (the active compound in medications marketed as Lexapro, Celexa, Cipralex, etc.). Mean QIDS-SR-16 scores were 14.5 for the psilocybin group and 16.4 for the SSRI group. Six weeks post-treatment, the change from baseline for the psilocybin group was −8.0±1.0. For the SSRI group, the number was −6.0±1.0.

The randomized, controlled study by Davis et al. (2021) used a design with two groups. The psilocybin group received treatment with psilocybin immediately and the delayed treatment group received psilocybin eight weeks after the immediate treatment group. This design made it possible to differentiate the psilocybin intervention from spontaneous improvement of depression. The mean baseline score on GRID-HAMD was 22.9 for the psilocybin group. Five weeks post-treatment the mean score was 8.0, eight weeks post-treatment the mean score was 8.5. For the delayed treatment group, the mean score was 22.5 at baseline, 23.8 at week five, and 23.5 at week eight.

Gykasyan et al. (2022) was a follow-up study measuring depression up to 12 months after treatment with psilocybin. They found that according to GRID-HAMD, 58% achieved remission after one week. The percentage for remission was the same at the 12-month check-in. The response (≥50% reduction from pre-treatment) rate after one week was 71%, and after 12 months the response rate was 75%. The number of patients who had begun treatment with antidepressants post-treatment was 0% at week 4, 12.5% at 3 months, 20.8% at six months, and 33.3% at 12 months post-treatment.

Discussion

Research on psilocybin's effectiveness in treating major depressive disorder is still in its early stages. The studies published on the subject are not yet many and involve only a

small number of participants. Only three of the five studies processed in this review were randomized controlled studies, and only one was double-blind. It's wise not to draw too strong of conclusions from the results presented in this review. However, all five studies were able to achieve reduced symptoms of depression, suggesting that psilocybin is a fast-acting antidepressant able to produce a sustained effect up to twelve months post-treatment. When compared to a conventional SSRI antidepressant (Carhart-Harris et al., 2021), results suggest that psilocybin is more effective in treating depression.

The study by Davis et al. (2021) showed remarkedly positive results. Mean score on the GRID-HAMD pre-treatment was 22.9 for the psilocybin group, which represents moderate depression (17-23) leaning to severe depression (≥24). Five weeks post-treatment, the mean score had been reduced to 8.5, which represents mild depression (8-16) leaning to no depression (0-7). For the delayed treatment group, who received only psychotherapy during the same time, mean score on the GRID-HAMD were even higher (23.8) at the five-week check-in than it had been at baseline (22.5). The follow-up study by Gukasyan et al. (2022) suggests that the antidepressant effect is long-lasting since the response rate 12 months post treatment was equivalent to or even higher than the response rate one-week post-treatment. Psilocybin was generally well-tolerated, and no adverse effects occurred in any of the studies. There were cases of mild nausea, headache, and anxiety, but these symptoms were transient and passed within 24 hours.

If psilocybin continues to prove effective in the treatment of depression, we are standing before a revolutionary shift of paradigms in the medical and scientific community. Not only will we be able to efficaciously treat depression, which will reduce a substantial amount of human suffering and financial losses to society, but psilocybin and other classic psychedelics could be rescheduled, allowing for further research on their therapeutic potential. As it is today, psilocybin is labelled (in the U.S.) as a Schedule 1 drug, meaning that it carries a high potential for abuse and has no currently accepted medical use. Present research points to a different truth. Cognitive neuroscience and the scientific community in large would benefit greatly from a rescheduling of psychedelic drugs. Research on psilocybin and its effect on the brain has already provided us with valuable knowledge, and with less restrictions, more important insights are possible.

The process of legal reconsideration has already begun by the legalization of psilocybin therapy in the state of Oregon, USA. By the start of 2023, it will be possible to seek out psilocybin therapy legally within the state. Psilocybin seems to be following the path of ketamine, which antidepressant effect was discovered in the 21'st Century. Ketamine became approved by the FDA (U.S.) and EMA (Europe) as treatment for depression in 2019.

Limitations

Several limitations can be identified in the five studies reviewed here. In the two studies measuring depression six- and twelve-months post-treatment with psilocybin (Carhart-Harris et al., 2018; Gukasyan et al., 2022), numerous patients had begun new treatments of regular antidepressants. This makes it difficult to distinguish whether the reduced symptoms of depression were due to the psilocybin treatment or not. In Davis et al. (2021), participants were required to refrain from using antidepressants for four months post-treatment with psilocybin, an approach that results in more "clean" data but might be ethically questionable.

Further limitations of the studies reviewed here are the fact that many of the participants were self-referred. Carhart-Harris et al (2021) report that many participants had preferred psilocybin before escitalopram. Expectancy effects may be part of the clinical benefits that these studies suggest. None of the studies used an active placebo, so all the participants were aware that they were treated with psilocybin. It is called for to proceed with further research, with the use of a psychoactive agent that can act as an active placebo.

This systematic review has some limitations, too. The search process was not evaluated by a second opinion and the selection of the search string depended on the authors' knowledge of the subject. The construction of the search string may have caused the search to be too limited, excluding relevant studies. There is also a considerable risk of the "file-drawer effect", meaning that studies with non-significant results are never published.

Societal and ethical aspects

The increasing number of people being diagnosed with depression is concerning, and the consequences for society are vast. It could be argued that society has an ethical duty to provide support and reduce the levels of human suffering we see today. Consequently, new treatments for depression need to be developed, no matter how unconventional they may be. However, new treatments present new challenges.

The ethical aspects of psychedelic research were briefly discussed previously in this review. The importance of information-based guidelines to assure harm reduction cannot be stressed enough. The studies performed so far serve as a great model of how research can be done in a safe manner. In the study by Carhart-Harris et al. (2016), tranquillizing medications (lorazepam and risperidone) were available to terminate the psychedelic experience if necessary. This is a great tool which can act as a sort of safety net, making the participants feel more secure, knowing that no matter how intense, the psychedelic experience can be terminated.

However safely psychedelic research is performed, there are considerable risks associated with publishing results speaking in favor of psilocybin. Even though there is a substantial number of people already using psychedelic drugs despite the fact it's illegal,

published research might create an increased demand. We would benefit by learning from the mistakes from the past and treat psychedelic drugs with caution.

Conclusion

What does the accumulated evidence have to say about psilocybin's effectiveness in treating major depressive disorder? Psilocybin shows great promise in being able to treat many cases of major depressive disorder, with rapid and sustained effect. However, the evidence comes from a few studies with a relatively small number of participants. Further research, using double-blind randomized control with larger samples and an active placebo is needed before psilocybin can be considered as a potential treatment for MDD. In conclusion, psychedelic research is on the uprise, and the future for treating mental illness looks bright.

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