Journal of Complementary Medicine And Alternative Healthcare
ISSN: 2572-1232

Juniper Publishers key to the Researchers

Review Article
Volume 13 Issue 1- September 2024
DOI: 10.19080/JCMAH.2024.13.5558512

J Complement Med Alt Healthcare

Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinical Trials

Danielle B Rodrigues*, Victor HA Santos and Renato GC Leça

Faculdade de Medicina do ABC, Santo André, São Paulo, Brasil

Submission: August 01, 2024; **Published:** September 17, 2024

***Corresponding author:** Danielle Rodrigues Faculdade de Medicina do ABC, Santo André, São Paulo, Brasil

Abstract

Title: Use of psilocybin in the treatment of mental disorders: systematic review of clinical trials.

Objective: To evaluate the high-impact evidence on the neurobiology, efficacy, safety, and feasibility of using psilocybin in the treatment of mental disorders such as depression, anxiety, obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), smoking, and alcoholism.

Method: Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we conducted a comprehensive search in the PubMed database up to December 2023. We used the following MeSH terms: "psilocybin AND mental health", "psilocybin AND psychiatric disorders", "psilocybin AND PTSD", "psilocybin AND depression", "psilocybin AND anxiety", "psilocybin AND smoking", "psilocybin AND tobacco", "psilocybin AND alcohol", "psilocybin AND addiction", "psilocybin AND compulsive disorder". We applied the "randomized controlled trial" and "clinical trial" filters to focus on the most scientifically impactful trials. We included randomized, open-label or double-blind clinical trials conducted on humans in a clinically controlled environment. We excluded duplicates, animal studies, healthy volunteers, recreational use analyses, secondary analyses, microdose studies, studies unrelated to the review topic, and those without full-text access. Two independent reviewers screened the titles, abstracts, and full texts of the identified studies, with a third reviewer assisting in the discussion and analysis of the evidence. We extracted relevant data from the 18 included studies and compiled them in a table, and also evaluated the risk of bias using the Rob2.0 (Revised Cochrane risk-of-bias tool for randomized trials) criteria, even though not all articles were randomized.

Results: The review of the 18 clinical trials, including 9 randomized and 9 open-label, showed that the administration of one or two doses of psilocybin (10-30 mg/70 kg) in a controlled setting results in significant therapeutic effects from the first day post-session. There was a substantial and lasting reduction in depressive symptoms, with benefits persisting for up to 12 months. Higher doses (25-30 mg/70 kg) were more effective in increasing positive feelings, reducing negative feelings, and improving patients' anxiety and functionality. The psilocybin experience was often described as transformative, promoting positive changes in self-knowledge, mood, relationships, and spirituality, facilitating a re-evaluation of beliefs and a new perspective on life. Neurobiologically, these effects are attributed to the stimulation of serotonergic receptors, changes in cerebral blood flow in the amygdala, and alterations in the integrity of the default mode network, accompanied by mood improvements. Cancer patients at the end of life reported greater acceptance and willingness to face emotions, including negative ones, resulting in better quality of life. Psilocybin also showed promising therapeutic effects in the treatment of substance abuse such as alcohol and tobacco, obsessive-compulsive disorder (OCD), and post-traumatic stress disorder (PTSD). Most smokers reported changes in perspective, with an abstinence rate of over 60% after one year. In alcoholic patients, there was a significant reduction in days of excessive alcohol consumption compared to placebo. A single clinical trial on OCD was found, showing a significant reduction in symptoms 24 hours after the administration of the doses, however, we did not have access to the full text. Although there are no clinical trials evaluating the efficacy of psilocybin in the treatment of PTSD, there is potential due to its action on the default mode network. The substance was well tolerated, with transient side effects such as increased blood pressure, heart rate, headache, and nausea. A case of passive suicidal ideation and some reports of transient fear or anxiety were observed, but no persistent psychotic disturbances or hallucinations. However, there is a high risk of bias, as most studies were conducted on small and homogeneous samples, mostly composed of white individuals with a high level of education. The lack of control groups and possible selection bias due to the exclusion of patients with psychiatric comorbidities limit the applicability of the results to a specific population. Only 7 studies were double-blind, and the effectiveness of blinding is questionable due to the perceptibility of the effects of psilocybin, compromising the control of factors such as patient expectations and the quality of the therapeutic relationship.

Conclusion: The combination of psilocybin with psychotherapy appears promising in the treatment of depression, end-of-life anxiety, smoking, and alcoholism, often resistant to conventional treatments. There is potential to improve OCD and PTSD symptoms, despite less evidence. Psilocybin can increase emotional sensitivity and acceptance, providing participants with insights and promoting neuroplasticity for the restructuring of ideas and behaviors. Participants reported lasting positive effects, such as feelings of gratitude, well-being, and openness to new experiences. However, more double-blind randomized clinical trials with larger samples are needed to confirm its long-term efficacy and safety.

Keywords: Psilocybin; Mental disorders; Treatment-resistant depression; Anxiety; End-of-life Anxiety, Post-Traumatic Stress Disorder (PTSD); Obsessive-Compulsive Disorder (OCD); Substance use Disorder; Smoking; Alcoholism

Abbreviations: PTSD: Post-Traumatic Stress Disorder; OCD: Obsessive-Compulsive Disorder; BDNF: Brain-Derived Neurotrophic Factor; TrkB: Tropomyosin receptor kinase B; PAP: Psilocybin-Assisted Psychotherapy; ECT: Electroconvulsive Therapy; CBT: Cognitive-Behavioral Therapy; Y-BOCS: Yale-Brown Obsessive Compulsive Scale; SSRIs: Selective Serotonin Reuptake Inhibitors

Introduction

From Cultural use to Science: a Historical Overview

Psilocybin is the substance responsible for the psychedelic effects of "magic mushrooms", being found in more than 180 species of psilocybin-containing mushrooms. Several cultures, mainly the Aztecs, used these mushrooms to learn and supposedly communicate with the dead. In the 16th century, a Spanish Franciscan friar named Bernardino de Sahagún wrote a manuscript based on ethnographic research on Aztec culture. He mentioned the terms "teonancatl" and "flesh of the gods" to refer to the "sacred mushrooms of Mesoamerica". However, it was only in the 1930s that researchers from Harvard University found the manuscript, when they traveled to Huautla, Mexico, to witness mushroom ceremonies and bring specimens for research in the United States, which were interrupted by the context of the Cold War.

In the 1950s, mycologists Gordon and Valentina Wasson received a letter describing the ritual use of the substance by Mesoamericans in the 16th century. Intrigued, they began to search for the mushrooms until they were invited to participate in a ceremony in Huautla de Jiménez, Oaxaca, Mexico. The trip was photographed and published in the "Life" magazine with the title "Seeking the Magic Mushrooms", being a milestone in the dissemination of psychoactive mushrooms to the general public.

After that, a sample of the mushroom was sent to the Swiss chemist Albert Hoffman, who had already discovered the effects of LSD in 1943, a synthetic substance with properties similar to psilocybin. In 1959, Hoffman ingested about 2.4g of the substance, proving its psychedelic effects, in addition to isolating, crystallizing, and naming the compound as psilocybin. The drug was later synthesized and marketed by Sandoz as "Indocybin" [1]. In parallel, research with LSD, a classic psychedelic with some effects similar to the mushroom, had been advancing since its discovery, culminating in the first international conference on the therapeutic uses of LSD [2].

Chronology of Scientific Advances

After these discoveries, many clinical research studies were conducted in the fields of psychology and psychiatry to explore the mystical and introspective effects of psychedelics, mainly LSD, as well as their possible therapeutic applications [2]. A meta-analysis that evaluated 19 studies of psychedelics for mood disorders [3] published between 1949 and 1973 found that 79% of patients showed "clinically judged improvement" after treatment. In 1962, at Harvard University with the support of the pharmaceutical company Sandoz, psychology professor Timothy Leary led several studies, including studies on psilocybin in psychotherapy with guests, artists, religious professionals, and psychology students. These studies were motivated by his psychedelic experience in the Cuavernaca region, which he reported as one of the most remarkable of his life [4]. Additionally, in the following years, several studies were conducted, showing that classic psychedelics, when associated with psychotherapy, generate promising results in patients with psychiatric suffering secondary to cancer and substance dependence [5-7].

In the mentioned context, there was an increase in the non-medical use of psychedelics by young people, associated with the counterculture movement in the United States. This generated a political reaction that significantly limited the continuity of research in this area. In addition, there was a tightening of regulations in pharmaceutical research, causing ongoing research to lose credibility for not meeting the required scientific standards [8]. Until then, there was no convincing evidence on the efficacy and safety of psychedelics for the treatment of clinical conditions, which resulted in the prohibition of pharmaceutical research with these substances. Additionally, for political reasons, in 1970 the United States classified psilocybin, mescaline, and LSD as drugs of abuse, criminalizing their consumption and possession and denying any therapeutic value, mandatory without any scientific basis. Clinical studies with psychedelics practically ceased for more than 20 years until the founding of the Heffter Research Institute in 1993, dedicated to the clinical research of the therapeutic potential of these substances.

This period marked the "New Psychedelic Renaissance", characterized by research advances, showing few adverse effects and great efficacy when combined with psychotherapy [9]. In this systematic review article, we will conduct a literature review of current clinical trials on the use of Psilocybin in the treatment of mental disorders such as treatment-resistant depression, anxiety, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder, smoking, and alcoholism, with the purpose of presenting consistent or inconsistent findings in the field.

Mechanism of action

Psilocybin is an alkaloid pro-drug derived from tryptamine precursors found in various species of fungi and is classified as a classic psychedelic (serotonin 2A [5-HT2A] receptor agonist) [10], along with LSD, mescaline, and DMT, which have the ability to promote profound alterations of consciousness, modulating emotions, sensory perception, and sense of self [11]. The substance, after administration, undergoes dephosphorylation in vivo and gives rise to psilocin (the active drug), responsible for the psychomimetic effects. The active drug is an agonist not only of 5-HT2A receptors and other serotonergic receptors, but current evidence shows that it also binds allosterically to the TrkB receptor, improving BDNF signaling, responsible for neuroplasticity, whose reduced levels have been associated with depressive symptoms [12]. The 5HT2A receptors are widely distributed in various brain areas, including the frontal, parietal, temporal, and occipital lobes, related to attention, perceptual awareness, thinking, language, and cognitive control. Additionally, the amygdala, a brain region

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

that functions as a sensory connection during the process of emotional learning, also has a high expression of 5HT2A receptors, significantly impacting the creation and retention of emotion-related memories [13].

The cellular neurobiology of psychedelics is still being studied, and a systematic review on the topic [7] showed a variety of molecular, circuit, and overall brain-level mechanisms that are interconnected. The basic mechanism for the others is the molecular one, through the activation of serotonergic receptors, tropomyosin receptor kinase B (TrkB) receptor, and dopamine receptors, promoting the following effects: increased glutamate and oxytocin, production of brain-derived neurotrophic factor (BDNF) that stimulates neurogenesis, neuroplasticity, and leads to increased connectivity between neurons. At the brain level, an increase in the flow of information modulated by sensory signals was observed, associated with cognitive and sensory cortical region changes.

Adverse Effects

An analysis demonstrated that psilocybin has a benign profile [14] being considered low-risk for self-harm and harm to others compared to more common drugs of abuse such as alcohol. A systematic review and meta-analysis examined the acute adverse effects of therapeutic doses of psilocybin [15], observing that these effects generally resolve within 24 to 48 hours. The most common include headache, nausea, anxiety, dizziness, changes in blood pressure and/or heart rate, visual perceptual effects, and physical discomfort.

The most serious adverse effects found in the literature include persistent psychosis, mania, and suicide attempt, especially in case reports [71-74] [16-19] with recreational use of mushrooms, where there was no dose control or psychological support for the experience. The risks increase significantly when psychedelics are mixed with other drugs and/or alcohol [20], which can even result in death. Additionally, there is no record of a withdrawal syndrome associated with the use of psychedelics [21], indicating a low risk of dependence according to current DSM-V diagnostic criteria.

Due to the possibility of psychosis, the use of psilocybin is contraindicated in patients with a personal or family history of schizophrenia, psychosis, bipolar disorder, and borderline personality disorder. It is also a relative contraindication for people with severe or uncontrolled cardiovascular conditions, due to the frequently reported increase in blood pressure and heart rate during the sessions [22]. With appropriate inclusion and exclusion criteria and clinical supervision, adverse physiological reactions are minimal, and this was the case in the clinical trials included in this review.

Therapeutic Effect

Therapeutic doses of psilocybin allow patients to experience positive changes in their lives, such as greater self-knowledge, mood improvement, relationships, spirituality, well-being, and life satisfaction, impacting their behaviors. Studies also point to subjective effects on empathy, creative thinking, ego dissolution, a positive sense of self, and the enhancement of expectations [5,23]. It is often speculated that, after the psychedelic experience, patients acquire "insights" that motivate them to change negative thought patterns, as in depression, or behavior, as in tobacco abuse.

However, the "mind", "set", and "setting" aspects significantly influence the effects of the psychedelic experience. The "mind" refers to the emotional state and any pre-existing psychopathology in the individual; the "set" refers to the expectations and attitudes, where an open mindset and positive attitude contribute to a more rewarding experience; and the "setting" refers to the physical and social environment, where a safe and comfortable environment, with soft lighting, appropriate music, and the presence of compassionate guides or therapists, enhances the positive effects of the substance [24]. The combination of these elements is crucial in shaping the nature of the psychedelic experience and its long-term outcomes, highlighting the importance of careful preparation and a supportive environment to maximize therapeutic benefits and minimize possible adverse effects [1].

Thus, Psilocybin-Assisted Psychotherapy (PAP) has been extensively studied as a therapeutic approach that combines the use of psilocybin with psychotherapy techniques, which is structured in three phases - pre-treatment, treatment, and post-treatment - that prepares participants, provides psychological support during the administration of psilocybin in a controlled environment, and helps in the integration of the insights obtained, promoting lasting improvements in mental health through a safe and emotionally supportive environment [1].

Method

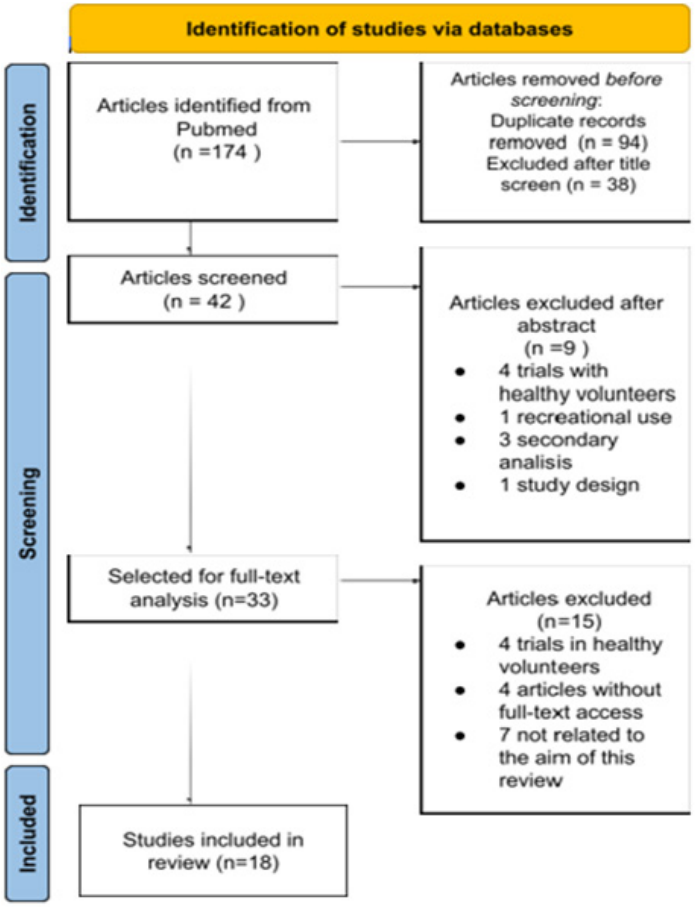
The systematic review search was performed in the PubMed electronic database up to December 2023. The MeSH terms used for the search were: "psilocybin AND mental health", "psilocybin AND psychiatric disorders", "psilocybin AND PTSD", "psilocybin AND depression", "psilocybin AND anxiety", "psilocybin AND smoking", "psilocybin AND tobacco", "psilocybin AND alcohol", "psilocybin AND addiction", "psilocybin and compulsive disorder". We also used the "randomized controlled trial" and "clinical trial" filters to assess the clinical trials, which have greater scientific impact compared to case reports or observational studies, for example. In addition, parallel searches with the "systematic review" and "meta-analysis" filters were performed to strengthen the findings. With the filter for evaluating clinical trials, which is the main objective of this systematic review, a total of 174 articles were identified and superficially analyzed by their titles and abstracts.

To obtain more comprehensive results of relevant clinical findings, we included randomized, open-label or double-blind

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

clinical trials, as long as they were conducted on humans. We excluded duplicates, animal studies, healthy volunteers, recreational use analyses, secondary analyses, microdose studies, studies unrelated to the review topic, and those without full-text access, leaving 33 to be read and evaluated in full. It is worth noting that articles that evaluated recreational use, case report, or retrospective study were relevant in some points, although they were not included in the systematic review. Additionally, one clinical trial was included [58] even without full-text access, compiling information from its abstract and citations in other articles.

The most relevant ones for the chosen scope were reviewed by 2 or 3 authors who discussed and reached a consensus, with the third author being consulted when there was any disagreement. Finally, 18 articles were selected and summarized in a table with the main points (Figure 2) reporting evidence when investigating the efficacy of psilocybin for the treatment of treatment-resistant depression, anxiety, obsessive-compulsive disorder (OCD), smoking, and alcoholism, which also contributed to its historical scientific elucidation and the neural mechanisms involved. In addition, we also analyzed the risk of bias (Figure 3) using the Rob2.0 [79] (Revised Cochrane risk-of-bias tool for randomized trials) criteria for all articles, except for the OCD one, given the insufficient information.



Development

Depression

According to the WHO, around 280 million people worldwide suffer from depression, with approximately 700,000 people with depression dying by suicide each year. This disorder is one of the leading global causes of disability, with loss of pleasure or interest in activities and depressed mood, affecting all aspects of the individual's life [25]. It is assumed that this is related to dysfunctions in the amygdala, particularly its hypersensitivity to negative stimuli, leading to disturbances in emotional processing [26]. This is because the amygdala is a brain area responsible for the formation of emotional memories, making a sensory interface during emotional learning [27], a fact that has made it a target of antidepressant medications [26]. Despite the availability of pharmacological therapies, the treatment response is limited and with many adverse effects, leading to low patient adherence [27]. A meta-analysis involving 38 studies showed that the average response to conventional treatment is about 27%, that is, only one in 3 patients substantially improve [28]. In this context, in

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

recent years, there has been a significant increase in the search for alternative treatment options, which has been accompanied by a series of studies involving the use of psilocybin and other psychedelics [3,15,29-33].

Some studies show that the vast majority of patients already have an improvement in depressive symptoms within 1 week after the high-dose (25mg) psilocybin session [26,34-38], with the positive effects lasting for [35, 36] and up to 12 months [39] of psilocybin-assisted psychotherapy. The average response rate to treatment is about 69% in 1 week, with complete remission of depressive symptoms of approximately 57% in the same period.

Neuroimaging studies evaluated brain function changes before and one day after psilocybin administration, one of which showed that the changes in brain activity during the acute psychedelic experience are different from those observed one day later. A transient activation of the amygdala was observed, followed by a decrease in its blood flow one day after treatment, which was related to the reduction in depressed mood35,36. In addition, an acute decrease followed by an increase in the integrity of the default mode network, responsible for self-perception, was observed. This process is similar to that observed in a study with depressed patients who responded to electroconvulsive therapy (ECT) [40], which promotes a "brain reset", offering the patient the opportunity to restructure their mental processes, allowing a new perspective and approach in relation to their thoughts and experiences.

Two additional studies used magnetic resonance imaging to evaluate changes in the amygdala's response to facial expressions before and after psilocybin sessions. These studies [36,26] revealed that, after treatment, there was a significant increase in the amygdala's responsiveness to faces expressing fear. This increased emotional reactivity was correlated with reports from most patients about greater acceptance of their own emotions, including negative ones [36], as well as an increase in emotional sensitivity [26]. It was observed that the increase in amygdala activity, along with the reduction in functional connectivity with prefrontal control regions, may be related to a decrease in emotional rumination and an increase in the ability to accept [26]. On the other hand, conventional antidepressants, especially Selective Serotonin Reuptake Inhibitors (SSRIs), tend to reduce amygdala activity, resulting in a decreased emotional responsiveness to both negative and positive stimuli, leading to a sense of emotional numbness [41].

In a comparative study between escitalopram and psilocybin [42], it was found that over a 6-week period, there was no significant difference in changes in depression levels between the groups. However, the response to psilocybin was significantly better and showed faster efficacy compared to escitalopram. Additionally, participants who received psilocybin reported a considerable improvement in their perceived ability to cry and feel compassion, as well as experiencing intense emotions and pleasure. They also reported feeling less sleepy compared to the escitalopram group.

Two recent randomized double-blind clinical trials published in 2023 [39,43] - one involving 233 individuals suffering from treatment-resistant depression and another with 104 participants meeting DSM-5 criteria for major depressive disorder - provided new evidence on the immediate beneficial effects of a single dose of psilocybin. The results highlighted its remarkable efficacy, when combined with psychotherapy, in reducing depressive symptoms, improving anxiety levels, increasing positive feelings, as well as enhancing functionality and quality of life in these patients.

In this context, psilocybin and other psychedelic substances are the only known agents that show a positive correlation between a temporary mechanism of brain reset and antidepressant response. This finding has the potential to revolutionize the treatment of depression after ECT, opening new perspectives and possibilities in the field of mental health [41].

Anxiety

Anxiety is the most common mental disorder in the world, affecting over 370 million people, according to the WHO mental health report [25]. In fact, patients with a highly lethal disease often suffer considerable anxiety, discouragement, indignation, personal devaluation, social withdrawal, lack of hope, and vulnerability [45]. The attribute of lethality of cancer and the uncertainty related to its evolution can cause considerable psychological turmoil, with the fear of cancer recurrence and death also contributing to anxiety [30]. This leads to insufficient recovery from medical interventions and lower life expectancy in terminal patients [45]. Even though psychopharmacological and psychosocial interventions are used in the approach to anxiety in patients with life-threatening illnesses, the effect is limited, leading to an analysis of the effectiveness of psilocybin in these cases through clinical trials [30].

The clinical trials show that, even at a low dose, psilocybin reduced anxiety levels at 1 and 3 months post-treatment, reflecting a reduction in stress [46], significantly increased spiritual well-being [7], mood, quality of life, and improved perspective and anxiety regarding death [5,7]. Furthermore, a double-blind randomized clinical trial involving 51 cancer patients showed an 83% clinical response rate assessed in relation to anxiety after 6 months [5], significantly reflecting their satisfaction with life. Such repercussions were closely linked to the mystical experience promoted by psilocybin, which includes commonly reported reflections on insights and new perspectives, evaluating the disease and death differently, with greater acceptance [46].

The analyzed studies indicate that a careful application of psilocybin combined with psychotherapy manifests itself as a possible revolutionary pharmacological-psychosocial therapy

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

to manage the psychological and existential suffering linked to cancer. However, the evidence is still insufficient, and more clinical trials are needed to reach a more consistent conclusion.

Post-Traumatic Stress Disorder (PTSD)

Post-Traumatic Stress Disorder (PTSD) involves distressing symptoms such as persistent psychological distress, mood changes, dissociative reactions, and avoidance of trauma-related stimuli. This can occur after exposure to a traumatic event, such as serious injury, sexual violence, or death [47]. The pathophysiology of PTSD is still being studied, but it is mainly related to functional changes in neural connectivity, such as hyperexcitation of the amygdala to traumatic events, leading to a dysregulated fear response, and hypoactivation of the default mode network, associated with symptoms of avoidance, dissociation, and intrusive thoughts [48]. The first-line treatment for this disorder is exposure-based psychotherapy, however, 40-60% of patients do not respond adequately to this treatment and suffer from chronic effects [49].

Additionally, the difficulty of patients in tolerating the re-experiencing of traumatic memories can impair the treatment response and lead to dropout [50]. In view of this, some research has aimed to explore the psychedelic effects associated with psychotherapy, seeking to increase the cognitive and emotional processing capacity through pharmacological reduction of fear and arousal [51]. Before the introduction of PTSD as a psychiatric diagnosis in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) in the 1980s, hundreds of patients in the Netherlands with the so-called concentration camp syndrome were treated with psilocybin by psychiatrist Jan Bastiaans, with the idea of re-living the traumatic event with emotional abbreviation associated with psychological support. This method was used by Ossebaard and Maalsté in 1999 in a long-term study involving 12 traumatized participants, in which all except 1 reported moderate to strong improvements [51].

Among the current studies with psychedelics, no completed clinical trials involving psilocybin in the treatment of this disorder were found, only with MDMA [31] and ketamine [32,33], which are currently more explored as alternative therapy for PTSD. Despite this, there is great potential for psilocybin in the treatment of PTSD, through the reduction of fear response. In this way, its association with psychotherapy could facilitate trauma exposure, by decreasing the negative reaction that the patient may have during the session, along with acute effects of greater understanding and acceptance [35]. However, the research gap does not sufficiently demonstrate whether psilocybin is useful in the treatment of PTSD.

Obsessive-Compulsive Disorder (OCD)

Obsessive-Compulsive Disorder (OCD) manifests through obsessions and/or compulsions that are not attributed to substance use or physical disturbances, which results in personal distress and dysfunction, through a chronic or episodic course. Obsessions consist of recurrent thoughts that cause anxiety, while compulsions are repetitive actions performed in response to these thoughts or according to specific rules, with the aim of relieving distress [52]. We still do not fully understand the physiology of this disorder, however, some theories point to a possible influence of dysfunction in the cortico-striato-thalamo-cortical circuits, which are closely related to sensory-motor, cognitive, affective, and motivational processes. Furthermore, it is speculated that imbalances, particularly in the functioning of the main neurotransmitter systems, such as dopamine, GABA, and, especially, serotonin and glutamate, may also be associated with this condition [39]. Thus, the first-line treatment is cognitive-behavioral therapy (CBT) and pharmacological intervention with a selective serotonin reuptake inhibitor (SSRI), however, between 40-60% of patients suffer from therapeutic response failure and relapses after discontinuation or completion of these treatments. In more severe and refractory cases, neurosurgical procedures focused on the lesion of specific components of the neural circuits implicated in OCD may be indicated [53]. Thus, it is extremely important to explore other treatment alternatives for refractory cases, in a minimally invasive manner and with greater efficacy.

A variety of case reports were found in the literature on the effects of psilocybin in patients with OCD [54-56], highlighting remarkable improvements in obsessive thought patterns and compulsive behaviors after the experience. However, the vast majority occurred in a recreational manner, without any clinical control, making it impossible to relate dose, effect, and duration of the therapeutic effect. Among them, a retrospective online study published in September 2023 [57] explored the recreational use of psychedelics and the improvement of OCD symptoms, evaluating changes in negative emotions, obsessions, compulsions, acceptance of the condition, and avoidance of anxiety-provoking situations. It was concluded that among the psychedelic users (90 participants), 42% reported that the use of psilocybin had a significant impact on symptom reduction, with more than 30% reporting persistence of effects for more than 3 months, and 10% reporting a worsening of OCD symptoms. However, no significant predictors were identified that could explain the variation in participant reports.

In addition, a single double-blind clinical trial conducted in 2006 was found [58], evaluating the safety, tolerability, and potential therapeutic effects of psilocybin in OCD with 9 individuals who had failed previous treatment. In this study, the participants received oral doses of psilocybin combined with unstructured psychological support, once a week, for 4 weeks. The results showed a significant reduction in OCD symptoms, with decreases of 23 to 100% in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores 24 hours after dosing. No serious adverse events were observed, and one participant maintained complete remission of symptoms at the 6-month follow-up. It is noted that the evidence is insufficient to affirm anything regarding the

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

efficacy of psilocybin in the treatment of OCD, despite its potential in facilitating the reprocessing of negative emotions and core beliefs associated with aversive past events, in order to allow behavioral changes.

Smoking

Smoking is a chronic disease caused mainly by nicotine dependence present in cigarettes. Nicotine is a highly addictive substance that acts on nicotinic receptors present in the central nervous system, activating the brain's reward system and increasing the release of dopamine, a neurotransmitter related to pleasure and well-being. This mechanism causes the compulsive use of cigarettes, even in the face of health harms [59]. Smoking is one of the leading preventable causes of death worldwide, being associated with a variety of diseases such as cancer, cardiovascular, and respiratory diseases [60].

Although there are various treatment options to aid in smoking cessation, which includes behavioral interventions through psychotherapy [20] and pharmacological treatments such as nicotine replacement therapy and medications like bupropion and varenicline, the success rates are still relatively low[61]. It is estimated that about 70% of smokers who try to quit without medical assistance relapse within a month. With conventional treatments, success rates range from 20% to 30% after one year of treatment, which shows that there is still room for the development of more effective therapies [62]. Some mechanisms of action are defended to justify the therapeutic use of psilocybin, such as the effect on the serotonergic system activity, which modulates the reward-seeking behavior, and the ability to increase brain neuroplasticity, reducing stress response and improving the individual's cognitive ability to resist the temptation to smoke [63,64].

In a pilot study conducted at Johns Hopkins University [63] with psychiatrically healthy nicotine-dependent patients, 80% of participants showed tobacco abstinence over 10 weeks of treatment with psilocybin combined with cognitive-behavioral therapy for smoking cessation, which persisted at the 6-month follow-up. Additionally, participants frequently reported that the experience strengthened their belief in their ability to quit smoking and changed their perspective on the situation, so that the long-term benefits outweighed the immediate pleasure of smoking. The long-term follow-up of this same study [65] showed that the abstinence level after more than 1 year of the psychedelic experience was 60%. A systematic review on the topic [29] strengthens the evidence found here, allowing to elucidate that high doses of psilocybin in association with cognitive-behavioral therapy and counseling for smoking cessation favor tobacco abstinence.

Therefore, psychedelic therapy can be a promising therapeutic option for the treatment of tobacco dependence. The results suggest that such therapy can lead to profound changes in patients' perception and behavior towards smoking, which may result in a significant reduction in dependence and tobacco abuse. However, controlled clinical trials are needed to evaluate the efficacy and safety of psychedelic therapy in the treatment of tobacco dependence.

Alcoholism

Alcoholism, also known as alcohol use disorder, is a chronic disease characterized by the excessive and uncontrolled use of alcoholic beverages, negatively affecting various aspects of the individual's life. The mechanism of alcohol addiction is related to the activation of the brain's reward system, which releases dopamine in response to alcohol consumption, generating a sense of pleasure and well-being [66]. Over time, the continuous use of alcohol can lead to a reduction in the sensitivity of dopamine receptors, causing the individual to need increasingly higher doses to achieve the same pleasurable sensation. In addition, alcohol can affect other brain systems, such as the GABA and glutamate neurotransmitter systems, which are involved in mood regulation, anxiety, and sleep, contributing to the disorder [67].

The conventional treatment of alcoholism aims to reduce alcohol consumption and prevent relapse. Treatment options include psychotherapy, participation in support groups, and the use of medications such as naltrexone and acamprosate [68]. Although there are some treatment options, the success rate is still low. It is estimated that only about 10% of people suffering from alcoholism are able to fully recover [32] and > 65% experience relapse within 12 months after treatment [29]. Given this, alternative treatment with psilocybin seems to be a good option, as it acts on the serotonergic system, modulating the reward-seeking behavior and increasing brain neuroplasticity. This can help reduce the brain's stress response and enhance the individual's ability to resist the temptation to drink [13].

A 2016 pilot study with 10 participants investigated the use of psilocybin in the treatment of alcoholism and showed promising results: a significant reduction in the frequency of drinking days and the amount of alcohol consumed, as well as a relationship between the intensity of the psychedelic experience and the change in drinking behavior, desire, and self-efficacy in most participants [69]. In addition, in 2022, a larger randomized clinical trial [70] was published involving 95 participants with alcohol use disorder who were divided into 2 groups: 49 for psilocybin and 46 for the active placebo control diphenhydramine, in order to evaluate improvement in alcohol consumption associated with psilocybin-assisted psychotherapy. A significant reduction in the percentage of heavy drinking days was observed in patients treated with psilocybin (9.7%) compared to the active placebo (23.6%), in addition to a moderate to large reduction in various categories of alcohol-related problems that persisted after 24 and/or 36 weeks after the first medication session.

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

In summary, regarding the application of psilocybin in substance use disorder, the impact of the mystical-type experience on the lasting effect of psilocybin was addressed, since it induces behavioral change in the individual, facilitating the reduction in the compulsivity to drink, with positive and lasting effects [29]. Despite these promising results, the evidence is scarce, and more randomized double-blind placebo-controlled clinical trials are still needed to evaluate the efficacy and safety of using psilocybin in the treatment of alcoholism.

Discussion

It is observed that there is currently a deeper exploration in clinical research on the therapeutic effects of psilocybin in the treatment of mental disorders. This systematic review analyzed 18 clinical trials in humans that evaluated the application of psilocybin-assisted psychotherapy in treatment-resistant depression and anxiety primarily, and to a lesser extent in smoking and alcoholism. As for OCD and PTSD, the studies are scarce and limited to a few case reports or very old studies, with only one clinical trial found in OCD.

In the field of depression, more research was conducted, with 10 clinical trials identified, 5 of them open [26,34-37] and 5 randomized [42,43,38,39,71], including a recent larger double-blind study published in 2023 [71], which included 233 participants with treatment-resistant depression. The analysis of these studies revealed a significant improvement in depressive symptoms as early as the first week, with sustained effects over periods that extended up to 12 months, suggesting that psilocybin, combined with psychotherapy, is a promising option for treating unipolar depression resistant to conventional treatments.

It is notable that the effects of psilocybin are different in the acute, subacute, and long-term phases, as evaluated by studies that reached different results. During the acute phase, characterized in general by a period of 6 to 8 hours, with the peak of effect occurring between the second and third hour [34], an interaction of the substance with several receptors, with emphasis on the serotonergic ones, is pointed out. This process induces a hyperactivation of the amygdala, a reduction in connectivity in the default mode network, and an improvement in the connection between different brain networks, resulting in the hallucinogenic effects associated with a transient increase in anxiety, possible intrusive thoughts, and a deeper reflection on one's own life. In the subacute phase, which covers the period from the day after the experience to approximately one month after, some studies using brain imaging methods pointed to a decrease in blood flow in the amygdala, correlating with the reduction of depressive symptoms, in addition to an increase in the integrity of the default mode network, associated with self-perception [35].

Additionally, some of the studies indicated increased amygdala sensitivity to fear stimuli [36,26] and reduced functional connectivity between the prefrontal cortex and the amygdala, which was associated with a decrease in emotional rumination due to greater acceptance of their emotions. The fact that there is an increase in the integrity of the default mode network (after an acute decrease) accompanied by mood improvement was the basis for the comparison of the psychedelic experience with electroconvulsive therapy [35], in which an acute modular disintegration allows a reintegration and resumption of normal functioning, like a "brain reset", resulting in behavioral and cognitive changes, in addition to providing insights into life. This period after the experience, called the "psychedelic afterglow", opens a therapeutic window that enhances the beneficial effects of psychotherapy, allowing an extension of these benefits over time. Thus, after one week of treatment, on average, 67% of the evaluated patients showed a significant reduction in negative thoughts, a broader perception of the situation, and a greater capacity for acceptance [5,36,26].

The significant improvement in depressive symptoms observed in the evaluated clinical trials represents a revolutionary advance in psychiatry. This is particularly relevant considering that conventional antidepressant treatments, such as selective serotonin reuptake inhibitors (SSRIs), generally require weeks to months of daily consumption to produce significant effects, associated with side effects such as emotional numbness, drowsiness, weight gain, and increased risk of suicidal ideation. Additionally, about 1 in 3 patients do not respond adequately to treatment [72]. In contrast, it was observed that one or two doses of psilocybin produce rapid and lasting effects by addressing central psychological issues through profound and transformative experiences, with fewer side effects and at least comparable efficacy to SSRIs, as evidenced by a comparative study with escitalopram [42].

Regarding anxiety, three double-blind randomized clinical trials were identified that investigated the therapeutic potential of psilocybin in reducing end-of-life anxiety in cancer patients [5,7,46]. These patients often experience a chronic syndrome of psychosocial distress, characterized by depressed mood, anxiety, and deterioration in quality of life. The largest randomized clinical trial included 51 patients diagnosed with potentially fatal cancer. In the three trials found, a significant improvement in quality of life, a decrease in anxiety related to death, and a change in perspective regarding their condition were observed, with participants demonstrating greater acceptance and reflection on their limited life expectancy.

In the context of smoking, two studies were identified [63,65] from the same population data, although with distinct follow-up periods: an open-label pilot clinical trial was followed by a long-term evaluation of 15 smokers who received psilocybin treatment. The results were encouraging, and approximately 70% of participants reported that psilocybin made them reconsider their habits, valuing long-term benefits over immediate pleasure, and reevaluating their priorities and life values. Regarding alcoholism,

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

two clinical trials were identified, one open [69] and a more recent randomized, double-blind, placebo-controlled [70] trial, which involved 93 participants. These studies showed a reduction in the frequency of heavy drinking episodes, with effects persisting for up to eight months in patients undergoing psilocybin sessions.

Regarding Obsessive-Compulsive Disorder (OCD), only one clinical trial [71] conducted in 2006 was found, but we did not have access to the full text and made an exception to the exclusion criteria, given the relevant information found in other review articles. In this sole study, nine individuals were included and showed significant reductions in obsessive-compulsive symptoms even with the administration of low doses of psilocybin, suggesting a possible influence of the placebo effect. In addition, there are only a few isolated case reports that, despite demonstrating frequent changes in thought patterns and behavior, provide limited evidence. The same scenario applies to Post-Traumatic Stress Disorder (PTSD), for which no clinical trials with psilocybin meeting our inclusion criteria were found, despite the promising possibilities and preliminary studies conducted in the past. Considering the impact of psilocybin on the amygdala, it is plausible that this substance may be effective in the treatment of PTSD, allowing patients to address their traumas openly and with greater acceptance, which may facilitate psychotherapy. However, its efficacy cannot be affirmed.

Regarding the adverse effects reported in the evaluated studies, the majority were of a transient nature, including mainly increases in blood pressure, heart rate, headache, and nausea. In terms of psychiatric adverse effects, transient symptoms of anxiety, transient psychotic symptoms, and a single case of passive suicidal ideation [72] that lasted approximately 15 minutes during a session were reported. No persistent psychotic disturbances or hallucinations were reported. Given this, it is emphasized that the immediate effects of psilocybin are influenced by various factors, including the environmental context of the experience, the user's expectations, and their emotional processes [73]. In inadequate circumstances, the recreational use of the substance can lead to rare cases of psychological harm, as reported in some cases associated with the use of psychedelics [74-78]. Therefore, all clinical trials conducted in this research carefully considered the context of psilocybin administration. This included the psychological preparation of participants through pre-experience therapy sessions, which addressed aspects of the participants' personal life, the expected psychological effects of psilocybin, guidance for openness to new perceptual possibilities, and the establishment of bonds with the therapists. During the experience, the participants received psychological support to minimize harm, control possible challenging experiences ("bad-trips"), and promote the acceptance of images, visions, and perceptions. Additionally, the environment where the sessions took place was carefully prepared to be comfortable and quiet, with soft lighting and selected music to complement the therapeutic experience.

The significant role of music in this context is also highlighted, as it plays a crucial role in guiding and improving the therapeutic experience, assisting in the processes of meaning attribution, emotional regulation, and the creation of mental images. This probably occurs due to the fact that the brain regions involved in the auditory processing of music overlap, in part, with the brain areas whose activity is altered after the administration of psychedelics [79]. Therefore, the appropriate context acts in synergy with the pharmacology of psychedelics to promote the desired therapeutic effect. In this circumstance, the significant role of the mystical experience was also observed in many of the analyzed studies [5,7,69,29,34,39,46], positively influencing the results. It is suggested that this experience may provide frequent insights, expanding personal perception through neuroplasticity, which allows the restructuring of ideas and behaviors. In the long term, participants consistently reported an amplification of positive effects, including feelings of gratitude, well-being, life satisfaction, humility, motivation, mindfulness, and openness to new experiences.

Although these studies present promising results, they face significant bias challenges, as highlighted in a recent systematic review on the risk of bias in psychedelic medicine [80]. It is common to have bias in deviations from intended interventions, as the effective blinding of participants is complicated due to the strong effects of psilocybin, which often reveals who received placebo and who received the active compound, impairing the ability to control factors that may affect treatment efficacy, such as patient expectations and the quality of the therapeutic relationship. Additionally, most trials have small samples, which do not adequately reflect the real effect of the treatment and limit the representativeness of the target population, restricting the generalization of the results.

It is important to note that the study participants are predominantly of white ethnicity, with high educational level, and belong to social groups that include little representation of LGBTQ+ people or other marginalized populations. This lack of diversity is concerning, as different groups may react differently to treatments, influenced by genetic, cultural, and socioeconomic factors, in addition to having various perspectives and resources to address mental health issues. The absence of diversity may limit the applicability of the results to a wider range of populations. Furthermore, there is no standard methodological protocol, resulting in variations in the administered doses, which makes comparative analysis difficult. Finally, the studies present considerable selection bias due to rigorous exclusion criteria, which reduces clinical applicability, especially by excluding patients with comorbidities such as psychotic disorders, borderline personality disorder, and bipolar disorder, thus limiting the usefulness of psychedelics in the real-world context.

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

Limitations

This systematic review has significant limitations. First, the search was conducted in a single database, PubMed, which may restrict the breadth of the results. Additionally, the lack of access to articles considered relevant [81-84] due to payment restrictions compromises the inclusion of important information (except for one, which we found relevant to include as much as possible, also being a limitation). The evaluated studies also have characteristics that limit the robustness of the findings, such as the conduct of open-label trials, the use of small and homogeneous samples, and concerns about bias. Furthermore, the dependence on funded research and the publication bias associated with the current psychedelic renaissance may distort the available evidence. Finally, the speed with which new discoveries are disseminated can quickly make this review obsolete, requiring constant updating of the information.

Conclusion

The systematic review on the use of psilocybin in the treatment of mental disorders indicates promising results. The analyzed clinical trials suggest that, when administered in controlled environments and combined with psychotherapy, psilocybin can provide significant improvements in patients with treatment-resistant unipolar depression, end-of-life anxiety, as well as problems related to alcoholism and smoking. Although only one clinical trial was found for obsessive-compulsive disorder (OCD) and none for post-traumatic stress disorder (PTSD), the potential of psilocybin to alleviate the symptoms of these disorders is evident, as it acts on brain mechanisms that influence the fear response and promote changes in thought and behavior patterns.

The studies demonstrate a significant reduction in depressive and anxiety symptoms, with therapeutic effects that manifest quickly and are maintained over time, resulting in improvements in quality of life and well-being of patients. This contrasts with conventional treatments, which often take longer to show results and are frequently associated with adverse effects. In contrast, the side effects of psilocybin tend to be temporary and manageable in appropriate therapeutic contexts, highlighting the importance of careful psychological preparation and a conducive environment to maximize the benefits of the psychedelic experience. Additionally, elements such as music and mystical experiences are fundamental to the effectiveness of the treatment. In summary, psilocybin stands out as a promising alternative in the treatment of mental disorders, presenting a profile of efficacy and safety that justifies the need for

additional investigations to validate its clinical applications.

Figure 2: Articles summarized in table, highlighting the most relevant points for the research.

Authors / Year / Journal of Publication	Study Type / Sample	Intervention	Results / Adverse Effects	Conclusions / Limitations
DEPRESSION				
Robin L Carhart-Harris, Mark Bolstridge, James Rucker, Camilla M J Day, David Erritzoe, Mendel Kaelen, Michael Bloomfield, James A Rickard, Ben Forbes, Amanda Feilding, David Taylor, Steve Pilling, Valerie H Curran, David J Nutt. / (2016) - The Lancet Psychiatry	Open-label, pilot feasibility study in a single arm, without a control group, with 12 patients with moderate to severe treatment- resistant unipolar depression.	The individuals participated in two sessions of psilocybin-assisted psychotherapy at different doses (10 and 25mg), with a one-week interval between them. Psychological support was provided before, during, and after the sessions, along with a positive therapeutic environment. For the clinical assessment of depression severity, the HAM-D, MADRS, and GAF questionnaires were used, along with self-assessment scales for depressive symptoms (QIDS and BDI), anxiety levels (STAI-T), and pleasure sensation (SHAPS). The primary outcome measured	The acute psychedelic effects of psilocybin typically became detectable between 30 minutes and 60 minutes after administration, peaking between 2 hours and 3 hours after administration, and diminished to insignificant levels by 6 hours post-administration. All patients showed a reduction in depression severity within 1 week, which was maintained for at least 3 months. 67% of the patients achieved complete remission within 1 week, and 42% maintained remission at 3 months. Adverse effects observed included anxiety at the onset of the drug, confusion or thought disorder, mild nausea, and headache, all of which were transient.	The results support the feasibility of using psilocybin-assisted psychotherapy in patients with unipolar depression that does not respond to conventional treatments. Psilocybin has a distinct pharmacological action compared to currently available therapies for depression, specifically 5- HT2A receptor agonists. Therefore, it may represent a valuable addition to the existing therapeutic options for treating depression. However, it is limited by being an open-label study, without a control group, small sample size, and potential bias due to expectancy and suggestibility.

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

Robin L Carhart-Harris, Leor Roseman, Mark Bolstridge, Lysia Demetriou, J Nienke Pannekoek, Matthew B Wall, Mark Tanner, Mendel Kaelen, John McGonigle, Kevin Murphy, Robert Leech, H Valerie Curran e David J Nutt / (2017) - Scientific Reports	Open-label clinical trial that evaluated changes in brain function before and one day after psilocybin administration in 19 patients with treatment-resistant depression	The patients received 10mg followed by 25mg of the drug with a one-week interval, accompanied by psychological support. Changes in cerebral blood flow (CBF) and resting-state functional connectivity were assessed before and one day after the 25mg dose. The QIDS- SR-16 questionnaire was used to evaluate depressive symptoms	All patients showed a decrease in depressive symptoms within one week, and all but one maintained this decrease at week five. A decrease in CBF was observed bilaterally in the temporal lobes, including the left amygdala, one day after treatment, along with a decrease in absolute CBF in subcortical association areas. An increase in the integrity of the default mode network (after an acute decrease) was also observed, accompanied by mood improvement. This process is comparable to electroconvulsive therapy, which promotes a "reset" where acute modular disintegration allows reintegration and resumption of normal functioning. Additionally, a decrease in CBF between the bilateral parahippocampus and the prefrontal cortex was observed, which was also predictive of treatment response at five weeks. No serious adverse effects were reported.	Changes in resting cerebral blood flow and functional connectivity were observed post- psilocybin treatment for resistant depression. The decrease in amygdala blood flow was related to reduced depressive mood. The increase in the integrity of the default mode network and bilateral vmPFC was predictive of treatment response at five weeks. Finally, a decrease in CBF between the bilateral parahippocampus and the prefrontal cortex was also predictive of treatment response at five weeks. An exploratory analysis revealed that the acute "peak" or "mystical" experience during high-dose psilocybin sessions was predictive of these changes. The study is limited by the small sample size and lack of a control group.
Leor Roseman, Lysia Demetriou, Matthew B Wall, David J Nutt, Robin L Carhart-Harris / (2018) - Neuropharmacology	Open-label clinical trial including 20 patients with moderate to severe treatment-resistant depression.	The patients underwent two psilocybin dosing sessions, with psychological support provided before, during, and after these sessions. Functional magnetic resonance imaging (fMRI) scans were performed one week before the first session and one day after the second and final session, focusing on amygdala response changes to neutral, fearful, and happy faces, with a specific focus on the response to fearful faces. Depressive symptoms and the relationship between the amygdala and depression were assessed using the QIDS and BDI questionnaires. Anxiety levels were also evaluated using the STAI (State-Trait Anxiety Inventory).	One day after psilocybin administration, 68.4% of the patients responded significantly to the treatment, with greater amygdala activation related to better outcomes. The BDI score remission rate at one week was 57.9%. The response rate at five weeks according to the QIDS was 47.3%, with no relation to changes in the amygdala. Greater right amygdala responsiveness to fearful and happy facial expressions was observed, with the response to fearful faces being more significant. No adverse effects were reported.	Increased amygdala responsiveness to fearful faces after psilocybin treatment was associated with better clinical outcomes. This contrasts with observations of decreased amygdala responses following antidepressant treatment, particularly SSRIs, which are linked to the correction of negative interpretations of depression but also interfere with positive interpretations, leading to blunted positive mood. An analysis of patient experiences in this study showed that most reported greater acceptance of their emotions, including negative ones, facilitating the confrontation of these emotions. This study is limited by the lack of a control group, the inability to differentiate the contribution of psilocybin from psychological support, and the lack of long-term follow-up.

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

RL Carhart-Harris, M Bolstridge, CMJ Day, J Rucker, R Watts, DE Erritzoe, M Kaelen B Giribaldi, M Bloomfield, S Pilling, JA Rickard, B Forbes, A Feilding, D Taylor, HV Curran, DJ Nutt / (2018) - Psychopharmacology	Open-label clinical trial involving 20 patients with major unipolar depression, mostly severe and treatment-resistant, followed for 6 months	In a supportive environment, two oral doses of psilocybin (10 and 25mg, with a 7-day interval) were administered, and the self-assessment questionnaire QIDS-SR-16 was used to evaluate depressive symptoms from 1 week to 6 months after treatment. The BDI and HAM-D were also used for assessing depressive symptoms, the STAI for anxiety, the SHAPS for anhedonia, and the GAF for global functioning.	Marked reductions in depressive symptoms were observed in the first 5 weeks after treatment, influenced by the quality of the acute psychedelic experience. There were also decreases in anxiety and anhedonia scores, along with an increase in patient functionality. Suicidal scores on the QIDS and sexual dysfunction scores on the HAM-D significantly reduced one week after the high dose. The positive results persisted at 3 and 6 months. No serious adverse effects were reported, only some episodes of headache, transient anxiety, and nausea, and 3 reports of paranoia that were limited to the acute experience	Tolerability was good, effect sizes were large, and improvements in depressive symptoms appeared rapidly after just two psilocybin treatment sessions and remained significant 6 months post-treatment in a treatment-resistant cohort. However, the conclusions are limited due to the open-label design, lack of randomization and control group, and the small, homogeneous sample.
Lea J Mertens, Matthew B Wall, Leor Roseman, Lysia Demetriou, David J Nutt e Robin L Carhart- Harris / (2020) - Journal of Psychopharmacology	Open-label clinical trial with MRI evaluation involving 20 patients with moderate to severe treatment-resistant depression.	Participants underwent 2 psilocybin sessions (10mg and 25mg) with a one- week interval and psychological support before, during, and after the high-dose session. To assess amygdala functional connectivity, pre- and post-psilocybin brain functional magnetic resonance imaging (fMRI) was used during the presentation of facial expressions (fear, neutral, or happy). Additionally, the BDI and QIDS-SR-16 questionnaires were used to assess depressive symptoms and their severity, the RRS to evaluate the tendency for ruminative thoughts, and the STAI to assess state and trait anxiety.	BDI scores were significantly reduced one week after the high- dose psilocybin session. 63.2% of patients responded to the treatment, and 57.9% met the criteria for remission of depressive symptoms. Emotional rumination levels decreased within one week but increased again at three months, still remaining lower than baseline. A reduction in functional connectivity (FC) from the ventromedial prefrontal cortex (vmPFC) to the right amygdala during the processing of fearful and neutral faces was observed, which was associated with less rumination. A decrease in prefrontal-amygdala FC was also noted, but it was not associated with anxiety levels. Finally, greater FC was observed between the vmPFC and, independently, the bilateral amygdala and occipital-parietal cortex, which was related to improvements in depression symptoms. No adverse effects were reported.	These results provide further insights into the mechanisms of psilocybin treatment, which may be relevant to patients' reports of greater ability and willingness to engage with their emotions. Thus, the observed increase in amygdala responsiveness combined with a decrease in FC to prefrontal control regions may be related to increased emotional sensitivity and acceptance post-psilocybin treatment. However, the study is limited by its open-label design, lack of a control group, small sample size, multiple comparisons, and potential residual effects of antidepressants.

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

Alan K Davis, Frederick S Barrett, Darrick G May, Mary P Cosimano, Nathan D Sepeda, Matthew W Johnson, Patrick H Finan, Roland R Griffiths (2021) JAMA Psychiatry	Randomized clinical trial including 24 participants diagnosed with major depressive disorder, without the use of antidepressants at the time of the study.	Participants were randomized into two groups: immediate treatment, which received two psilocybin sessions (20 mg/70 kg and 30 mg/70 kg) administered in capsules in a supportive psychotherapy context, and delayed treatment (waitlist), which received the same intervention after 8 weeks. The severity of depressive symptoms was assessed using the GRID-Hamilton Depression Rating Scale (GRID-HAMD) before and several weeks after the last session, comparing the outcomes of the groups at weeks 5 and 8 between immediate and delayed treatment. Depressive symptoms were evaluated using the Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR) one day after the first session and 1 and 4 weeks after the second session. Depression Rating Scale (GRID-HAMD) before and several weeks after the last session, comparing the outcomes of the groups at weeks 5 and 8 between immediate and delayed treatment.	The immediate treatment group showed a significant reduction in depressive symptoms evaluated by GRID-HAMD compared to the delayed treatment group. There was a significant clinical response (≥50% reduction in GRID-HAMD) in 71% of participants at weeks 1 and 4 post- intervention, and remission (GRID- HAMD ≤7) in 58% and 54% at the same weeks, respectively. No serious adverse effects were reported, only mild to moderate headaches and challenging emotional and physical experiences, which were limited to the session time.	This study revealed that the combination of psilocybin and psychotherapy resulted in significant antidepressant effects, which were observed quickly and were long-lasting. Among the limitations are the small sample size, short follow-up (4 weeks), and predominantly white sample, limiting the generalization of the results.
Robin Carhart-Harris, Bruna Giribaldi, Rosalind Watts, Michelle Baker-Jones, Ashleigh Murphy- Beiner, Roberta Murphy, Jonny Martell, Allan Blemings, David Erritzoe, David J. Nutt. / (2021) - The New England Journal of Medicine	Phase 2, double-blind, randomized, controlled clinical trial involving 59 patients with long-standing, moderate to severe major depressive disorder.	A total of 59 patients were recruited, with 30 allocated to the psilocybin group and 29 to the escitalopram group. The patients received two doses of psilocybin (25 mg or 1 mg) at 3-week intervals, in addition to 6 weeks of daily treatment with either placebo (psilocybin group) or escitalopram (escitalopram group). All patients received psychological support.	Both groups showed a reduction in depression scale scores at week 6, with no significant difference between them. Secondary outcomes generally favored psilocybin, although confidence intervals were not adjusted for multiple comparisons. Patients in the psilocybin group reported greater perceived improvements in their ability to cry and feel compassion, intense emotion, and pleasure, as well as feeling less drowsy. The incidence of adverse events was similar between the groups. Common events included headaches and nausea in the psilocybin group and anxiety and dry mouth in the escitalopram group.	This study comparing psilocybin with escitalopram in a selected group of patients showed that the change in depression scores at 6 weeks did not differ significantly between the groups. Secondary outcomes favored psilocybin, but confidence intervals were not adjusted for multiple comparisons. Additionally, the study has limitations, such as the absence of a placebo group, short duration of escitalopram treatment, a selected sample, and limited ethnic and socioeconomic diversity.

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

Natalie Gukasyan, Alan K Davis, Frederick S Barrett, Mary P Cosimano, Nathan D Sepeda, Matthew W Johnson e Roland R Griffiths / (2022) - Journal of Psychopharmacology	A randomized, wait-list-controlled clinical trial that included 27 patients with moderate to severe unipolar depression, followed for 12 months.	The patients underwent preparatory psychotherapy, followed by the administration of two doses of psilocybin (20mg/70kg and 30mg/70kg, approximately 2 weeks apart) with psychological support. After the treatment, the patients were periodically evaluated for depressive symptoms using the QIDS and BDI-II questionnaires, with the primary outcome measure being the GRID- HAMD. Suicidal ideation, mystical experience, and general well-being were also assessed through questionnaires. All these parameters were evaluated at 1 week post-treatment and at 1, 3, 6, and 12 months post-treatment.	Significant decreases in depressive symptom scores (GRID-Hamilton) were observed at all treatment time points. There was a 75% response rate to treatment and 58% remission at 12 months. Most participants also reported an increase in general well-being over the 12 months, related to personal and spiritual meaning. Additionally, no adverse events were considered serious.	The results suggest that treatment of major depressive disorder with psilocybin-assisted psychotherapy produces stable antidepressant effects for at least 12 months, while also enhancing patients' sense of well-being. However, this study had a small sample size, with a predominance of non-Hispanic white participants, and lacked an active control group after the initial phase.
Guy M Goodwin, Scott T Aaronson, Oscar Alvarez, Merve Atli, James C Bennett, Megan Croal, Charles DeBattista, Boadie W Dunlop, David Feifel, David J Hellerstein, Muhammad Ishrat Husain, John R Kelly, Molly R Lennard- Jones, Rasmus W Licht, Lindsey Marwood, Sunil Mistry, Tomáš Páleníček, Ozlem Redjep Dimitris Repantis, Robert A Schoevers Batya Septimus, Hollie J Simmons, Jair C Soares, Metten Somers, Susan C Stansfield, Jessica R Stuart, Hannah H Tadley, Nisha K Thiara, Joyce Tsai, Mourad Wahba, Sam Williams, Rachel I Winzer, Allan H Young, Matthew B Young, Sid Zisook, Ekaterina Malievskaia / (2023) - Journal of Affective Disorders.	A phase 2 double-blind clinical trial with 233 participants with treatment-resistant depression (TRD), defined as failure to respond to 2 to 4 antidepressants	The 233 participants were randomized to receive a single dose of either 25 mg, 10 mg, or 1 mg of psilocybin, with sessions accompanied by psychotherapy lasting 6 to 8 hours. Participants were followed for 12 weeks, with self-reported measures of depression severity, anxiety, positive and negative affect, functioning and associated disability, quality of life, and cognitive function being analyzed.	Three weeks after the dose, 25 mg of psilocybin, compared to 1 mg, was associated with greater improvements from baseline across all measures. The 10 mg dose produced smaller effects on these outcomes. The 25 mg dose was associated with an increase in positive feelings and a decrease in negative ones, as well as improvements in anxiety and functionality. Serious adverse events occurred in 5% of the 25 mg group and 5% of the 10 mg group, with details previously published.	This large study reinforces the evidence on the immediate efficacy of a single administration of psilocybin, bringing highly relevant benefits to patients, such as reduced depressive symptoms, improved anxiety, increased positive feelings, enhanced functionality, and quality of life. However, the study is limited by the absence of an active comparator and the potential for functional unblinding in participants who received a low dose of psilocybin.
Charles L. Raison, Gerard Sanacora, Joshua Woolley, Keith Heinzerling, Boadie W. Dunlop, Randall T. Brown, Rishi Kakar, Michael Hassman, Rupal P. Trivedi, Reid Robison, Natalie Gukasyan, Sandeep M. Nayak, Xiaojue Hu, Kelley C. O'Donnell, Benjamin Kelmendi, Jordan Sloshower, Andrew D. Penn, Ellen Bradley, Daniel F. Kelly, Tanja Mletzko, Christopher R. Nicholas, Paul R. Hutson, Gary Tarpley, Malynn Utzinger, Kelsey Lenoch, Kasia Warchol, Theraysa Gapasin, Mike C. Davis, Courtney Nelson-Douthit, Steffanie Wilson, Carrie Brown, William Linton, Stephen Ross, and Roland R. Griffiths / (2023) - JAMA	A phase 2 randomized clinical trial involving 104 volunteers who met DSM-5 criteria for moderate to severe major depressive disorder (MDD) with a current depressive episode lasting at least 60 days	The 104 participants were randomized to receive a single dose of 25 mg of psilocybin or an active placebo (niacin) with psychological support and a 6-week follow-up, aiming to evaluate the efficacy and safety of psilocybin in treating major depressive disorder. The primary outcome was assessed through the MADRS scale, along with other questionnaires and scales evaluating symptom impairment in work/school, social responsibilities, anxiety levels, quality of life, pleasure, among others.	Improvements in depression were apparent within 8 days after psilocybin administration, with a rapid onset of action, and were maintained throughout the 6-week follow-up without attenuation of the effect. There were also improvements in social functioning, disease severity, anxiety, and quality of life in the psilocybin group. In contrast to other studies, there was no significant reduction in depressive symptoms between the active placebo and psilocybin one day after administration.	The substance was generally well tolerated, with most adverse events being mild or moderate and occurring mainly during the acute administration period. Treatment with psilocybin was associated with a sustained, clinically significant reduction in depressive symptoms and functional disability without serious adverse effects. These findings add to the growing evidence that psilocybin, when administered with psychological support, may be promising as a new intervention for MDD

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

ANXIETY				
Charles S. Grob MD, Alicia L Danforth, Gary S. Chopra, M.D., Marycie Z Hagerty, RN, Cheryl R. McKay, BA, Adam L. Halberstadt, George R Greer / (2011) - Archives of General Psychiatry	A double-blind randomized clinical trial involving 12 participants with advanced-stage cancer and a DSM-IV diagnosis of anxiety disorder, related or not to cancer.	The individuals were psychologically prepared and received 2 experimental treatment sessions, one with active psilocybin (0.2 mg/kg) and the other with placebo, niacin (250 mg), in a randomized order. After the sessions, there were discussions about the psychedelic experience and completion of assessment questionnaires (BDI, POMS, STAI, 5D-ASC, and Psychiatric Rating Scale). These questionnaires were administered from 2 weeks before the first treatment session up to 6 months after the second. Physiological measures (BP, HR, and temperature) were also evaluated	Even at a low dose, psilocybin promoted a sustained reduction in anxiety at 1 and 3 months post- treatment, reflecting a reduced level of stress. There was also an improvement in mood at 2 weeks and a reduction in depressive symptoms at the 6-month follow-up. As an adverse effect, it induced mild but significant increases in heart rate and blood pressure. All individuals tolerated the treatment well, with no reports of "bad trips."	This research suggests that the careful and supervised use of psilocybin may offer an innovative model for addressing conditions that are often poorly responsive to traditional therapies, such as intense existential anxiety and despair frequently associated with advanced stages of cancer. However, it was a small sample that focused on safety and feasibility, not efficacy
Stephen Ross, Anthony Bossis, Jeffrey Guss, Gabrielle Agin-Liebes, Tara Malone, Barry Cohen, Sarah E Mennenga, Alexander Belser, Krystallia Kalliontzi, James Babb, Zhe Su, Patricia Corby e Brian L Schmidt / (2016) - Journal of Psychopharmacology	A double-blind, randomized, placebo-controlled, crossover clinical trial involving 29 patients with advanced-stage cancer and clinically significant symptoms of anxiety and depression.	The study evaluated the efficacy of a single psilocybin session (0.3 mg/kg) compared to a placebo session (250 mg of niacin), with a 7-week interval between them and random order, combined with psychotherapy. Anxiety and depression levels (measured by scales such as HADS, BDI, and STAI), existential distress, quality of life, spirituality, and the immediate effects of psilocybin on cognition, affect, and behavior were assessed.	In the psilocybin group, there were immediate, substantial, and sustained clinical benefits (lasting at least 7 weeks, but potentially up to 6 months), including reductions in anxiety and depression. Additionally, psilocybin promoted persistent positive effects on life attitudes, self-perception, mood changes, increased altruism, behavior, and spirituality. Adverse effects included slight increases in BP and HR (76%), headaches (28%), and nausea (14%). Psychiatric adverse effects included transient anxiety (17%) and transient psychotic symptoms (7%)	The conclusion was that psilocybin, administered alongside psychotherapy, may become an effective new pharmacological-psychosocial treatment for cancer-related psychological and existential stress, alleviating existential distress and promoting significant improvements in spiritual well-being, quality of life, and perspectives on death. The main limitations included the relatively small sample size and lack of national representativeness of the studied population.
Roland R Griffiths, Matthew W Johnson, Michael A Carducci, Annie Umbricht, William A Richards, Brian D Richards, Mary P Cosimano e Margaret A Klinedinst / (2016) - Journal of Psychopharmacology	A randomized, double-blind, crossover clinical trial involving 51 patients with potentially fatal cancer and a DSM-IV diagnosis including symptoms of depression and/or anxiety.	The study included two sessions of psilocybin combined with psychotherapy, comparing a high dose (22 or 30 mg/70 kg) with a low dose (1 or 3 mg/70 kg), with a 5-week interval between sessions, a 6-month follow-up, and randomization of the dose order. Depression measures (GRID-HAM-D-17), anxiety (HAM-A), cardiovascular measures, participant behavior or mood, mystical scores, state of consciousness, and transcendence of time and space were assessed using various questionnaires.	The high dose of psilocybin produced large and sustained reductions in depression and anxiety symptoms. Individuals who received the higher dose reported transformative experiences associated with positive changes in their life perspective, self- awareness, mood, relationships, and spirituality. Over 80% of participants reported moderate or greater increases in their well-being and life satisfaction. These positive effects remained consistent up to 6 months after treatment. Some transient effects, such as increased blood pressure and nausea/vomiting, were more common with the high dose. No serious adverse events were attributed to psilocybin	nder controlled conditions, with psychological support and maintaining confidentiality about the dosage, a single dose of psilocybin significantly reduced depressed mood and anxiety in patients with advanced cancer facing significant life threats. There was an improvement in quality of life and a reduction in anxiety related to death, with lasting effects for at least six months. However, the study sample was small, predominantly white, and with higher educational levels, and the crossover design of the study prevented a double-blind evaluation.

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

OBSESSIVE-COMPULSIVE DISORDER (OCD)				
Francisco A Moreno 1 , Christopher B Wiegand, E Keolani Taitano, Pedro L Delgado / (2006) - Journal Clin Psychiatry	A modified, double-blind clinical trial involving 9 participants with Obsessive-Compulsive Disorder (OCD), defined by the DSM-V, who had experienced at least one failure with SSRIs and had previously tolerated psychedelics.	Up to 4 administrations of psilocybin (with at least a 1-week Interval) were conducted, ranging from sub- hallucinogenic to hallucinogenic doses. Low (100 µg/kg), medium (200 µg/kg), and high (300 µg/kg) doses were administered in that order, with a very low dose (25 µg/kg) randomly inserted double-blind at any point after the first dose. Each session lasted 8 hours in a controlled environment at an outpatient clinic; participants were then transferred to a psychiatric unit for overnight observation. Obsessive-compulsive symptoms were assessed using the Yale-Brown Obsessive Compulsive Scale (YBOCS) and the Visual Analog Scale (VAS). Additionally, the Hallucinogen Rating Scale (HRS) was assessed and vital signs were monitored.	Of the nine patients, all showed reductions of 23 to 100% in OCD symptoms, as assessed by the YBOCS, 24 hours after administration of all doses. VAS scores also showed a significant reduction after psilocybin ingestion. Only one patient experienced transient hypertension, which was not related to anxiety or somatic symptoms. No other significant adverse effects were observed.	It is concluded that psilocybin can be used safely in patients with OCD and may be associated with acute reductions in the main symptoms of the disorder. However, a clear dose-response relationship or correlation between OCD symptom reduction and perceived psychedelic intensity was not found. Additionally, the study is limited by the small homogeneous sample, lack of a control group, short follow-up period (limited to 24 hours), and dose variability among participants.
SMOKING				
Matthew W. Johnson, Albert Garcia-Romeu, Mary P. Cosimano e Roland R. Griffiths / (2014) - Journal of Psychopharmacology	An open pilot study involving 15 psychiatrically healthy nicotine- dependent smokers.	Moderate (20 mg/70 kg) and high (30 mg/70 kg) doses of psilocybin were administered, with the first dose (moderate) given in week 5, the second dose (high) in week 7, and a third optional dose in week 13, as part of a structured 15-week smoking cessation treatment protocol. Patients underwent weekly cognitive-behavioral therapy (CBT) sessions for smoking cessation and preparation for the psilocybin experience. The day after psilocybin sessions, the experiences were discussed with the team, and support for smoking cessation was provided.	Twelve patients completed the study. 80% of participants showed biologically verified smoking abstinence throughout the 15 weeks of treatment and remained abstinent from cigarettes at the 6-month follow-up. Additionally, about 70% of participants reported that psilocybin promoted a shift in perspective, such that long-term benefits outweighed immediate cravings, strengthened their belief in their ability to quit smoking, and changed their life priorities and values. Only one participant reported that psilocybin did not help with smoking cessation. Adverse effects included acute and modest increases in blood pressure and heart rate, as well as transient fear, anxiety, and headache.	The results are promising regarding the safety of psilocybin as an adjunct in smoking cessation treatment. No definitive conclusions can be drawn about the causal role of psilocybin in smoking cessation due to the open design without a control group; however, abstinence rates were substantially higher than typical.
Matthew W. Johnson, Albert Garcia-Romeu e Roland R. Griffiths / (2017) - American Journal of Drug and Alcohol Abuse	Long-term follow-up of the above study, including abstinence outcomes at 12 months and an average of 30 months post- treatment, as well as data on persistent psychological effects at the 12-month follow-up.	n addition to the pilot study intervention, volunteers were followed for 12 months and long-term (>16 months and on average 30 months), with data from a questionnaire assessing long-term positive and negative changes, as well as personal and spiritual meaning attributed to the sessions after this period.	At the 12-month follow-up, 67% of participants were confirmed biologically as smoking abstinent, and in the long term, 60%. Additionally, at the 12-month follow- up, 86.7% rated their experiences with psilocybin among the top 5 spiritually significant experiences. There was a significant correlation between reductions in urinary cotinine levels and the mystical effects and personal meaning of the psilocybin sessions. Adverse effects were limited to mild headaches and moderate increases in blood pressure and heart rate	The results suggest that the persistent effects of psilocybin treatment extend well beyond the acute action of the drug. There was a strong association between greater success in smoking cessation and the mystical effects of psilocybin, raising questions about the role of spirituality in such situations. The findings indicate that 5HT2AR agonists may have therapeutic potential in treating various substance use disorders within a structured treatment program. However, this study has limitations due to the small sample size, open design, and lack of a control group.

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

ALCOHOLISM				
Michael P Bogenschutz, Alyssa A Forcehimes, Jessica A Pommy, Claire E Wilcox, PCR Barbosa e Rick J Strassman / (2015) - Journal of Psychopharmacology	Open-label, proof-of-concept clinical trial involving 10 volunteers with alcohol dependence according to DSM-IV and no other psychiatric disorders.	Participants underwent 4 weeks of weekly psychotherapy focused on alcohol abstinence, followed by supervised administration of 1 or 2 doses of psilocybin: the first dose of 0.3 mg/kg at week 4, and the second dose of 0.4 mg/kg at week 8, which could be a lower dose or even omitted if necessary. Various scales were used to assess abstinence, behavior, craving, mood, anxiety, and spirituality	Abstinence did not significantly increase in the first 4 weeks of treatment (before psilocybin administration), but increased significantly after psilocybin administration. The intensity of the effects varied among patients. Significant correlations were observed between measures of acute psychedelic effect intensity and changes in drinking behavior, such as changes in craving and self-efficacy in some cases. The gains were largely maintained during follow-up up to 36 weeks. There were no serious adverse events; blood pressure increased slightly, and heart rate did not change significantly.	The observed changes over time and the notable relationship between response intensity and clinical improvement provide a basis for the idea that psilocybin can promote lasting benefits in alcohol use disorder when administered under controlled conditions to carefully selected patients, in conjunction with appropriate psychosocial interventions. However, this study has limitations due to the small sample size, lack of a control group, and lack of biological verification of alcohol use.
Michael P. Bogenschutz, Stephen Ross, Snehal Bhatt, Tara Baron, Alyssa A. Forcehimes, Eugene Laska, Sarah E. Mennenga, Kelley O'Donnell, Lindsey T. Owens, Samantha Podrebarac, John Rotrosen, J. Scott Tonigan, Lindsay Worth / (2022) - JAMA Psychiatry	A double-blind, randomized clinical trial involving 95 participants diagnosed with alcohol dependence according to DSM-IV and with at least 4 days of heavy drinking prior to the study screening.	Over a 4-week period, two doses of psilocybin (25-40 mg/70 kg) were administered blindly to about half of the participants, while the other half received a placebo (diphenhydramine 50-100 mg). Psychological follow-up included cognitive-behavioral therapy techniques and motivational reinforcement. Questionnaires assessed states of consciousness and alcohol-related problems, in addition to a timeline follow- back evaluating percentage of drinking days, average daily intake, abstinence, and other factors	The percentage of days of excessive alcohol consumption during the 32-week double-blind follow-up was significantly lower in the psilocybin group (9.7%) compared to the diphenhydramine group (23.6%). The average daily alcohol consumption was also lower in the psilocybin group. This difference persisted after 8 months, with higher abstinence rates and greater reductions in WHO risk levels 1 and 3 in the psilocybin group compared to the diphenhydramine group. Participants treated with psilocybin also showed moderate to large reductions in various categories of alcohol-related problems after 5 and/or 8 months from the first medication session. Adverse effects with psilocybin included transient headaches, anxiety, and nausea, with one participant experiencing passive suicidal ideation for 15 minutes during the session. No persistent psychosis or hallucinations were reported	Psilocybin administered in combination with psychotherapy resulted in robust reductions in the percentage of days of excessive alcohol consumption compared to active placebo and psychotherapy alone. However, the study lacked adequate power to evaluate effects in subgroups, did not provide information on the duration of psilocybin effects beyond the 32-week follow-up, and did not allow for assessment of the effects of psychotherapy or the interaction between psychotherapy and medication.

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

Risk of bias assessment using the RoB 2.0 criteria

Legend: 1: Bias arising from the randomization process; 2: Bias due to deviations from intended interventions; 3: Bias due to missing outcome data; 4: Bias in measurement of the outcome; 5: Bias in selection of the reported results; LR: Low Risk of bias; SC: Some Concerns; HR: High Risk of Bias.

Article	1	2	3	4	5	Conclusions
Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study - The Lancet Psychiatry	SC	SC	LR	SC	HR	**Some concerns:** open-label study, it's not clear if the measurement or evaluation of outcomes may have differed between groups since there was no blinding, and the reported numerical results appear to have been selectively chosen.
Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms	SC	SC	LR	SC	SC	**Some concerns:** open-label study, no blinding, no details on the outcome measurement method, and whether the evaluation may have differed between intervention groups, and it is unclear if the data were selected based on multiple analyses.
Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression	SC	SC	LR	SC	SC	**Some concerns:** open-label study, no blinding. It's unclear if the measurement/evaluation of outcomes differed between groups; the authors reported results from multiple analyses (contrasts) in the amygdala, which may indicate selective outcome reporting.
Psilocybin with psychological support for treatment-resistant depression: six-month follow-up -	SC	SC	LR	SC	SC	**Some concerns:** open-label study, no blinding, no information on potential deviations from intended interventions due to the study context, and it's unclear if the outcome evaluation may have differed between intervention groups. The numerical outcome assessed appears to have been the primary planned outcome.
Therapeutic mechanisms of psilocybin: Changes in amygdala and prefrontal functional connectivity during emotional processing after psilocybin for treatment-resistant depression	SC	SC	LR	SC	SC	**Some concerns:** open-label study, no blinding of caregivers and evaluators, which may have affected the outcome, along with potential selective outcome reporting.
Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder	LR	SC	LR	LR	LR	**Low to moderate risk of bias:** concerns are related to participants and staff being aware of the assigned intervention, which may introduce some bias. However, the researchers used robust methods for randomization, allocation concealment, and blind outcome assessment, **minimizing other domains of bias risk.**
Trial of Psilocybin versus Escitalopram for Depression	LR	SC	LR	SC	SC	**Moderate risk of bias:** some concerns mainly related to participants, caregivers, and evaluators being aware of the assigned intervention, as well as unadjusted analysis of some secondary outcomes.
Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up	LR	SC	LR	LR	LR	**Low risk of bias:** some concerns related to participants' awareness of the intervention received and the lack of mention of a pre-specified analysis plan.
Single-dose psilocybin for a treatment-resistant episode of major depression: Impact on patient-reported depression severity, anxiety, function, and quality of life	LR	SC	LR	SC	LR	**Low risk of bias:** concerns related to the fact that caregivers and staff were aware of the assigned intervention, and it is possible that the measurement or evaluation of outcomes differed between groups due to the nature of the intervention.
Single-Dose Psilocybin Treatment for Major Depressive Disorder	LR	SC	LR	LR	LR	**Low risk of bias:** concerns related to the potential for reduced blinding due to the use of niacin as an active placebo. **However, the measures taken to minimize other types of bias, such as blind outcome assessment, largely offset this limitation.**
Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer	LR	SC	LR	SC	SC	**Moderate risk of bias:** some concerns related to allocation concealment, knowledge of the intervention by participants and staff, possible differences in outcome measurement between groups, and lack of information about the pre-specified analysis plan.
Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial	LR	SC	LR	LR	LR	**Low risk of bias:** only a few concerns as participants, caregivers, and intervention staff were aware of the assigned intervention.

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial	LR	LR	LR	LR	LR	**Low risk of bias:** raises concerns only about the lack of information on a **pre-specified analysis plan for outcome selection.**
Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction	SC	SC	LR	SC	HR	**Some concerns:** open-label study, lacking some details on deviations from interventions and outcome measures. The numerical outcome evaluated was likely selected based on the results of multiple eligible measurements or analyses.
Long-term Follow-up of Psilocybin-facilitated Smoking Cessation	SC	SC	LR	SC	LR	**Moderate risk of bias:** concerns related to the randomization process and allocation concealment, lack of information on deviations from intended interventions, and the possible awareness of outcome evaluators about the intervention received by participants.
Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study	SC	SC	LR	SC	SC	**Some concerns:** the authors used a variety of self-report measures, some of which may have been influenced by the participants' awareness of the intervention received. The study does not mention a pre-specified protocol or analysis plan, so the possibility of selective outcome reporting cannot be ruled out.
Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder	LR	LR	LR	LR	LR	**Low risk of bias:** the overall assessment indicates that this randomized study presents a low risk of bias across all analyzed domains, which provides confidence in the internal validity and robustness of the results presented.

References

1. Horton DM, Morrison B, Schmidt J (2021) Systematized Review of Psychotherapeutic Components of Psilocybin-Assisted Psychotherapy. Am J Psychother 74(4): 140-149.
2. Nichols DE (2020) Psilocybin: from ancient magic to modern medicine. J Antibiot (Tokyo) 73(10): 679-686.
3. Rucker JJ, Jelen LA, Flynn S, Frowde KD, Young AH (2016) Psychedelics in the treatment of unipolar mood disorders: a systematic review. J Psychopharmacol 30(12): 1220-1229.
4. Kazahaya D, Oliver R, Tófoli LF (2023) Teonanácatl: pode um cogumelo psicodélico interessar ao psicanalista? Lacuna: uma revista de psicanálise, São Paulo.
5. Griffiths RR, Johnson MW, Carducci MA, Annie U, William AR, et al. (2016) Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. J Psychopharmacol 30(12): 1181-1197.
6. Grob CS, Danforth AL, Chopra GS, Marycie H, Charles RM, et al. (2011) Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry 68(1): 71-78.
7. Ross S, Bossis A, Guss J, Gabrielle AL, Tara M, et al. (2016) Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol 30(12): 1165-1180.
8. Johnson MW, Griffiths RR (2017) Potential Therapeutic Effects of Psilocybin. Neurotherapeutics 14(3): 734-740.
9. Byock I (2018) Taking Psychedelics Seriously. J Palliat Med 21(4): 417-421.
10. Reiff CM, Richman EE, Nemeroff CB, Linda LC, Alik SW, et al. (2020) Psychedelics and Psychedelic-Assisted Psychotherapy. American Journal of Psychiatry 177(5): 391-410.
11. Gattuso JJ, Perkins D, Ruffell S, Andrew JL, Daniel H, et al. (2023) Default Mode Network Modulation by Psychedelics: A Systematic Review. Int J Neuropsychopharmacol 26(3): 155-188.
12. Moliner R, Girych M, Brunello CA, Vera K, Caroline B, et al. (2023) Psychedelics promote plasticity by directly binding to BDNF receptor TrkB. Nat Neurosci 26(6): 1032-1041.
13. de Veen BT, Schellekens AF, Verheij MM, Homberg JR (2017) Psilocybin for treating substance use disorders?. Expert Rev Neurother 17(2): 203-212.
14. Nutt DJ, King LA, Phillips LD (2010) Drug harms in the UK: a multicriteria decision analysis. Lancet 376(9752): 1558-1565.
15. Goel DB, Zilate S (2022) Potential Therapeutic Effects of Psilocybin: A Systematic Review. Cureus 14(10): e30214.
16. Kramer EN, Reddy K, Shapiro B (2023) A suicide attempt following psilocybin ingestion in a patient with no prior psychiatric history. Psychiatry Res Case Rep 2(1): 100118.
17. Hendin HM, Penn AD (2021) An episode of mania following self-reported ingestion of psilocybin mushrooms in a woman previously not diagnosed with bipolar disorder: A case report. Bipolar Disord 23(7): 733-735.
18. Halim HJ, Burk BG, Fargason RE, Birur B (2023) Manic episode following psilocybin use in a man with bipolar II disorder: a case report. Front Psychiatry 14: 1221131.
19. Honyiglo E, Franchi A, Cartiser N, Charline B, Anne Sophie A, et al. (2019) Unpredictable Behavior Under the Influence of "Magic Mushrooms": A Case Report and Review of the Literature. J Forensic Sci 64(4): 1266-1270.
20. Mottillo S, Filion KB, Bélisle P, Lawrence J, André Gervais, et al. (2009) Behavioural interventions for smoking cessation: a meta-analysis of randomized controlled trials. Eur Heart J 30(6): 718-730.
21. Carhart-Harris RL, Goodwin GM (2017) The Therapeutic Potential of Psychedelic Drugs: Past, Present, and Future. Neuropsychopharmacol 42(11): 2105-2113.
22. MacCallum CA, Lo LA, Pistawka CA, Deol JK (2022) Therapeutic use of psilocybin: Practical considerations for dosing and administration. Front Psychiatry 13: 1040217.
23. Irizarry R, Winczura A, Dimassi O, Dhillon N, Minhas A, et al. (2021) Psilocybin as a Treatment for Psychiatric Illness: A Meta-Analysis. Cureus 14(11): e31796.

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

24. Carhart-Harris RL, Roseman L, Haijen E, David E, Rosalind W, et al. (2018) Psychedelics and the essential importance of context. J Psychopharmacol 32(7): 725-731.

25. (2023) Depressive disorder (depression).

26. Mertens LJ, Wall MB, Roseman L, Demetriou L, Nutt DJ, et al. (2020) Therapeutic mechanisms of psilocybin: Changes in amygdala and prefrontal functional connectivity during emotional processing after psilocybin for treatment-resistant depression. J Psychopharmacol 34(2): 167-180.

27. Kolovos S, van Tulder MW, Cuijpers P, Amelie P, Karine C, et al. (2017) The effect of treatment as usual on major depressive disorder: A meta-analysis. J Affect Disord 210: 72-81.

28. Kolovos S, van Tulder MW, Cuijpers P, Amelie P, Karine C, et al. (2017) The effect of treatment as usual on major depressive disorder: A meta-analysis. J Affect Disord 210: 72-81.

29. van der Meer PB, Fuentes JJ, Kaptein AA, Jan WS, Marleen MW, et al. (2023) Therapeutic effect of psilocybin in addiction: A systematic review. Front Psychiatry 14: 1134454.

30. Yu CL, Yang FC, Yang SN, Ping-Tao T, Brendon S, et al. (2021) Psilocybin for End-of-Life Anxiety Symptoms: A Systematic Review and Meta-Analysis. Psychiatry Investig 18(10): 958-967.

31. Tedesco S, Gajaram G, Chida S, Arham A, Meghan P, et al. (2021) The Efficacy of MDMA (3,4-Methylenedioxymethamphetamine) for Post-traumatic Stress Disorder in Humans: A Systematic Review and Meta-Analysis. Cureus 13(5): e15070.

32. Albuquerque TR, Macedo LFR, Delmondes GA, Modesto LRN, Theles MA, et al. (2022) Evidence for the beneficial effect of ketamine in the treatment of patients with post-traumatic stress disorder: A systematic review and meta-analysis. J Cereb Blood Flow Metab 42(12): 2175-2187.

33. Du R, Han R, Niu K, Jiaqiao X, Zhiou Z, et al. (2022) The Multivariate Effect of Ketamine on PTSD: Systematic Review and Meta-Analysis. Front Psychiatry 13: 813103.

34. Harris RLC, Bolstridge M, Rucker J, Camilla MJ Day, David E, et al. (2016) Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 3: 619-627.

35. Carhart-Harris RL, Roseman L, Bolstridge M, Lysia D, Nienke JP, et al. (2017) Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Sci Rep 7(1): 13187.

36. Roseman L, Demetriou L, Wall MB, David JN, Robin LCH, et al. (2018) art-Harris, Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression. Neuropharmacology 142: 263-269.

37. Carhart-Harris RL, Bolstridge M, Day CMJ, et al. (2018) Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology (Berl) 235(2): 399-408.

38. Davis AK, Barrett FS, May DG, Mary PC, Nathan DS, et al. (2021) Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry 8(5): 481-489.

39. Gukasyan N, Davis AK, Barrett FS, Mary PC, Nathan DS, et al. (2022) Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. J Psychopharmacol 36(2): 151-158.

40. Mulders PC, van Eijndhoven PF, Pluijmen J, Schene AH, Tendolkar I, et al. (2016) Default mode network coherence in treatment-resistant major depressive disorder during electroconvulsive therapy. J Affect Disord 205: 130-137.

41. Qasim S, Zaheer Z, Youshay MJ, Shad MU (2023) Neurobiological Correlates of Psilocybin Response in Depression. Prim Care Companion CNS Disord 25(3): 22r03419.

42. Harris RC, Giribaldi B, Watts R, Michelle BJ, Ashleigh MB, et al. (2021) Trial of Psilocybin versus Escitalopram for Depression. New England J Med 384(15): 1402-1411.

43. Raison CL, Sanacora G, Woolley J, Keith H, Boadie WD, et al. (2023) Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial. JAMA 330(9): 843-853.

44. Qasim S, Zaheer Z, Youshay MJ, Shad MU (2023) Neurobiological Correlates of Psilocybin Response in Depression. Prim Care Companion CNS Disord 25(3): 22r03419.

45. Vargas AS, Luís A, Barroso M, Gallardo E, Pereira L (2020) Psilocybin as a New Approach to Treat Depression and Anxiety in the Context of Life-Threatening Diseases-A Systematic Review and Meta-Analysis of Clinical Trials. Biomedicines 8(9): 331.

46. Grob CS, Danforth AL, Chopra GS, Marycie H, Charles RM, et al. (2011) Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer. Arch Gen Psychiatry 68(1): 71-78.

47. Shalev A, Liberzon I, Marmar C (2017) Post-Traumatic Stress Disorder. N Engl J Med 376(25): 2459-2469.

48. Elsouri KN, Kalhori S, Colunge D, Grant G, George H, et al. (2022) Psychoactive Drugs in the Management of Post Traumatic Stress Disorder: A Promising New Horizon. Cureus 14(5): e25235.

49. Watkins LE, Sprang KR, Rothbaum BO (2018) Treating PTSD: A Review of Evidence-Based Psychotherapy Interventions. Front Behav Neurosci 12: 258.

50. Goetter EM, Bui E, Ojserkis RA, Zakarian RJ, Brendel RW, et al. (2015) A Systematic Review of Dropout From Psychotherapy for Posttraumatic Stress Disorder Among Iraq and Afghanistan Combat Veterans [published correction appears in J Trauma Stress 28(5): 401-409.

51. Krediet E, Bostoen T, Breeksema J, van Schagen A, Passie T, Vermetten E (2020) Reviewing the Potential of Psychedelics for the Treatment of PTSD. Int J Neuropsychopharmacol 23(6): 385-400.

52. Stein DJ, Costa DLC, Lochner C, Nanthia S, Daniel ANB, et al. (2019) Obsessive-compulsive disorder. Nat Rev Dis Primers 5(1): 52.

53. Hirschtritt ME, Bloch MH, Mathews CA (2017) Obsessive-Compulsive Disorder: Advances in Diagnosis and Treatment. JAMA 317(13): 1358-1367.

54. Leonard HL, Rapoport JL (1987) Relief of obsessive-compulsive symptoms by LSD and psilocin. Am J Psychiatry 144(9): 1239-1240.

55. Moreno FA, Delgado PL (1997) Hallucinogen-induced relief of obsessions and compulsions. Am J Psychiatry 154(7): 1037-1038.

56. Wilcox JA (2014) Psilocybin and Obsessive Compulsive Disorder. J Psychoactive Drugs 46(5): 393-395.

57. Buot A, Pallares C, Oganesyan A, Charles D, Valerie B, et al. (2023) Improvement in OCD symptoms associated with serotoninergic psychedelics: a retrospective online survey. Sci Rep 13(1): 13378.

58. Moreno FA, Wiegand CB, Taitano EK, Delgado PL (2006) Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J Clin Psychiatry 67(11): 1735-1740.

59. Chiara G Di (2000) Role of dopamine in the behavioural actions of nicotine related to addiction. Eur J Pharmacol 393(1-3): 295-314.

60. Oberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A (2011) Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. Lancet 377(9760):

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

139-146.

61. Cahill K, Stevens S, Perera R, Lancaster T (2013) Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013(5): CD009329.

62. Livingstone-Banks J, Norris E, Hartmann-Boyce J, West R, Jarvis M, et al. (2019) Relapse prevention interventions for smoking cessation. Cochrane Database Syst Rev 2(2): CD003999.

63. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR (2014) Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol 28(11): 983-992.

64. Garcia-Romeu A, Davis AK, Erowid F, Erowid E, Griffiths RR, et al. (2019) Cessation and reduction in alcohol consumption and misuse after psychedelic use. J Psychopharmacol 33(9): 1088-1101.

65. Johnson MW, Garcia-Romeu A, Griffiths RR (2017) Long-term follow-up of psilocybin-facilitated smoking cessation [published correction appears in Am J Drug Alcohol Abuse 43(1): 127.

66. Smith JP, Randall CL (2012) Anxiety and alcohol use disorders: comorbidity and treatment considerations. Alcohol Res 34(4): 414-431.

67. Kattimani S, Bharadwaj B (2013) Clinical management of alcohol withdrawal: A systematic review. Ind Psychiatry J 22(2): 100-108.

68. Alcohol's Effects on Health (2024) Treatment for Alcohol Problems: Finding and Getting Help. National Institute on Alcohol Abuse & Alcoholism.

69. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, et al. (2015) Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol 29(3): 289-299.

70. Bogenschutz MP, Ross S, Bhatt S, Tara B, Alyssa AF, et al. (2022) Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial. JAMA Psychiatr 79(10): 953-962.

71. Goodwin GM, Aaronson ST, Alvarez O, Merve A, James CB, et al. (2023) Single-dose psilocybin for a treatment-resistant episode of major depression: Impact on patient-reported depression severity, anxiety, function, and quality of life. J Affect Disorder 327: 120-127.

72. Kautzky A, Melich PB, Kranz GS, et al. (2017) A New Prediction Model for Evaluating Treatment-Resistant Depression. J Clin Psychiatry 78(2): 215-222.

73. Barrett FS, Preller KH, Kaelen M (2018) Psychedelics and music: neuroscience and therapeutic implications. Int Rev Psychiatry 30(4): 350-362.

74. Hovmand OR, Poulsen ED, Arnfred S, Storebø OJ (2023) Risk of bias in randomized clinical trials on psychedelic medicine: A systematic review. J Psychopharmacol 37(7): 649-659.

75. Matthew WJ, Albert Garcia-R, Roland RG (2017) Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse 43(1): 55-60.

76. Depressive disorder (depression) (2023).

77. Goodman WK, Storch EA, Sheth SA (2021) Harmonizing the Neurobiology and Treatment of Obsessive-Compulsive Disorder. Am J Psychiatry 178(1): 17-29.

78. Yerubandi A, Thomas JE, Bhuiya NMMA, Harrington C, Villa Zapata L, et al. (2024) Acute Adverse Effects of Therapeutic Doses of Psilocybin: A Systematic Review and Meta-Analysis. JAMA Netw Open 7(4): e245960.

79. Sterne JAC, Savović J, Page MJ, Roy GE, Natalie SB, et al. (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366: l4898.

80. Banushi B, Polito V (2023) A Comprehensive Review of the Current Status of the Cellular Neurobiology of Psychedelics. Biology (Basel) 12(11): 1380.

81. Fogg C, Michaels TI, de la Salle S, Jahn ZW, Williams MT (2021) Ethnoracial health disparities and the ethnopsychopharmacology of psychedelic-assisted psychotherapies. Experimental and Clinical Psychopharmacology 29(5): 539-554.

82. Matthew BW, Cynthia L, Natalie E, Mendel K, Leor R, et al. (2023) Increased low-frequency brain responses to music after psilocybin therapy for depression. J Affect Disorder 333: 321-330.

83. Skosnik PD, Sloshower J, Safi-Aghdam H, Pathania S, Syed S, et al. (2023) Sub-acute effects of psilocybin on EEG correlates of neural plasticity in major depression: Relationship to symptoms. J Psychopharmacol 37(7): 687-697.

84. Agrawal M, Richards W, Beaussant Y, Shnayder S, Ameli R, et al. (2024) Psilocybin-assisted group therapy in patients with cancer diagnosed with a major depressive disorder. Cancer 130(7): 1137-1146.

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852

DOI: 10.19080/JCMAH.2024.12.555852

How to cite this article: Danielle B R, Victor HA S, Renato GC L. Use of Psilocybin in the Treatment of Mental Disorders: Systematic Review of Clinal Trials. J Complement Med Alt Healthcare. 2024; 13(1): 555852. DOI: 10.19080/JCMAH.2024.12.555852