Journal of Advances in Medicine and Medical Research

Volume 36, Issue 8, Page 53-62, 2024; Article no.JAMMR.119044
ISSN: 2456-8899, NLM ID: 101711724
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

PTSD Treatment: An Inquiry into the Promising Potential of Psilocybin

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: https://doi.org/10.9734/jammr/2024/v36i85525

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/119044

Review Article

Received: 17/05/2024
Accepted: 19/07/2024
Published: 24/07/2024

ABSTRACT

Post-Traumatic Stress Disorder (PTSD) is a debilitating mental health condition that can occur after experiencing or witnessing a traumatic event. The impact of PTSD extends beyond the individual, affecting families, communities, and society as a whole. This study aims to investigate

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Cite as: *Folorunsho, Ibrahim L., Nkechinyere Mary Harry, Chukwubueze Obiajunwa, Oluwatosin Arubuolawe, Adeniyi Kayode Busari, Chidalu Ibeneme, and Gibson O. Anugwom. 2024. "PTSD Treatment: An Inquiry into the Promising Potential of Psilocybin". Journal of Advances in Medicine and Medical Research 36 (8):53-62. https://doi.org/10.9734/jammr/2024/v36i85525.*

the potential of psilocybin as a treatment for PTSD. Psilocybin, after being metabolized to psilocin, binds to various serotonergic receptors to exert some major effects such as a reduction in negative mood and an increase in optimism, enhanced ability for introspection and perceptual changes, a reduction in amygdala reactivity during emotion processing, and—as has been found in animal studies—an extinction of the fear response and increased hippocampal neurogenesis. However, psychedelics such as psilocybin may lead to brief episodes of nausea, vomiting, and physical discomfort. This study indicated that there is an urgent need for innovative therapies that could enhance the effectiveness of PTSD treatments. As this review highlights, psilocybin and some other psychedelics offer prospects for an additional method of treating PTSD. They have the potential to directly address PTSD symptoms and can also be used as an adjunct to psychotherapy.

Keywords: Post-traumatic stress disorder nausea; vomiting; psychotherapy; mental health.

1. INTRODUCTION

Post-Traumatic Stress Disorder (PTSD) is a debilitating mental health condition that can occur after experiencing or witnessing a traumatic event. According to the Diagnostic and Statistical Manual of Mental Disorders [1], PTSD is characterized by intrusive thoughts, avoidance behaviors, negative alterations in cognition and mood, and hyperarousal symptoms. These symptoms can significantly impair an individual's daily functioning and quality of life. PTSD has a substantial global impact, affecting individuals from various backgrounds and ages, including military personnel, first responders, and survivors of abuse, accidents, or natural disasters [2]. The impact of PTSD extends beyond the individual, affecting families, communities, and society as a whole. Individuals with PTSD often experience difficulties in interpersonal relationships, social functioning, and occupational performance [3]. It is also associated with an increased risk of comorbid conditions such as depression, substance abuse, and physical health problems, resulting in a substantial economic burden on healthcare systems and lost productivity [4].

Traditional treatments for PTSD have primarily focused on psychotherapy and pharmacotherapy. Cognitive-behavioral therapies (CBT), such as prolonged exposure therapy and cognitive processing therapy, have been widely used to help individuals process traumatic memories and restructure maladaptive thoughts and beliefs [5]. However, these approaches have limitations, including high dropout rates, limited efficacy for some individuals, and the potential for symptom exacerbation during exposure-based treatments [6]. Pharmacological interventions, such as selective serotonin reuptake inhibitors (SSRIs) and other antidepressants, sympatholytic or nightmare-suppressing treatments such as alpha blockers (e.g. prazosin) or topiramate, have also been utilized in the management of PTSD symptoms. While these medications can provide symptomatic relief, they often have limited efficacy in addressing the underlying traumatic memories and may be associated with significant adverse effects [7].

In recent years, there has been a growing interest in exploring novel and innovative approaches to PTSD treatment, particularly psychedelic-assisted therapies [8,9]. Psychedelics, such as psilocybin (the active compound in magic mushrooms), have shown promising potential in various clinical trials and research studies [10]. Psychedelics include psilocybin, lysergic acid diethylamide (LSD), Mescaline, 3,4-methylenedioxymethamphetamine (MDMA), N, N-dimethyltryptamine (DMT), etc. Psychedelics typically have agonistic properties at the 5-HT2_A receptor [11]. Psilocybin, a naturally occurring psychedelic compound, potentially reduces symptoms of PTSD, depression, and anxiety. Psilocybin-assisted therapy is believed to promote neuroplasticity, facilitate the processing of traumatic experiences, and foster psychological flexibility and emotional regulation [12].

While the use of psychedelics in therapeutic settings is still in its early stages, the emerging research has sparked renewed interest and debates within the scientific community and broader society. Proponents argue that these substances, when used in controlled and supervised settings, may offer novel and potentially more effective treatments for individuals suffering from PTSD and other mental health conditions that have been resistant to conventional treatments [13,10].

The recent decision by the U.S. Food and Drug Administration (FDA) to reject 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for PTSD treatment [14] highlights the challenges in developing novel therapies. On June 4, 2024, the Psychopharmacologic Drugs Advisory Committee of the U.S. FDA voted against the application, citing concerns regarding efficacy, safety, and human abuse potential. Specifically, the FDA raised issues with expectation bias, durability of treatment, and the role of psychotherapy in assessing efficacy. Additionally, the agency expressed concerns about inadequate safety data, limited clinical trial data, and the lack of information on MDMA's positive effects. This ruling underscores the need for continued research on psychedelic treatments, such as utilization of psilocybin in the treatment of PTSD.

Hence, the objective of this review article is to critically examine the potential of psychedelic-assisted therapies, specifically psilocybin as novel and promising treatments for PTSD. Since many individuals with PTSD continue to experience persistent symptoms despite the availability of traditional therapies, this highlights the need for more effective and innovative treatment approaches. By conducting a literature review, this study aims to synthesize the existing evidence from clinical trials and research studies to critically examine the utilization, efficacy, challenges, risks, and ethical considerations associated with psychedelic-assisted therapies for PTSD. Ultimately, the goal is to contribute to the ongoing discourse and provide insights that can inform future research directions and the development of novel therapeutic interventions for individuals suffering from this debilitating mental health condition.

2. PSYCHEDELICS: A BRIEF HISTORY AND THERAPEUTIC POTENTIAL

Native Americans have been using psychedelics for millennia; the first documented usage of these plants' dates to 5700 years ago, and they were utilized in sacred ceremonies in Northeastern Mexico [15]. Psychedelics were introduced to the western world by Arthur Heffner when he separated mescaline components from peyote cactus in 1897. In 1938, Albert Hoffman produced lysergic acid diethylamide (LSD). In 1958, Albert Hoffman also extracted and produced psilocybin [16,17]. The LIFE Magazine first used the term "magic mushrooms" in 1957 [18]. There was a rather open approach to the usage and regulation of magic mushrooms, LSD and mescaline until 1967, when the United Nations designated all psychedelics as Schedule I drugs, thereby removing them from the market and making them almost impossible to purchase [19]. This was due to illicit use and a larger amount of the population misusing and abusing it, questioning their effectiveness and safety.

The early 1990s saw a resurgence in interest in psychedelics [20]. According to a 2006 study [21], those who had psychedelic experiences said they were among the top five most significant, meaningful, and influential events of their lives, ranking on par with the birth of a child. Subsequently, psychedelic research has progressively resumed. There are currently over 60 ongoing psilocybin clinical trials overseen by the United States National Institute of Health [22].

Psychedelics tend to modify or enhance sensory feelings, mental activities, and agility [23]. Psilocybin, a natural psychedelic, can be found in a few hundred different species of mushrooms, some of which the Mesoamerican Mayan and Aztec societies employed for spiritual and medicinal purposes. Other naturally occurring psychedelics are DMT (included in ayahuasca) and mescaline (found in peyote and San Pedro cactus). Some chemicals, like MDMA and LSD, are synthetic and were found during pharmaceutical development efforts [24,23]. Psilocybin ($C_{12}H_{17}N_2O_4P$), the active component of magic mushrooms, is an organic phosphate and a tryptamine alkaloid, a tertiary amino acid. Over 200 species of *Basidiomycota* mushrooms have active psilocybin in their caps and stems, which is where tryptamines, which are generated from the amino acid tryptophan, are present [19].

In the western paradigm, the precise long-term medical usefulness of psilocybin in treating mental health issues is still unknown because many clinical trials involving the drug are still in the early stages of development. Yet, early research indicates that psilocybin treatments are successful in treating a variety of conditions, including depression [25,26], Obsessive-Compulsive Disorder (OCD) [27], tobacco use disorder [28,29], and alcohol use disorder [30]. Furthermore, a group of researchers [31] observed a statistically significant improvement in demoralization among elderly long-term AIDS survivors with psilocybin-assisted group therapy.

3. NEUROBIOLOGICAL MECHANISMS OF PTSD AND THE POTENTIAL ROLE OF PSILOCYBIN IN TREATMENT

Uncertainty surrounds the precise processes by which psychedelics alter perception and cognition. However, they may involve heightened functional connectivity among various brain regions and decreased activity in the brain's default mode network. Trauma and possible genetic predisposition cause changes in the neural networks (cingulate, insular, prefrontal cortex, amygdala, and hippocampus) that involve the monoamine neurotransmitters, such as serotonin, dopamine, and glutamate, in PTSD. These network changes then affect the endocrine and autonomic nervous systems, leading to the subjective and physiological symptoms of PTSD. The most noticeable impacts of psychedelic-assisted therapy are at the subjective and neural network levels of this process [11].

The amygdala is a crucial limbic component that mediates fear reactions and emotional processing. The brainstem and subcortical motor structures receive an emotional reaction produced by the amygdala, which then determines the appropriate reflex or motor response, such as facial expressions or a startle reaction. In PTSD patients, the amygdala responds more intensely to both neutral and emotional cues, potentially leading to irritation, aggression, and heightened vigilance. The endocrine system disruption in PTSD does not consistently show changes in cortisol levels. However, people with PTSD often exhibit decreased cortisol in response to prolonged stress, which can cause dysregulation of the negative feedback loop between the HPA axis and cortisol production. This is predicted to result in aberrant fear processing and stress encoding [32].

Psychedelic drugs primarily act as nonselective serotonin agonists, and their psychotropic effects are largely associated with agonism of the 5-hydroxytryptamine 2_A (5-$HT2_A$) receptor subtype. The 5-$HT2_A$ receptor, a G protein-coupled receptor (GPCR), preferentially couples with a Gq-protein, thereby inducing the activation of phospholipase C. This initiates a signaling cascade that ultimately activates protein kinase C and mobilizes calcium from intracellular stores [33]. As with other classical psychedelics, the behavioral effects of psilocybin are partly attributable to its agonist activity at the 5-$HT2_A$ receptor. However, the mechanisms behind its full range of effects remain unclear. Psilocybin is a substituted indolealkylamine with limited affinity for dopamine D2 receptors and a variety of actions mediated by the serotonin system. It belongs to the structural class of traditional psychedelics, which includes an indole ring and is based on the tryptamine structure. Its agonist actions at 5-$HT2_A$ serotonin receptors are linked to symptoms such as mydriasis, a decreased threshold for knee reflex, elevated blood pressure and heart rate, and nausea. Visual and auditory hallucinations, distortion of sensory inputs, altered temporal perception, and changed body image are some of the ways it can affect mood and feelings. Due to its capacity to resemble psychotic experiences, it was classified, alongside LSD, as a psychotomimetic. Its introspective and frequently enhanced receptivity to guidance and psychotherapy effects led to its use in psychotherapy and studies conducted by psychologists and psychiatrists [34].

4. PSILOCYBIN-ASSISTED PSYCHOTHERAPY FOR PTSD

Psychopharmacology has benefited many with psychiatric disorders, though drugs often fall short of resulting in a cure. Medications can help decrease symptoms, but long-term use has drawbacks. Psychotherapy, especially for PTSD, can be more effective than drugs, but some patients do not respond adequately [35]. Current treatment guidelines for PTSD recommend trauma-focused Cognitive Behavioral Therapy (TF-CBT) and Eye Movement Desensitization and Reprocessing (EMDR) as first-line treatments. However, up to two-thirds do not respond, possibly due to trauma's impact on the patient-therapist alliance [6]. Access to these treatments is also challenging, as many clinicians lack training. Thus, research into new or combination PTSD treatments is needed [36].

Psilocybin, after being metabolized to psilocin [36], binds to various serotonergic receptors [37] to exert the following effects: a reduction in negative mood and an increase in optimism [38], enhanced ability for introspection and perceptual changes [39], a reduction in amygdala reactivity during emotion processing [40], and—as has been found in animal studies—an extinction of the fear response and increased hippocampal neurogenesis [41]. This is especially important because research has shown that PTSD patients often experience increased amygdala

stimulation. Other acute therapeutic effects of classical psychedelics like psilocybin include enhanced insightfulness, greater acceptance, increased emotional empathy, and transformative emotional experiences. These effects have been demonstrated to be crucial mediators in the long-term psychological change observed in various mental illnesses [11]. Some drivers for inquiry into its use in PTSD include its success with reducing depressive symptoms in patients with Major Depressive Disorder and in cancer patients with comorbid depression [42]. Additionally, it has been shown to reduce suicidal ideation [43].

Starting in the 1960s, psychedelic research was largely abandoned in the United States due to regulatory concerns [44]. However, an agreement was reached between the National Institute on Drug Abuse and the FDA in 1992, which facilitated the resumption of clinical research with classical psychedelics [45]. In the year 2000, a group of Johns Hopkins researchers was the first to obtain regulatory approval in the United States to resume research with psychedelics in healthy volunteers who had no previous experience with psychedelics [46]. Again, in 2021, Johns Hopkins Medicine received the first federal grant for psychedelic research in 50 years [47].

Encouraging results from clinical trials of psilocybin-assisted therapy (PAT) for depression [12] and anxiety [32] suggest that PAT may effectively treat PTSD, given the high comorbidity and symptom overlap between PTSD, depression, and anxiety. A pilot study examining psilocybin-assisted therapy for veterans with PTSD has therefore been proposed to evaluate the safety and efficacy of this approach [12]. It will take place within the Wexner Medical Center at The Ohio State University (OSU) in Columbus, Ohio, USA. The aim is to provide insights into the use of psilocybin in treating PTSD and its effectiveness in improving symptoms in veteran populations.

The efficacy and safety of psilocybin has been demonstrated in proof-of-concept trials for the treatment of alcohol and tobacco addiction [30,29], major and treatment-resistant depression [48,49,50], and depression in end of life care [21,38,51]. Preliminary studies on the efficacy of this approach in PTSD have been encouraging, though further research is needed. When administered within the correct set and setting, psilocybin may temporarily increase anxiety, fear, heart rate, and blood pressure. Acute adverse effects such as nausea and mild headaches may also be reported [30,52]. Without careful oversight, these reactions could lead to dangerous behavior like fleeing the study site [53].

The therapeutic protocols used in psilocybin-assisted psychotherapy typically involve a series of preparation sessions, a psilocybin session, and integration sessions [35,51]. Preparation sessions are crucial to build rapport and trust, which helps reduce the risk of fear or anxiety during psilocybin sessions [12]. In these sessions, the participant's life history, current situation, intentions, and expectations for the psilocybin session are discussed. Side effects and skills for navigating these experiences are also covered [12].

According to a recently proposed proof-of-concept trial [12], the psilocybin session unfolds as follows. Psilocybin is administered in opaque capsules with water. Participants are encouraged to lie on a couch, wear eyeshades, and listen to music. Vital signs and symptoms are assessed at regular intervals. Acute anxiety is handled with reassurance and appropriate treatment if needed. This usually takes 8 hours. At the end, participants complete questionnaires to assess acute subjective experiences, such as mystical experience [54], psychological insight [12], and challenging experience [55]. Participants also write a narrative description of the psilocybin session before their next in-person meeting [12]. Integration strategies, such as journaling, meditation, and group therapy, are used to facilitate the processing of emotions and insights gained during the psilocybin experience [26].

5. CHALLENGES AND LIMITATIONS

Federal and state laws have historically restricted research into therapeutic uses of psychedelic drugs for mental illness, largely due to the perception that these drugs pose greater risks than benefits. However, a recent shift in policies has created new opportunities for exploring the use of psychoactive drugs like psilocybin in treating PTSD [56].

Psychedelics such as psilocybin may lead to brief episodes of nausea, vomiting, and physical discomfort. They can also induce anxiety and confusion. Post-therapy, patients may exhibit emotional vulnerability, emphasizing the need for psychological support. Moreover, they can cause

tachycardia and hypertension, making them unsuitable for individuals with severe cardiovascular conditions. If taken inappropriately outside of clinical setting, there is a risk of developing severe psychosis and triggering schizophrenia in individuals with an underlying predisposition. Nevertheless, when administered under proper medical supervision, they are generally safe, non-addictive, and do not cause significant adverse effects [11].

While the potential of psilocybin in treating PTSD is promising, previous research lacks clarity and precision, and there is paucity of PTSD-specific clinical trials. Also, certain molecular aspects of the mechanism of psilocybin, like other psychedelics, is not fully understood.

6. CONCLUSION

The prevalence of PTSD ranges from 6-8% in the general public and is significantly higher among veterans. Symptoms can include intrusive thoughts, phobic avoidance, hyperarousal, hypervigilance, irritability, anger, and depression. Conventional treatments typically involve trauma-focused cognitive behavioral therapy and/or medication. While around two-thirds of patients have responded to traditional pharmacotherapy, remission has been observed in 40% or fewer patients. As a result, there is growing interest in researching alternative options such as psilocybin [56]. It should be noted that other factors including comorbidities influence patients' response to traditional PTSD treatments [11]. The details of these factors are beyond the scope of this study.

Psychotherapy is strongly considered as a first-line treatment for PTSD [11]. According to the American Psychological Association, four interventions are strongly recommended for the treatment of PTSD, all of which are variations of Cognitive Behavioral Therapy. However, PTSD often persists as a chronic condition with high rates of psychological and medical comorbidities. There is an urgent need for innovative therapies that could enhance the effectiveness of PTSD treatments. As this review highlights, psilocybin and some other psychedelics offer prospects for an additional method of treating PTSD. They may swiftly and directly address PTSD symptoms and can also be used as an adjunct to conventional psychotherapy.

The current research suggests that psychedelics like psilocybin hold therapeutic potential for individuals suffering from PTSD. Further research is needed to establish the safety and efficacy of psilocybin and identify the patient profiles for whom these treatments might be most effective. Future studies should review and overcome the methodological and conceptual constraints present in the current literature. They should strive to evaluate the effects of these psychedelics on the neural connectivity and neuroanatomy of PTSD patients. Moreover, future research should focus on evaluating the long-term impacts of these treatment modalities.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/119044