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Clinical potential of psilocybin as a treatment for mental health conditions

Jeremy Daniel, PharmD, BCPS, BCPP[1]
Margaret Haberman, PharmD, BCPP[2]

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Abstract

Psilocybin, a classic hallucinogen, is a chemical produced by more than 100 species of mushrooms worldwide. It has high affinity for several serotonin receptors, including 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}, located in numerous areas of the brain, including the cerebral cortex and thalamus. With legislation introduced in 1992, more work is being done to further understand the implications of psilocybin use in a number of disease states. Certain mental health disease states and symptoms have been studied, including depressed mood, anxiety disorders, obsessive-compulsive disorder, alcohol use disorder, and tobacco use disorder. This article provides an in-depth review of the study design and results of psilocybin in each of these conditions and discusses the clinical potential for use.

Keywords: hallucinogen, psilocybin, tobacco, addiction, depression, anxiety, psychedelic, obsessive-compulsive disorder, alcohol

[1] (Corresponding author) Assistant Professor, South Dakota State University College of Pharmacy, Sioux Falls, South Dakota; Psychiatric Clinical Pharmacist, Avera Behavioral Health Center, Sioux Falls, South Dakota, Jeremy.Daniel@avera.org, ORCID: http://orcid.org/0000-0002-2172-410X; [2] Psychiatric Clinical Pharmacist, Avera Behavioral Health Center, Sioux Falls, South Dakota, ORCID: http://orcid.org/0000-0002-6714-2295

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Background

Psilocybin was first isolated by Albert Hofmann in 1957 from the Central American mushroom *Psilocybe mexicana*. The first synthetic psilocybin product was created shortly thereafter in 1958 and continues to be widely used today, both recreationally and in spiritual or religious rituals.[1] It has since been found in more than 100 mushroom species worldwide with varying potency. These mushrooms are both cultivated and found in the wild. Cultivated mushrooms tend to be more potent through selection of stronger mushroom strains with more active ingredient (up to 10 times that of some wild mushroom species).[2]

Psilocybin, a classic tryptamine hallucinogen, has similar properties to lysergic acid diethylamide (LSD) and mescaline with a slightly different chemical structure. Cross-tolerance between the different hallucinogens has been demonstrated, and research shows a common mechanism of action through serotonergic (5-HT) pathways. Psilocybin is a strong agonist at 5-HT_{2A} as well as a moderate agonist at 5-HT_{1A} and 5-HT_{2C}.[3] 5-HT_{2A} receptors are located within the thalamus and cortex of the brain. Activation of 5-HT_{2A} receptors in the thalamus, the area of the brain responsible for sensory input, appears to decrease thalamic activity, thus leading to sensory alterations commonly referred to as hallucinations.[4,5] Hallucinogenic effects typically onset within the first 20 to 40 minutes of use then disappear within 3 to 6 hours. Psilocybin's threshold for intoxication is approximately 40 mcg/kg of body weight. There is a low percentage of psilocybin in most mushroom varieties, so this corresponds to approximately 1 to 2 g of dried mushrooms.[2,6] Due to this alteration in sensory perception and serotonergic activity of the substance, much of the research for this agent has been focused on those mental health conditions with abnormalities in sensory perception, such

as depressive disorders and anxiety or anxiety-related disorders. Psilocybin has also been researched for use in substance use disorders.

Since the Controlled Substance Act (CSA) of 1970, clinical studies using hallucinogens and psychedelics essentially ceased. Much of the research completed on these agents in the 1950s and 1960s was not taken seriously due to the small nature of the studies or methodology inconsistent with current research standards. However, interest in understanding the neuropsychiatric effects of these agents and their potential role in medical therapy persisted. Because of the CSA Schedule I status of these agents, clinical research in humans seemed unlikely and locating funding sources virtually impossible. In 1992, the National Institute on Drug Abuse worked with a Food and Drug Administration advisory committee that ultimately allowed for the resumption of research of psychedelic agents.[7]

The Heffter Research Institute, founded in 1993 by Nichols and colleagues, is the only institute solely dedicated to clinical research of the medicinal value of psychedelic agents. They ultimately have focused their research on psilocybin, the active ingredient in *magic mushrooms* or '*shrooms*.[7] As the search for novel treatments for mental illness grows, new energy is being focused on older treatments, such as ketamine, and more Schedule I substances, such as marijuana, LSD, and psilocybin. This article will explore the literature behind psilocybin and the potential for the agent as a treatment for select mental health conditions. However, due to the CSA Schedule I nature of the substance, safety should first be reviewed.

Safety

In 2011, Studerus et al[8] compiled data from 8 different studies involving psilocybin administration from 1999 to 2008. This pooled analysis consisted of 110 healthy human subjects who received 1 to 4 different oral doses of psilocybin for a total of 227 psilocybin administrations. The doses used throughout the studies ranged from 45 mcg/kg to 315 mcg/kg. All subjects underwent extensive screening prior to entering the studies and were excluded if they had any active *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV) diagnosis or emotional liability.[8,9] All of the studies used the Altered States of Consciousness Rating Scale, which is a visual self-rating scale. Short- and long-term safety was evaluated, and there was no indication of increased drug abuse, persisting perception disorders, prolonged psychosis, or other long-term deficits in functioning. The number of adverse reactions from psilocybin was few in number, resolved quickly, and was mostly associated with the highest doses of psilocybin. The subjects were followed for 8 to 16 months post psilocybin administration and exhibited no long-term negative side effects.[8] The safety demonstrated in this study opened the door for more research on psilocybin. It should be noted, however, that the administration of psilocybin in these studies followed strict protocols and therefore may lack external validity to the general population.

There has been some concern that use of psychedelic agents in a mental health population could exacerbate the underlying disease or cause suicidal behavior despite little clinical data showing significant safety issues or development of addiction with the administration of hallucinogens. Johansen and Krebs[10] set out to examine this claim and published a population study detailing their findings. This population study of 135 095 random adults in the United States included 19 299 psychedelic users (which included LSD, mescaline, and psilocybin). No significant association was found between lifetime use of psychedelics and increased mental health treatment or suicidal thoughts, plans, or attempts.[10]

Additionally, a review of psilocybin use in the Netherlands demonstrated similar findings. Per the authors' conclusions, dependence potential was low, acute toxicity was moderate (few mild or severe adverse reactions), chronic toxicity was low, and public health risks were negligible.[11] In contrast to this conclusion, 1 article describes severe adverse effects of high doses (approximately 420 mcg/kg), including a high incidence of significant fear and transient ideas of reference/paranoia (31% and 17%, respectively) in healthy volunteers.[12] Per the Netherlands article, the average lethal dose (LD_{50}) in rats was 280 000 mcg/kg, equating to approximately 17 kg of mushrooms ingested. The article details only 4 case reports directly attributing death to psilocybin use over a 41-year period. Many other fatal case reports mentioned in the article were in combination with other drugs of abuse (alcohol, heroin, and cannabis).[11] It appears that low-to-moderate doses of psilocybin are fairly well tolerated although it should be noted that the number of articles describing psilocybin use is small, and there have been fatalities reported. However, compared to other common drugs of abuse, such as heroin, the death risk appears to be much smaller.

Suicidality and Depressed Mood

Hendricks et al[13] examined the relationship of lifetime psilocybin use and psychological distress in the past month. They also collected past-year suicidal thinking, suicidal planning, and suicide attempts associated with psilocybin use in an adult population in the United States. Data used was from the National Survey on Drug Use and Health (2008-2012)[14] in which 191 831 participants were divided into 1 of 4 groups: psilocybin use only (n = 7550),

psilocybin and other psychedelics (n = 12 724), other nonpsilocybin psychedelics only (n = 6963), or no psychedelic use in their lifetime (n = 164 595). The odds of all of the outcomes were reduced in the psilocybin-only group compared to the no psychedelic use group. Past-year suicidal thinking and planning were lower in the psilocybin group compared to the psilocybin and other psychedelics group. Finally, the odds of past-month psychological distress were lower in the psilocybin group relative to the other psychedelics-only group. Based on this data, the psilocybin group appeared to fare better than any other group. This further supports the idea that psilocybin may play a role in reducing suicidality and improving mood although these patients did not necessarily have a diagnosis of major depressive disorder. It also highlights the potential safety of the substance in such a large population.[13]

Griffiths and colleagues[12,15] published articles in 2006 and 2008 examining the psychological effects of psilocybin in healthy volunteers. Hallucinogen-naïve adults were given oral psilocybin or methylphenidate in 2 or 3 sessions. They were told that they would receive a moderate or high dose of psilocybin during at least 1 of the sessions. At both 2 months postdrug sessions and 14 months follow-up, the patients had significantly increased ratings of positive attitudes, mood, social effects, and behavior with the psilocybin sessions compared to the methylphenidate sessions. The authors felt that the biggest finding of their study was that a large percentage of the patients rated their psilocybin experience as one of the most meaningful experiences of their lives. As patient buy-in to therapy is important with mental health, this level of satisfaction with treatment may actually increase efficacy. Also, the 14-month follow-up showed no evidence of adverse effects due to psilocybin exposure based on patient interview. Psilocybin was administered in a controlled environment in this study; thus, external validity may be decreased compared to the general mental health population.[15]

Anxiety Disorders

Some of the first clinical research on psilocybin studied its use in treating anxiety symptoms in patients with cancer. Grob et al[16] completed a double-blind, placebo-controlled study to examine the safety and efficacy of psilocybin in 12 patients for the treatment of psychological distress associated with the existential crisis of terminal disease. Inclusion criteria were a diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety per the DSM-IV criteria along with a diagnosis of advanced-stage cancer.[9,16] Patients were randomized to receive either active psilocybin (200 mcg/kg) or niacin 250 mg, both in oral capsule formulation. Niacin was chosen as the control because researchers thought it would provide the warm flushing effect, a common adverse effect of psilocybin, without altering the psychological state. Patients served as their own control and received 2 treatment sessions (1 with psilocybin and 1 with niacin) spaced several weeks apart. Patients were with staff for the entire 6-hour session, and vital signs were monitored. Several rating scales were used the day before, day of, and day after each session along with 2 weeks, monthly, and 6 months postsession. Anxiety significantly decreased as measured by the State-Trait Anxiety Inventory at 1 and 3 months posttreatment in the psilocybin group compared to niacin. Mood improved for 2 weeks after treatment and reached statistical significance on the Beck Depression Inventory at the 6-month point with the same comparison. In terms of safety data, the psilocybin group did have a modest increase in heart rate and blood pressure at 2 hours after ingestion. Holter monitoring did not show any increased risk of cardiac arrhythmias in the psilocybin group compared to the niacin group.[16] This small study of a relatively low dose of psilocybin supports further research on whether psilocybin could be used as a medication for the management of anxiety disorders.

Obsessive-Compulsive Disorder (OCD)

A case report[17] published in 2014 describes a 38-year-old male who had multiple medication failures in the treatment of his OCD. He consumed magic mushrooms given to him by a friend and immediately had an increase in anxiety but noticed his intrusive thoughts were significantly reduced the next day. He determined that every time he ingested approximately 2 g of psilocybin mushrooms, his OCD symptoms would be reduced for the following 3 weeks. It should be noted that the level of evidence in the case report is low as use of the specific agent and symptom improvement are all patient reported.[17] However, 1 other study has reviewed potential benefit for OCD.

Moreno and colleagues[18] conducted a study involving 9 patients with OCD as defined by the DSM-IV and at least 1 treatment failure (adequate treatment of at least 12 weeks with a serotonin reuptake inhibitor). They hypothesized that administration of psilocybin orally may be helpful in reducing OCD symptoms based on its serotonergic mechanism. The 9 patients each received up to 4 different doses (25 mcg/kg, 100 mcg/kg, 200 mcg/kg, and 300 mcg/kg) at least 1 week apart, and 88.9% of patients showed a greater than or equal to 25% decrease in symptoms per the Yale-Brown Obsessive Compulsive Scale (YBOCS) at the 24-hour mark, and 66.7% maintained a greater than or equal to 50% decrease in YBOCS scores at 24 hours post 1 of their testing doses. The study

found no significant effect of dose on response. One subject experienced transient hypertension (142/105 mmHg) after the 200 mcg/kg dose. No other safety concerns were reported.[18]

Alcohol Dependence

Prior to the 1970s, there was extensive research into the use of classic hallucinogens (specifically LSD) for alcohol dependence. With the recent growth in evidence for the use of psilocybin to treat various disorders via its serotonergic actions, Bogenschutz et al[19] conducted a proof-of-concept study for psilocybin to treat alcohol dependence, in which 10 patients with a diagnosis of alcohol dependence per the DSM-IV were enrolled in the study. Patients were provided psychosocial treatment with motivational enhancement therapy for 4 weeks, then received the first dose of psilocybin. A second dose of psilocybin was administered after an additional 4 weeks (study week 8). All 10 patients completed the first session (psilocybin dose of 300 mcg/kg), and 7 completed the second session (300 mcg/kg or 400 mcg/kg). Patients all had a significant decrease in alcohol use post psilocybin administration. Percentage of drinking days during weeks 5 through 12 decreased by 27.2% (95% confidence interval [CI] 9%-45.4%) relative to baseline and percentage of heavy drinking days decreased 26% (95% CI 8.7%-43.2%) from baseline. It should be noted that there was also a statistically significant decrease in the above measures relative to the first 4 weeks of psychosocial therapy (21.9% decrease in drinking days and 18.2% decrease in heavy drinking days). There were no clinically significant adverse effects although 5 of the 10 patients did report a mild headache that resolved within 24 hours of psilocybin administration.[19] Clearly, the small sample size in this study limits the utility of the data but opens the door for future studies of the impact of psilocybin in alcohol dependence.

Tobacco Cessation

Studies have shown that most interventions (pharmacological and behavioral modification) for tobacco cessation are only modestly successful at the 6-month mark. With growing positive evidence that the use of 5-HT_{2A} receptor agonists may be useful in treatment of addiction, Johnson et al[20] conducted a pilot study of psilocybin in the treatment of tobacco addiction. Fifteen participants were enrolled in a 15-week course of smoking cessation treatment that included psilocybin administration at weeks 5, 7, and 13. Participants had to smoke at least 10 cigarettes per day and have a history of unsuccessful quit attempts. Additionally, patients were excluded if they were taking any medications, including nicotine replacement therapy. Patients underwent a 4-week period of cognitive behavioral therapy while still using cigarettes. The first psilocybin administration at week 5 coincided with the participant's target quit date. Over the 15-week study, no significant adverse event occurred that required pharmacologic or physician intervention. Blood pressure and heart rate were mildly elevated 1.5 to 2.5 hours after drug ingestion, which is consistent with other studies utilizing psilocybin. Other common adverse events experienced were headaches and dysphoric subjective effects during administration. The results of this open-label study were promising with 80% of the participants remaining abstinent at the 6-month follow-up point.[20]

Conclusion

Based on the studies presented, it appears psilocybin may have some efficacy as an alternative agent to manage mental health conditions. However, there are multiple limitations to these studies. Many of them are small and are not able to be applied to larger populations. Additionally, because of the CSA Schedule I nature of psilocybin, it was administered under very controlled conditions. Because rates of nonadherence are higher in the mental health population than the general population, external validity of these studies may be lacking. If this substance were to be administered in a clinic, the adherence would not be an issue. Although, because it has oral bioavailability, the possibility exists for outpatient use. Very close monitoring during administration should occur until more is known about the drug. However, these studies all show potentially positive benefits with minimal safety concerns for psilocybin use in suicidality, anxiety disorders, OCD, alcohol use disorder, and tobacco use disorder with improvement in target symptoms.

Use of this agent does bring up the question of appropriateness of use in a population with high rates of substance abuse. Is it appropriate to use a controlled substance to treat symptoms of substance use disorders or use it to assist in management of other conditions with which substance use disorders could be present? Because there is no apparent modulation of the mesolimbic dopamine pathway in the discussed mechanism of action, the reward for use may simply be relief of symptoms. Thus, it is possible psilocybin may have a lower addiction potential than many other drugs of abuse although this has not been tested in studies. Clinic-only use would also decrease the potential for diversion and misuse.

The above studies demonstrate potential application for psilocybin in a variety of mental health disorders. As current studies are mostly limited to case reports, retrospective studies, or open-label trials, larger, more robust studies should be conducted with this agent to determine the true impact and clinical utility for each disease state.

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