Article

Psilocybin Use in the Future Psychiatric Practice: A Comprehensive Review

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Objective: Psilocybin, the psychoactive compound found in "magic mushrooms," is currently a Schedule I substance; as such, the United States Federal Drug Administration consider it to have a high potential for abuse and no medical benefit. However, recent research using psilocybin for the treatment of psychiatric disorders has shown that in certain conditions, it may have superior efficacy with fewer adverse effects than current psychotherapeutic agents. A review of the literature was conducted to elucidate the benefits of psilocybin further and explore the possible implication of future clinical use.
Search Methods: Pubmed search terms: psilocybin and depression, anxiety, alcohol, alcohol cessation, and mechanism of action, which resulted in 187 articles with 22 being selected for review.
Results: Severe studies with smaller sample studies have shown positive results in the use of psilocybin in treatment-resistant depression, anxiety and depression associated with advanced-stage cancer, along with alcohol and tobacco use disorders. Limited, but positive data show possible treatment use in OCD and anxiety disorders.

INTRODUCTION

Psilocybin is a naturally occurring compound found in approximately 200 different species of mushrooms that naturally exist in North and South America, along with several areas in Europe, Africa, and Australia[1]. Psilocybin is considered a hallucinogenic agent and has been classified as a Schedule 1 substance by the United States Drug Enforcement Agency (DEA). A Schedule 1 substance is defined as a substance with high abuse potential, no currently accepted medical use, and has no documented and accepted safety data[2]. Given this, it is a felony to knowingly purchase, possess, distribute, or use any amount of psilocybin and is punishable by a fine of $5,000 and up to a year in prison on a federal level.

Psilocybin and other hallucinogens are substances that alter reality, perceptions, and visual, auditory, olfactory, and gustatory sensations. Despite the name, hallucinations typically do not occur, and therefore a more appropriate name is psychedelics from the Greek meaning 'mind-manifesting[3]. Biochemically psilocybin is a tryptamine alkaloid and is structurally similar to serotonin[4].

Once ingested via oral consumption, the compound psilocybin is quickly digested into psilocin, a compound that can cross the blood-brain barrier via the enzyme alkaline phosphatase and nonspecific esterases. Further metabolism occurs via monoamine oxidase and aldehyde dehydrogenase enzymes in the liver**.** Psilocin is structurally similar to serotonin and temporarily increases levels of serotonin in the brain[3]. Serotonin is widely implicated in numerous psychiatric conditions and agents that modulate serotonin improve the symptoms associated with these conditions. Therefore, because psychedelics, including psilocybin, alter serotonin pathways, it is reasonable to hypothesize that they could be utilized as a treatment modality. Emerging evidence supports this hypothesis with psilocybin being used in the treatment of treatment-

resistant depression, anxiety or depression associated with terminal illnesses, and tobacco and alcohol use disorders[5]. Psilocybin's psychedelic effects are thought to contribute to its efficacy by inducing personally meaningful and spiritually significant experiences that result in positive changes in cognitive processes and behaviors. These effects are not exclusive to individuals with psychiatric illness, as Griffins et al. noted in a 2006 study of 30 volunteer subjects who were administered psilocybin, achieved a psychedelic experience, and continued to report positive outcomes at the 2 months follow up[6]. These findings have significant implications for the future use of psychedelics as psychopharmacologic agents and as adjuvants to psychotherapy.

Figure 1:

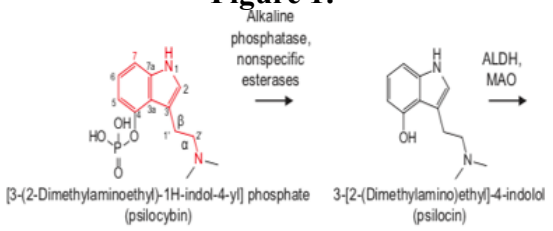
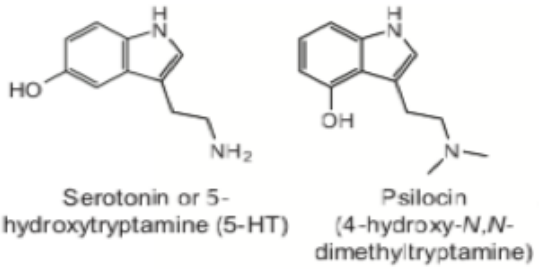


Figure 2:



SEARCH METHODOLOGY

This review included all studies published on the use of psilocybin for the treatment of psychiatric illness until September 1st, 2019. These studies included review articles and controlled trials. Search terms used included: psilocybin and depression, anxiety, alcohol, alcohol cessation, and mechanism of action. This query resulted in 187 articles with 22 being selected for the

MECHANISM OF ACTION AND SAFETY

Madsen et al. hypothesized that Psilocybin exerts its effects via Serotonin modulation by binding to the 5HT2A receptor. They also attempted to determine if there was a relationship between psilocybin ingestion and serotonin receptor occupancy. The study consisted of 8 participants that each had a baseline Positron Emission Tomography (PET) scan with a radio-labeled 5HT2A receptor ligand and then two subsequent PET scans following administration of psilocybin at doses ranging from 3-30mg. Following the administration of psilocybin, each participant underwent a follow-up PET scan (PET-1) 1 hour after consumption. Subjects 1-5 underwent a second follow-up PET scan (PET-2) later that same day. Table 1 indicates that increasing doses of psilocybin lead to higher receptor occupancy. This study showed that there was a significant increase at all doses of Psilocybin with a range in percent increase in serotonin occupancy from 42%-72%.

Table 1

Table 1. Descriptive data related to psilocybin interventions and corresponding 5-HT2AR occupancy estimates

ID	Dose (mg)	Weight-adjusted dose (mg/kg)	C_{max} (μg/L)	Mean psilocin PET 1 (μg/L)	Mean psilocin PET 2 (μg/L)	Occupancy PET 1 (%)	Occupancy PET 2 (%)
Subject 1	3	0.05	2.3	1.9	<LOQ*	42.9	1.8
Subject 2	6	0.07	4.4	3.5	0.7	56.2	26.7
Subject 3	12	0.14	16.7	12.6	3.4	66.4	42.9
Subject 4	15	0.2	11.7	10.5	2.3	63.2	30.9
Subject 5	18	0.2	11.8	10.6	2.6	72.4	47.0
Subject 6	24	0.27	12.0	9.0	NA	60	NA
Subject 7	24	0.3	18.9	11.5	NA	66	NA
Subject 8	30	0.3	19.3	15.6	NA	65.2	NA

*Below level of quantification

The safety profile for psychedelics, including psilocybin, is discussed in detail below. Common adverse effects include headaches, nausea, confusion, and hypertension all of which are generally self-limited to the psychedelic experience[7].

A study of 130,000 adults did not find an association between lifetime use of any psychedelic substance and the chance of suicidal thoughts[8]. In regard to the unpredictable and erratic behavior that is occasionally portrayed in the media, Honyiglo et al. details in a 2019 case report the history of an 18-year-old who was intoxicated on psilocybin mushrooms and jumped out his second-story window to his death. He had no other psychoactive substances in his system, and his blood and urine were positive for psilocybin; thus, his death was attributed to his fall, and the fall was attributed to the use of psilocybin. This report demonstrates that although in a controlled environment, there is no evidence of addiction, tolerance, or withdrawal effects when used in an unsupervised setting psilocybin, can result in adverse outcomes, and it is therefore essential these medications only be used in appropriate clinical situations[9].

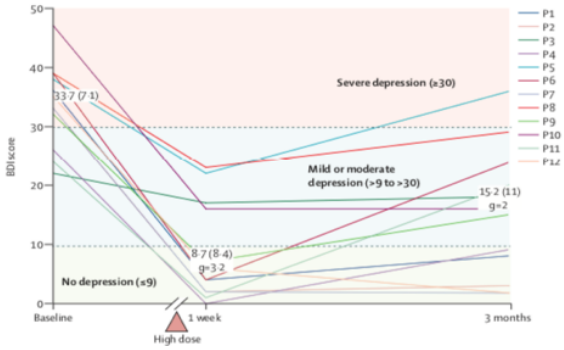
DEPRESSION

Major depression is defined as a constellation of symptoms consisting of depressed mood or anhedonia most days for at least 2 weeks, along with at least four contributing symptoms during this same time frame including weight changes, sleep changes, psychomotor agitation or retardation, changes in energy, feelings of worthlessness or guilt, concentration issues and recurrent thoughts of death[10]. In 2018 the Federal Drug Administration (FDA) examined the data associated with psilocybin therapy for treatment-resistant depression and allowed it to progress to phase II clinical trials[11].

Carhart-Harris et al., in 2016, details treatment-resistant depression and the response to psilocybin therapy; in this study, 12 patients were recruited who were screened with a Hamilton Depression Rating Scale (HAM-D) and scored in the moderate to severe range or above 17 on the scale. Once enrolled in the study baseline, Beck Depression Inventory (BDI) and Quick Inventory of Depressive Symptoms (QIDS) were obtained. The participants were required to have failed at least a 6-week trial of two separate antidepressants during the current depressive episode. Exclusion criteria in the study were current or previous psychotic disorder, family history of psychotic disorder, a medical condition that is not suitable for study, serious suicide attempt that required hospitalization, history of mania, needle phobia, positive pregnancy test or current alcohol or drug dependence. The Psilocybin was obtained from THC-Pharm in Germany and formulated into capsules. Each participant underwent a 4-hour preparatory session to try to identify the cause of their depression and discuss the effects of psilocybin during the dosing session. The administration protocol consisted of a low dose, 10mg, and was followed by a higher dose of 25mg 7 days later. During the psychedelic experience, the patients were allowed to “journey” and were mostly uninterrupted. Tranquilizing agents were available as needed that included lorazepam or risperidone in the case of panic attacks or psychotic or agitated behaviors. The participants reported only minimal effects from the psilocybin that peaked at 3 hours and abated by 6 hours. Follow up assessments using QIDS showed decreases for all patients starting at 1week post-dosing with maximum decreases noted at 2 weeks. BDI scores of less than 9 are indicative of remission and scores that were higher than 9 but still showed a 50% decrease from baseline are considered responsive to therapy. In this study 8 of 12 (66%) patients achieved remission at 1 week, and at 3 months, 5 of 12 (42%) of patients achieved sustained remission with two additional

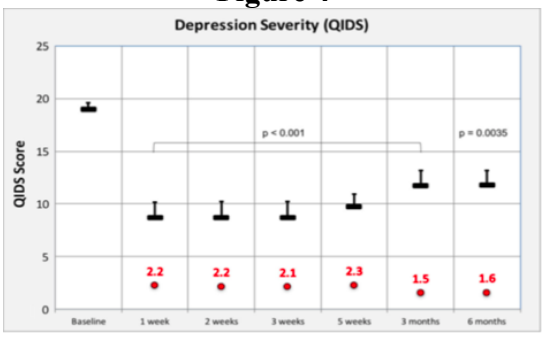
patients meeting criteria indicating a response to the therapy. All but one of the participants had a decrease in depressive symptoms at 3 months follow up as detailed in **Figure 3.** The main adverse effects associated with psilocybin dosing were transient anxiety, headache, nausea, and confusion at the initial administration and headaches 1-day post-administration that resolved after 1-2 days. There were no residual adverse effects reported[7]. The primary limitations identified in this study were the lack of a control group and a small sample size.

Figure 3



A second study looking at the antidepressant effect of psilocybin was also conducted by Carhart-Harris et al. in 2017 and using a similar research protocol and the same psychometric assessment standards. However, this study had a larger patient population of 20 participants, 12 of which came from the first psilocybin study above and were at the 6 months follow up period. The study included a psychological support component that involved three parts: preparation work, supportive therapy sessions during and after administration, and integration, which involves non-judgmental support after the experience. In this study, 18 out of 20 patients met the criteria for severe or very severe depression, based on a QIDS score >16. The mean number of years of illness was 17, and the median number of medication trials was four. One patient did not complete all of the assessments and was excluded from the final analysis. The results from the two dosage groups of 10mg and 25mg showed that all 19 patients had a statistically significant decrease in their QIDS scores with the maximal effect being seen 5 weeks post-administration, but scores continued to decrease over the 6-month observation period **(Figure 4)**. The BDI also showed improvement in all participants starting at 1-week post-administration, which was maintained at the 6 months follow up, with all the results being statistically significant. Of note, suicide scores also did decrease with 16 of 19 patients scoring 0 on the HAM-D 1-week post-administration. Six patients were started on an antidepressant medication by 3 months, five patients received therapy by the 3 month follow up, and five patients also administered additional psilocybin. All the treatments were well-tolerated, but one patient experienced a transient episode of uncommunicative time during the peak effects of the higher dose, that subsequently resolved without intervention, later during the therapy session. The patient described his experience as "blissful and overwhelming" but failed to complete further assessments[12]. Overall this study showed continued improvement in depressive symptoms 6 months post psilocybin administration. It had similar limitations to the previous study with a small study population and was also an open-label design.

Figure 4



QIDS scores done at baseline and the various times all showed a decrease in scores at all the time frames and all were statistically significant.

In the final study on depressive symptoms, Hendricks et al. conducted a review of participants who had used psilocybin in the past and rated their psychological distress in the past month (1= yes and 0=no), and suicidal planning or suicide attempt in the last year (1= yes and 0=no, as the primary outcome measures. All participants were contacted via the National Survey on Drug Use and Health from the years of 2008-2012, which had 191,832 total respondents. The participants were separated into four distinct groups: Psilocybin use only (7,550 or 2.47%), Psilocybin and other psychedelics (12,724 or 6.49%), Non-psilocybin psychedelics (6,963 or 4.59%) and no psychedelics (164,595 or 86.42%). Each of the groups were compared to each other. **Table 2** shows that the Psilocybin only group had a significant decrease in both psychological distress and suicidal behaviors when compared to the group with no reported psychedelic use. There was a statistically significant decline in suicidal thinking and suicidal planning categories for the Psilocybin only group when compared to Psilocybin and other psychedelic use groups. When the Psilocybin only group was compared to the non-psilocybin psychedelic use group. the only statistically significant result was that the psilocybin only group had a greater reduction in reported psychological distress. Several categories looking at measures of psychological function had to be excluded due to confounding factors in the no psychedelic use group that heavily skewed the data analysis process[13]. This study highlights the success that psychedelics and specifically psilocybin can have in the treatment of psychological distress and, more importantly, suicidality. These results support future prospective research, which aims to examine these relationships further. One major limitation of this study is the skewed sample size that favors non-psychedelic users, which, as a result, is likely to contain more psychopathology than the other groups. It is reasonable to presume that an increase in psychopathology within a group would make them more likely to experience and report symptoms of psychological distress and suicidality. Another significant issue with this data set is the lack of standardization of psilocybin use, time frame of use recall bias, and the inability to control for potential confounding factors.

Table 2

Table 1

Results of planned contrasts among four groups: Psilocybin Only, Psilocybin & Other Psychedelics, Non-Psilocybin Psychedelics Only, and No Psychedelics

Planned contrasts	Outcome variables			
	Psychological distress OR (95% CI)	Suicidal thinking OR (95% CI)	Suicidal planning OR (95% CI)	Suicide attemp OR (95% CI)
Psilocybin Only vs. No Psychedelics	.70 (.60-.81)†	.76 (.64-.90)**	.54 (.36-.82)**	.58 (.35-.94)*
Psilocybin Only vs. Psilocybin & Other Psychedelics	.89 (.75-1.05)	.80 (.67-.96)*	.59 (.43-.81)**	.75 (.49-1.14)
Psilocybin Only vs. Non-Psilocybin Psychedelics Only	.76 (.64-.90)**	.89 (.72-1.09)	.83 (.54-1.27)	1.06 (.62-1.80)
Psilocybin Only and Psilocybin & Other Psychedelics vs. No Psychedelics	.74 (.65-.84)†	.85 (.75-.96)*	.70 (.49-1.005)‡	.66 (.45-.98)*

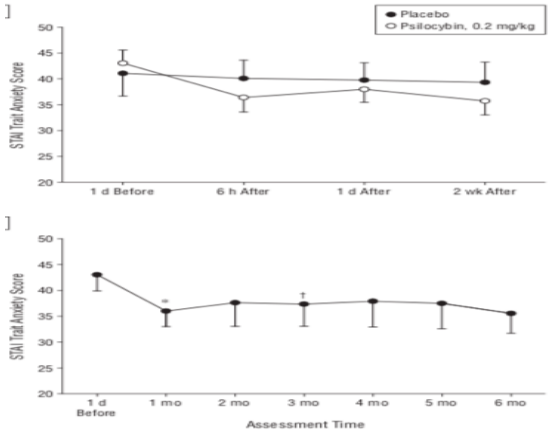
ANXIETY

Psilocybin has also shown potential treatment in anxiety disorders. Generalized anxiety is defined as excessive anxiety or worry that is present most days for at least 6 months with at least 3 of the following physical symptoms: restlessness, fatigue, concentration issues, irritability, muscle tension, and sleep changes[11]. Anxiety can be a symptom of numerous other conditions, including adjustment disorder, acute stress disorder, and anxiety disorder due to a general medical condition.

In 2010 Grob et al. conducted a study examining the use of psilocybin for the treatment of anxiety in patients diagnosed with cancer. The study looked at 12 patients diagnosed with an anxiety disorder, which included generalized

anxiety disorder, acute stress disorder, anxiety disorder due to cancer or adjustment disorder diagnosed using the DSM-IV diagnostic criteria. Eleven of the twelve patients were female, and all patients were diagnosed with one of the following types of cancer: breast, colon, ovarian, peritoneal, or salivary. During the study, two patients died due to complications of their cancer, and another two became too ill to continue to participate in the follow-up process. Exclusion criteria were malignancies involving the CNS, abnormal hepatic or renal function, diabetes, a history of schizophrenia, bipolar or other psychotic disorder, and pre-existing anxiety or affective disorder within 1 year of the cancer diagnosis. This study included a placebo dose of medication in addition to the two doses of psilocybin that were given to the patient several weeks apart. The process was double-blind, and the administration order of the medication was randomly determined for all of the patients. Niacin was chosen as a placebo due to its mild physiological reaction without any psychological effects. Participants were in the treatment room for 6 hours with staff there throughout treatment, staff engaged the patient every hour for assessment but otherwise allowed the patient to experience the effects of the psilocybin undisturbed. Each subject completed the BDI, profile of mood states (POMS), and State-trait anxiety inventory (STAI) before each session and then were re-administered the day after the session, at 2 weeks then monthly for a total of 6 months. A dose of 0.2mg/kg was administered in pill form. The results of this study showed a decrease in the STAI, which was not statistically significant at 6 hours. A sustained, though minimal, decrease in STAI scores was statistically significant at the 1, 3, and 6 months follow up assessments **(Figure 5).** The significance of the STAI score reductions likely represents an overall decrease in stress and anxiety decrease over time[14]. The significant finding of this study was that even small doses of psilocybin can still result in a reduction of anxiety. The limitations of this study were the small sample size, the fact that each patient had late-stage cancer as this limits the generalizability of the population, and the lower dose of psilocybin when compared to other studies that showed higher doses of psilocybin to be more effective in the treatment of affective disorders.

Figure 5

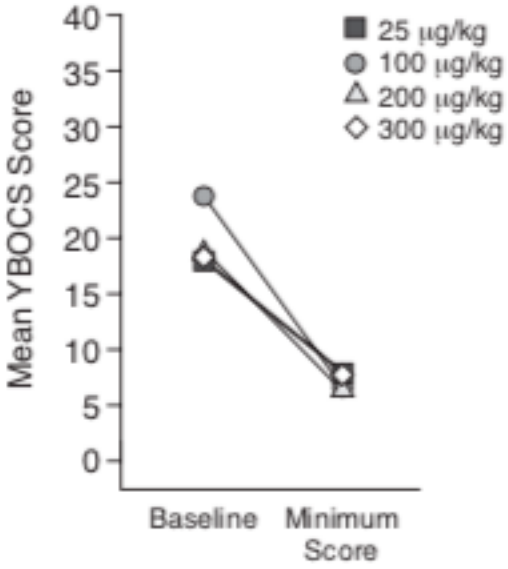


A case report by Wilcox in 2014 examined the effects of psilocybin on Obsessive-Compulsive Disorder (OCD) and found a decrease in symptoms post-administration. This case followed a 38-year-old male with a history of anxiety since childhood that gradually progressed into intrusive and disturbing thoughts, repetitive behaviors with ritualistic aspects, and an excessive degree of worry that occurred about 100 times per day. He previously failed several medications trials, including diazepam, fluoxetine, buspirone, and clomipramine. The patient had also attempted psychotherapy, which was as ineffective as the psychopharmacologic interventions. He decided to consume "magic mushrooms" obtained from a friend and reported that during the psychedelic

experience, he had extremely unpleasant feelings and increased anxiety levels. However, over subsequent days, his intrusive thoughts decreased significantly, and this decrease lasted about 3-4 weeks. The patient reported that he consumed approximately 2g of psilocybin and repeated this dose every 3 weeks for 1 year. At the end of that year, the patient was evaluated in the clinic and reported a complete resolution of his OCD symptoms[15]. While this is just a single case report, the significant response achieved in this patient is encouraging. One other major limitation in this study was the fact that the patient grew his mushrooms, making it difficult to determine the dose and potency of the psilocybin used.

Only one trial has been done that examined the relationship between psilocybin therapy and OCD symptomatology by Moreno et al. in 2006. In this study, 9 participants with DSM-IV diagnosis of OCD with a history of at least one treatment failure while on an SSRI for a minimum of 12 weeks. Treatment failure was defined as a lack of OCD symptom improvement during those 12 weeks. Overall, participants had an average failure of 3.4 medications. Yale-Brown Obsessive-Compulsive (YBOC) scales were obtained, and the ranges were 18-36 with an average score of 24. All participants had only a diagnosis of OCD. The participants received four different dosages during their sessions with increasing doses administered at each subsequent encounter. The doses were 0.025, 0.1, 0.2, and 0.3mg per kg (of note they measured their doses in μg/kg, but for ease of comparison, the doses were converted). All administration days were separated by 1 week, and the participants were able to wear blindfolds and listen to music. The psychedelic experience lasted approximately 8 hours on average. The only adverse effect noted was that one participant had transient hypertension after the ingestion of the 0.2mg/kg dose. Two of the participants dropped out after the first experience due to discomfort with the hospitalization. YBOC scoring was done 24 hours after administration and showed a decrease after all doses, even the very low dose of 0.025mg/kg. **Figure 6** shows the mean YBOCS score and mean minimum score at each dose. An average score of 5-10 on the YBOC was noted post-administration as opposed to the higher score of 20 at baseline. The lowest dose psilocybin did not induce any of the classic psychedelic effects and was meant to act as a control[16]. The significance of this study shows that even low doses of psilocybin are effective at decreasing symptoms of OCD based on validated psychometric questions like the YBOC.

Figure 6



ANXIETY AND DEPRESSION IN TERMINAL ILLNESS

Several studies looked at both depression and anxiety symptoms in terminally ill cancer patients and the effects that psilocybin has on decreasing symptoms

associated with these conditions in this population.

The first study was conducted by Griffins et al. in 2016 and followed 51 patients with various cancer diagnoses that were presumed to be terminal. Types of cancer in this group consisted of breast, upper aerodigestive, Gastrointestinal, Genitourinary, and hematological. All of the participants had a DSM-IV diagnosis of chronic adjustment disorder with anxiety (11), chronic adjustment disorder with mixed anxiety and depressed mood (11), dysthymic disorder (5), generalized anxiety disorder (5), Major depressive disorder (14) or a combination of the aforementioned diagnoses (5). This study was done in a two-session double-blind fashion with low (1-3mg/70kg) versus a high dose (22-30mg/70kg) psilocybin. The doses were administered approximately 5 weeks apart, and the low dose was intended to act as the placebo group. These groups were randomized and assigned to either high or low dose group first.

Assessments were done after enrollment, prior to administration, on both administration days during and at the end of the psychedelic experience, 5 weeks after each session, and 6 months after session two. The sessions were done in a living-room environment, and the patients were encouraged to lie down and use the eye mask while listening to universal music. Of note, the high dose group was decreased to 22mg after 3 of the first participants developed nausea and were discontinued from the study after administration, and the low dose was reduced from 3mg to 1mg after 12 participants had psychedelic effects on the 3mg and the concern was raised about the lack of placebo effect. The primary outcome measures for this study were the GRID-HAMD-17 for depression and HAM-A for anxiety. The results of this study are detailed in **Table 3.** Compared to baseline, there were significant decreases after the administration of the high dose of psilocybin, in both the GRID-HAMD-17 and HAM-A. These results were statistically significant. Although there was no further decrease at the 6 months follow up, the scores continued to remain stable[17]. Overall the primary outcome shows that psilocybin could be useful in the treatment of depression and anxiety in the setting of terminal illness such as cancer.

Table 3

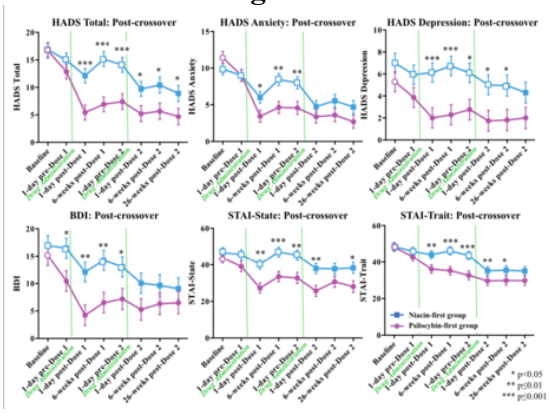
Measure	Group	Assessment time-point			
		Baseline[a]	Post-session 1[b]	Post-session 2[c]	6 months[d]
GRID-HAMD-17 (Depression)	Low-Dose-1st (High-Dose-2nd)	22.32 (0.88)	14.80 (1.45)	6.50 (0.86)***	6.95 (1.24)
	High-Dose-1st (Low-Dose-2nd)	22.84 (0.97)	6.64 (1.04)***	6.52 (1.44)	6.23 (1.30)
	[illegible]	[illegible]	[illegible]***	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]***	[illegible]	[illegible]

*** indicating a p<0.001.

Ross et al. conducted a similar study in 2016 that also examined the effects of psilocybin therapy in patients diagnosed with cancer who were suffering from symptoms of depression and anxiety. The treatment group was administered psilocybin 0.3mg/kg, and the control group was administered niacin 250mg for the reasons previously discussed, all participants received both medications as this was a cross-over study design. The 29 participants were randomized into treatment 1st and treatment 2nd groups in a double-blinded fashion. A unique feature in this study is that each participant underwent a session of psychotherapy during the psychedelic experience. Dose 1 occurred 2-4 weeks after baseline assessments and then the cross-over dose (dose 2) 7 weeks later. Assessments were done at baseline, 1 day before each session, the day of each session (7 hours post-administration), 2 weeks after

each session, 6 weeks after each session, and finally 26 weeks after session 2. All of the patients had been diagnosed with an anxiety disorder by DSM-IV criteria, and most had previously failed medications trials that included antidepressants and anxiolytics, but none were on psychotropics at the time of the study. The primary outcome scales used in this study were the Hospital Anxiety and Depression scale (HADS), BDI, and STAI. The results showed significant decreases in the psilocybin group only, shown in **Figure 7.** The effects of psilocybin have a rapid onset which results in a substantial reduction in symptoms associated with depression and anxiety in terminally ill cancer patients. Additionally, these effects appear to be maintained at long-term follow-up intervals[18].

Figure 7



ADDICTION

Psilocybin has also shown significant potential in the treatment of addiction and substance use disorders, such as alcohol use disorder and tobacco use disorder. Alcohol use disorder defined, per DSM-V, as a "problematic pattern of alcohol use leading to clinically significant symptoms with at least 2 of the following in a 12-month span: Alcohol taken in larger amounts than normally intended, unsuccessful attempts to cut down, a great deal of time is spent in obtaining alcohol or using or recovering, cravings for alcohol, alcohol causing issues with fulfilling major roles in life, continued use despite social or interpersonal problems, important activities given up to use, continued use in dangerous situations, continued use despite recurrent social and interpersonal issues while on alcohol, tolerance, and withdrawal." The severity is stratified by the number of symptoms: mild is 2-3, moderate is 4-5, and severe is 6 or more. Tobacco use disorder and all other substance use disorders use the same criteria listed above[11].

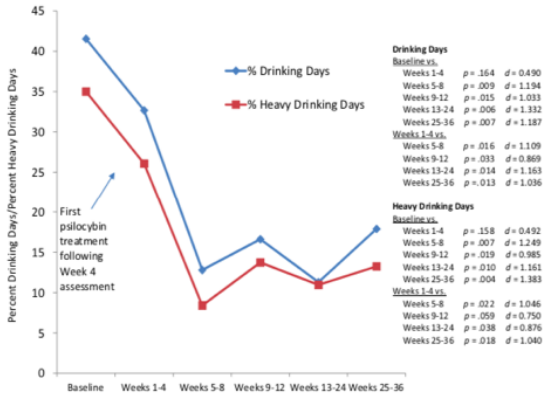
The first study was conducted by Bogenschutz et al. in 2015 and looked at the treatment of alcoholism with psilocybin. In this study, participants were recruited and screened for alcohol dependence based on DSM-IV criteria with at least 2 heaving drinking days per 30 days, and a total of 10 participants were selected for the study. Exclusion criteria included a history of bipolar, schizophrenia, and additional drug dependence. The participants underwent 12 sessions of therapy that included motivational enhancement therapy, a form of motivational interviewing, preparation sessions, and debriefing sessions. Four therapy sessions occurred before the first dose of psilocybin, four sessions after the first dose, and then four sessions after the second dose.

Before both dosing sessions, the participants were required to abstain from alcohol use for 24 hours and were evaluated for signs or symptoms of withdrawal. The treatment rooms were living-room-like and had headphones and eyeshades, and each session lasted 8 hours. The dose of psilocybin administered each time was 0.3mg/kg for the first session and 0.4mg/kg for the second session. Three participants dropped out of the study before the second dose, but two of them completed all of the follow-up assessments and were included in the final analysis. One of the participants

received 0.3mg/kg on both the first and second sessions due to having a mystical experience during the initial session. The first dose of psilocybin was administered at week 4 after the aforementioned psychotherapeutic interventions had been completed, and then the second dose was administered following week 8.

The study tracked the number of heavy drinking days, defined as drinking more than 5 drinks in a sitting for men and 4 drinks for women. Additionally, the authors assessed the number of drinking days as defined by the consumption of any alcohol. During weeks 1-4, in which only psychotherapy was given, there were no significant changes in drinking days and heavy drinking days. After the first dose of psilocybin both, heavy drinking days and total drinking days decreased significantly at all data points when compared to baseline and weeks 1-4, except heaving drinking days in weeks 9-12 compared to weeks 1-4, **Figure 8.** The results are incredibly encouraging, given the significant decrease in alcohol consumption after just one dose of psilocybin[19]. Limitations of this study include the small sample size and a concern about how severe the alcohol dependence/use disorders were given that no patients exhibited withdrawal symptoms after 24 hours of alcohol cessation.

Figure 8

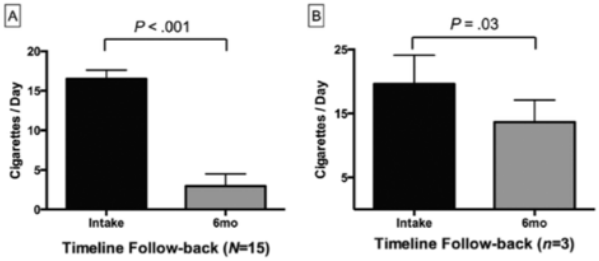


A meta-analysis examining the effects of different serotonergic psychedelics on patients with alcohol use disorder was performed by Garcia-Romeu et al. in 2019. The study design was based on surveys that were sent out requesting participants who had overcome alcohol or drug addiction after using psychedelics. Inclusion criteria were aged 18 years or older, read and write English, retrospectively had a DSM-5 diagnosis of alcohol use disorder, and had classic psychedelic use outside of a medical setting. In total, 343 respondents were included in the meta-analysis. The most common psychedelics used in the population were LSD and psilocybin. About 72% of participants met the criteria for alcohol use disorder, severe with the mean number of DSM-V symptoms being 7.3 and nearly 25.5 drinks per week. The average score on the Alcohol Use Disorders Identification Test - Concise (AUDIT-C) was 8.5 in the year prior to the psychedelic experience. These scores support the notion that the participants were heavy users with significant symptoms. An Alcohol Urge Questionnaire (AUQ) was conducted for cravings in the survey with most of the participants indicating they used “moderate or high” doses of the psychedelic substance and very few had intended to use it as a quitting agent. Nearly all of the participants had reported cessation or significantly reduced their drinking by self-reported number of drinks per week down to 4.3 from 25.5. The AUDIT-C scores decreased to 5.8 from 8.5, and approximately 83% of participants no longer met the criteria for alcohol use disorder. The data showed a significant decrease in AUDIT-C scores with the most significant changes occurring in the higher the pre-AUDIT-C score was[20]. This study strengthens the case that psychedelics and specifically psilocybin should be further

investigated as a treatment modality for alcohol use disorder. The major limitations of this study include the fact that all of the data was retrospectively collected, raising the concern for recall bias for both alcohol consumption and the psychedelic dose and agent, which could confound the data significantly. Another limitation was the study advertisement used to recruit implied that psychedelics were the cure, and it is not clear to what degree this caused a selection bias in the responding sample and does not take into account other potential variables that could have contributed to the patients reducing their alcohol intake.

In regard to tobacco use disorders, Johnson et al. in 2014 conducted a 15-week trial to see if psilocybin could be used to decrease tobacco consumption. The study team recruited participants by advertisements and then conducted phone interviews with 15 participants meeting the minimum smoking requirement of 10 cigarettes per day with multiple unsuccessful quitting attempts and the current desire to stop smoking. Exclusion criteria were personal, or family history of a psychotic disorder or bipolar disorder and a history of drug or alcohol dependence based on DSM-IV criteria. Participants underwent four weekly meetings consisting of CBT for smoking cessation in preparation for psilocybin administration with a targeted quit date that was the same as the psilocybin administration, approximately week 5. On that date, participants were given a dose of 20mg/70kg, this dose was repeated at week 7, and an optional higher dose of 30mg/70kg was offered at week 13 for those who requested it. The environment of the room was similar to the other studies detailed above. Smoking markers measured were exhaled Carbon monoxide (CO) (measures smoking over the last 24 hours) and urine cotinine level (measures smoking over the previous 6 days). These markers were obtained at intake, weekly during the intervention, and then at 6 months. Non-smoking status was considered to be a CO of less than 6ppm and a urine cotinine level of less than 200ng/ml. Twelve of the participants completed all three psilocybin sessions, with one of the participants electing the lower dose at session two. At the 6 months follow up assessment, the participants had significant decreases in self-reported number of cigarettes per day, breath CO levels, and urine continue level. Three of the participants reporting smoking at 6 months, but they also had significantly reduced the number of cigarettes per day, as shown in **Figure 9**[21].

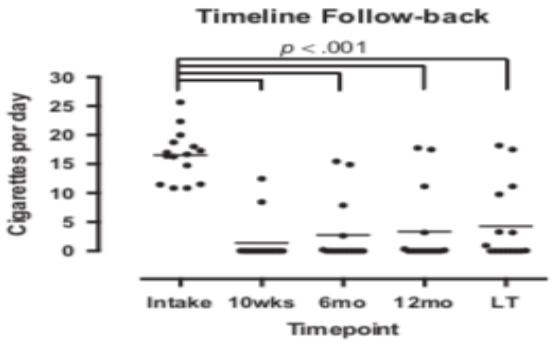
Figure 9



The second study was a longer-term follow up on the same 15 participants and was done by Johnson et al. in 2016. The researchers invited participants back at 12 months, and then long term follow up with a mean of 30 months, with all 15 of them participating in the 12-month follow-up and 12 in the long-term follow-up. At 12 months, 10 of the 15 participants reported being smoke-free, and this was confirmed using exhaled CO and urine cotinine testing. At the long-term follow-up 9 of the 12 participants reported and were confirmed to be smoke-free. All of these results at the follow-up time points were statically significant and are detailed in **Figure 10**[22]**.** This data is significant as it shows that both short term and long-term follow-up show substantial decrease in

smoking cessation when psilocybin is used in combination with CBT.

Figure 10



CONCLUSIONS

Based on the above articles and reviews examined, it does appear that there is significant evidence that psilocybin has efficacy in treating treatment-resistant depression and anxiety disorders. This efficacy extends over to the treatment of anxiety and depression in patients with terminal illnesses like cancer. While depression and anxiety disorders compose the large proportions of all psychiatric diagnoses, the treatment-resistant cases are a relatively small number due to the modest success of the standard treatment options. The same cannot be said for substance use disorders like alcohol and tobacco use. The significant potential that psychedelics like psilocybin have shown in the treatment of these conditions is highly encouraging and could be practice-changing in the not too distant future. It would be of great benefit to further examine the benefits that psilocybin can have on treating these different psychiatric disorders with larger sample sizes and longer follow-up.

DISCUSSION

Psychedelics are in a renaissance of psychiatric research, and based on the above studies, it appears that they have efficacy in treating depressive symptoms, anxiety disorders, and substance use disorders. The benefits of psychedelics and psilocybin in particular far outweigh the risks when these agents are used in a therapeutic environment under standardized protocols. With careful screening and a safe and supportive environment, psychedelics like psilocybin have the potential to revolutionize the landscape for the treatment of chronic refractory or resistant conditions that currently only have limited options for management. As discussed in a review article by Gardner et al. in 2019, the area of psychedelics is an emerging field, and much more research is needed. The legal classifications need to be re-evaluated as it is clear that psychedelics do have a clear medical benefit and are also not addictive or habit-forming. The negative social connotations associated with psychedelics have even begun to shift in a positive direction making the discussion about these agents more straightforward and honest. Further change will be required before psychedelics can be fully incorporated into a standard clinical practice, but based on the current research findings, it is reasonable to believe that these agents will be of substantial benefit when that day finally arrives[23].

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