PSILOCYBIN

A Review of Psilocybin in Treating Depression

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SYNOPSIS: This literature review examines the research that has gone into the use of psilocybin specifically to treat depression. An examination of the available evidence demonstrates significant promise in psilocybin’s efficacy to treat depression, although more research is needed to make the results generalizable.

Depression is one of the most common health issues, affecting more than 21 million Americans and with a higher prevalence among females, younger Americans, and people of color.¹ In the United States, its economic toll in 2018 was estimated at $326 billion, without considering the emotional toll it takes on individuals and their loved ones.²

Given the high prevalence and cost, developing effective treatment is critical. Monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) were the mainstay of pharmacotherapy until the advent of selective serotonin reuptake inhibitors (SSRIs). While effective, MAOIs and TCAs tend to have a narrow therapeutic window and undesired and potentially dangerous side effects. With their release in the late 1980s and 1990s, safer and more tolerable SSRI and serotonin-norepinephrine reuptake inhibitors quickly became first-line agents to address depression.

While these medications, along with improved psychotherapy techniques, have led to better treatment of

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Summary Points

- Multiple small clinical trials have demonstrated significant, rapid, and lasting antidepressant effects of psilocybin with as few as two doses.

- Clinical trials evaluating microdosing of psilocybin are limited, and there have not been any studies in the past five years that have demonstrated clinically significant positive effects.

- A head-to-head double-blind, placebo-controlled clinical trial for depression treatment with a selective serotonin reuptake inhibitor and psilocybin showed both treatments were effective after six weeks.

- In the clinical trials for treatment of depression, no significant adverse events occurred. In studies specifically evaluating cognitive and emotional effects, no clinically relevant negative findings were seen on cognitive testing.

- Psilocybin’s main therapeutic action is thought to be related to its activity on 5HT2a receptors. Neuroscience research using functional magnetic resonance imaging has shown psilocybin administration modulates connections between the frontal cortex and limbic areas and decreases activity in the brain’s default mode network, a network of brain structures that has shown increased activity in depression.

depression, unfortunately, a significant number of people still do not benefit from them or experience undesirable side effects. The number needed to treat using SSRI medication for depression is estimated to be around seven to eight people. Regrettably, this still leaves a large population refractory to treatment.

Recently, a comprehensive review and meta-analysis incorporating data points like gene expression, cerebrospinal fluid, brain tissue, and serotonin levels has challenged the biomedical theory on which SSRIs are based — namely, the idea that a serotonin deficiency is responsible for the constellation of symptoms defining depression. The clinical observation of the delayed effectiveness of SSRIs is inconsistent with the more rapid change in serotonin concentrations that SSRIs confer.

Given a lack of alternative therapies and recent challenges to the underlying biochemical model for depression, there has been a search for potential new therapeutics. One such class includes naturally occurring psychedelic substances, such as psilocybin, which have been used traditionally for their spiritual and healing properties across cultures, but they currently are widely illegal.

Historically, these plants often were used in shamanic ceremonies to address various emotional, spiritual and psychic ailments (some of them similar in phenotype to depression). Illegal in the United States since 1970, research into psilocybin and other psychedelics has been severely restricted.

Over the past few decades, overall interest in psychedelics has greatly increased. A quick PubMed search shows an increase in psilocybin-related articles from roughly 10 articles a year published more than a decade ago to more than 100 articles published yearly on psilocybin within the last few years. Given this renewed interest in psychedelics, this review will examine the current state of evidence for psilocybin in the treatment of depression.

REVIEW METHODOLOGY

PubMed was used to search for articles on human clinical trials in English in the last five years using the search terms “psilocybin” and “depression.” The main question was, “Can psilocybin be used safely and effectively for the treatment of depression?” In all, 18 articles were identified; 15 of which were trials.

Two articles were eliminated as irrelevant — they appeared in the results because of keywords in the disclosure sections and were not related to the clinical question. Meanwhile, one article was a qualitative review of trials whose discussion was relevant to generalizability, but it was not used in our main analysis. Of the 15 trials, six quantified various aspects of tolerability, mechanism,
and safety in healthy patients; eight examined psilocybin’s effect on treatment-resistant depression; and one was a head-to-head trial with an SSRI. Five trials’ publications were secondary analyses (magnetic resonance imaging [MRI] and speech algorithm) of previous trials.

INITIAL STUDIES: PSilocybin’s PROMISE
Several initial studies have shown positive results with psilocybin and depression. (See Table 1.) An open-label feasibility study by Carhart-Harris et al demonstrated benefit at six months for those with treatment-resistant depression. Twenty participants who had failed at least two pharmacologic interventions and scored 17 or above on Quick Inventory of Depressive Symptomatology score (QIDS-SR-16) were included. Patients with personal or family history of psychosis were excluded. Subjects received two doses of psilocybin (10 mg and 25 mg) seven days apart with psychological support during the treatment session. Nineteen subjects completed the study. Maximal effect sizes were seen at five weeks, showing a 9.2-point reduction on the QIDS-SR-16 from the baseline score of 19 ($P>0.001$). There was a high degree of correspondence between this and the secondary measures, which remained significant throughout the six-month study period. MRIs were obtained pre- and post-intervention, but results were not included in this paper.6

A waitlist control trial of 27 participants by Davis et al showed benefit for those with treatment-resistant depression. Adults 21-75 years of age with moderate to severe depression — defined as a GRID Hamilton Depression Rating Scale (GRID HAMD) score of 17 or above (range, 0-52) as assessed by blinded clinician rater — were recruited. Major exclusion criteria were patients who had been diagnosed with or who had first- or second-degree relatives diagnosed with psychotic or bipolar disorders, went through with a significant suicide attempt, or who had been hospitalized.

Participants were divided into immediate (15) vs. delayed intervention (12) arms. Participants were given two psilocybin doses — 20 mg/70 kg and then 30 mg/70kg — in a monitored setting with nondirective psychotherapy support used on session days. The primary outcome measured was a change in GRID HAMD score. Self-reports via QIDS-SR-16 also were collected. The immediate treatment group showed a rapid reduction compared to the delayed treatment group, whose mean scores remained relatively unchanged. Mean scores in the immediate treatment group’s GRID-HAMD scores went from 22.9 at baseline to 8.0 at week 1 ($P>0.001$) and 8.5 at week 4 ($P>0.001$). The effect size was approximately 2.5 times greater than that found in psychotherapy and four times greater psychopharmacological studies.7

This study then was extended to look at the effectiveness for the overall treatment group after 12 months by Gukasyan et al. When compared to group baseline of 22.8 on GRID-HAMD, scores at 3, 6, and 12 months remained significant ($P>0.001$) with large effect sizes. At 12 months, the average score was 7.7, with a Cohen d score of 2.4 suggesting a large and durable effect. Similar improvements and sustained decreases in self-reported depression scores were seen across all the follow-up intervals. Response rates, defined as a 50% decrease in GRID-HAMD scores, of 75 and remission rates, defined as a score of 5 or lower, of 38% were seen at 12 months.8

A study by Marschall et al did not validate effects seen with higher doses of psilocybin. The study attempted to assess the effect of psilocybin microdoses (defined as one-tenth of a typical medium dose) on emotional processing as well as anxiety and depression ratings. This was a double-blind, randomized controlled trial within-subject crossover design. Participants were recruited from a microdosing workshop with samples prepared by subjects and then randomized with placebo.

The study did not show any difference between groups, but it is difficult to draw conclusions from this study, given the self-selection bias, preparation based on mushroom weight as opposed to being standardized by active ingredient content, a large dropout rate that left the study underpowered, and a large number of participants straying from study guidelines. Two earlier studies in microdosing with psilocybin were conducted, but they were not specific to depression. Ultimately, based on current research, microdosing effects remain largely unanswered.8

PSilocybin vs. SSRI
The most rigorous study reviewed was by Carhart-Harris et al, which compared psilocybin to escitalopram. This was a double-blind, randomized controlled trial out of the United Kingdom. Adults aged 18-80 years with moderate to severe depression on the Hamilton depression scale (defined as 17 or above [range, 0-52]) were included. Subjects with prior psychosis or a first-degree relative with a history of psychosis, who were pregnant, who were currently or previously had used escitalopram, who had used other illicit drugs, or who had other significant medical or psychological conditions were excluded.

Fifty-nine participants were recruited and divided to receive either psilocybin or escitalopram. The start of the trial began with a pre-intervention MRI along with several cognitive and affective tests. On day 2, participants were given either 25 mg or 1 mg of psilocybin (considered an inactive dose) immediately followed with monitoring by mental health professionals and a debrief the following day. For the next three weeks, the psilocybin group took a placebo, whereas the escitalopram group took 10 mg of escitalopram. This was repeated with a 25-mg dose vs. the 1-mg dose of psilocybin at the three-week mark while the escitalopram group raised
their daily dose to 20 mg. The psilocybin group continued taking a daily placebo. Participants returned three weeks later for MRI and psychological assessment. Results showed improvement in both groups at six weeks. The primary outcome was change in QIDS-SR-16 (range, 0-27) with 16 other secondary outcomes. The

Table 1. Summary of Psilocybin Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of Study</th>
<th>Participants</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becker AM (2022)</td>
<td>DBRCT placebo-controlled crossover</td>
<td>27, healthy</td>
<td>Coadministration appears to be safe and does not interfere with the therapeutic effects of psilocybin.</td>
</tr>
<tr>
<td>Brown RT (2017)</td>
<td>Open-label</td>
<td>12, healthy</td>
<td>Psilocybin is well-tolerated, and renal adjustments likely are not needed.</td>
</tr>
<tr>
<td>Carhart-Harris R (2021)</td>
<td>Head-to-head, DBRCT placebo-controlled</td>
<td>59, moderate to severe MDD</td>
<td>Psilocybin was as effective as escitalopram at six weeks of treatment. Most measures favored psilocybin, but they were not statistically significant.</td>
</tr>
<tr>
<td>Carhart-Harris RL (2018)</td>
<td>Open-label</td>
<td>20, TRD</td>
<td>Psilocybin showed a large and durable effects size after six months for those with TRD.</td>
</tr>
<tr>
<td>Carhart-Harris RL (2017)</td>
<td>Open-label, secondary analysis</td>
<td>16, TRD</td>
<td>Findings suggest that psilocybin may reset the DMN.</td>
</tr>
<tr>
<td>Carillo F (2018)</td>
<td>Open-label with healthy matched controls, secondary analysis</td>
<td>35, TRD</td>
<td>An artificial intelligence speech algorithm may be useful in predicting treatment responders to psilocybin.</td>
</tr>
<tr>
<td>Dahmone E (2021)</td>
<td>Open-label</td>
<td>12, healthy</td>
<td>No clinically significant QTc prolongation was seen at typically used therapeutic doses of psilocybin.</td>
</tr>
<tr>
<td>Davis AK (2021)</td>
<td>Waitlist controlled RCT</td>
<td>27, MDD</td>
<td>Psilocybin in conjunction with therapy produced quick, positive, and durable results in those with MDD.</td>
</tr>
<tr>
<td>Daws RE (2022)</td>
<td>Open-label/head-to-head DBRCT, secondary fMRI analysis of two studies</td>
<td>16, TRD; 59, MDD</td>
<td>The fMRI study suggests psilocybin may work by increasing global integration (network cross talk) and decreasing DMN activity. It appears to increase DMN connections to specific executive and salience networks associated with higher processing. This was not seen with subjects treated with escitalopram.</td>
</tr>
<tr>
<td>Gukasyan N (2022)</td>
<td>Randomized wait list controlled</td>
<td>27, MDD</td>
<td>Two treatment sessions with psilocybin continued to show large positive and durable effects on MDD.</td>
</tr>
<tr>
<td>Marshall J (2022)</td>
<td>DBRCT placebo-within subject crossover</td>
<td>75, healthy</td>
<td>Microdosing did not affect emotion processing or symptoms of anxiety and depression compared with placebo.</td>
</tr>
<tr>
<td>Mason NL (2020)</td>
<td>DBRCT, placebo-controlled parallel group</td>
<td>60, healthy</td>
<td>Acute changes induced by psilocybin led to alterations in glutamate levels, especially in the medial prefrontal cortex and hippocampus, which have high density of 5HT2a receptors, the main target of psilocybin. This corresponds to “ego dissolution,” the degree to which correlates with psilocybin’s positive effects on depression.</td>
</tr>
<tr>
<td>Mertens LJ (2020)</td>
<td>Open-label, secondary analysis</td>
<td>19, TRD</td>
<td>This fMRI study suggest that the connection between the prefrontal cortex and the amygdala is disrupted in those who respond to psilocybin treatment, corresponding to less rumination.</td>
</tr>
<tr>
<td>Roseman L (2018)</td>
<td>Open-label, secondary analysis</td>
<td>19, TRD</td>
<td>Unlike SSRIs, successful treatment with psilocybin was associated with increased amygdala responses to fearful vs. neutral faces one day after treatment. Authors hypothesized that the therapeutic response was related to emotional acceptance as opposed to dulling of both negative and positive emotions seen in SSRI treatment.</td>
</tr>
<tr>
<td>Rucker JJ (2022)</td>
<td>Phase 1 DBRCT placebo-controlled</td>
<td>89, healthy</td>
<td>For those participants who received a single therapeutic dose of psilocybin, no detrimental effects on emotional or cognitive processing were observed when compared to placebo.</td>
</tr>
</tbody>
</table>

DBRCT: double blind randomized controlled trial; MDD: major depressive disorder; TRD: treatment-resistant depression; DMN: default mode network; fMRI: functional magnetic resonance imaging; SSRI: selective serotonin reuptake inhibitor
mean change was $8 \pm 1$ and $6 \pm 1$ in the psilocybin and escitalopram groups, respectively. Response, defined as > 50% change in QIDS-SR-16, occurred in 70% of psilocybin patients and 48% in the escitalopram patients. Remission, defined as QIDS-SR-16 scores of 5 or less, was 57% vs. 28% in the psilocybin and escitalopram groups, respectively. Subjects in the psilocybin group also demonstrated greater improvement in wellbeing and lower average sexual dysfunction scores. Of the 16 assessments used, most comparisons favored the psilocybin group, but confidence intervals were not adjusted for multiple comparisons, so no clinical conclusions can be drawn. MRI results were analyzed in a separate publication and are discussed in a later section.º

SAFETY PROFILE
No serious adverse events were attributed to psilocybin administration in these studies. Carhart-Harris et al noted similar adverse event numbers when comparing escitalopram and psilocybin. The majority of adverse events recorded in the psilocybin group were within the first 24 hours, with headache being the most common. Brown et al and Dahmane et al looked at the pharmacokinetics of psilocybin, each using data from 12 healthy subjects at escalating doses and measuring plasma levels and metabolites over 24 hours. Peak plasma time was two hours, with a half-life of three to five hours. Slight increases in blood pressure and heart rate were seen. They did not find that body weight had a significant effect on max concentrations or the rate at which the drug was processed, suggesting a body weight adjustment is not necessary. A dose response increase in QTc was seen, but it likely was not enough to be clinically significant. Brown et al found negligible amounts of the active metabolite psilocin excreted in the urine, suggesting renal dosing is not necessary. The active metabolite psilocin is metabolized by the liver to psilocin-O-glucuronide. Therefore, limited first-pass metabolism may increase concentrations, although more studies are needed for subjects with other comorbidities to further characterize optimal dosing for this population. The subjects in both of these pharmacokinetic studies consisted mostly of white men, limiting their generalizability.º,11

In 2022, the largest randomized controlled trial to date on psilocybin (89 participants) attempted to explore the cognitive and emotional safety of psilocybin administration in healthy subjects. They assessed both short and longer-term changes in cognitive functioning and emotional processing by following participants for 12 weeks after receiving a placebo, 10 mg of psilocybin, or 25 mg of psilocybin. Psilocybin was found to be well-tolerated, with no serious side effects reported nor withdrawals attributed to side effects. No clinically relevant negative findings were seen in cognitive testing, and there were no short- or long-term detrimental effects on the social cognition and emotional functions assessed.

PSilocybin with SSRI
Psilocybin is thought to activate the 5HT2A receptor, a serotonergic receptor responsible for psilocybin’s psychotropic properties. A study by Becker et al attempted to see if co-administration was safe and effective because previous studies often required or encouraged stopping SSRI antidepressants prior to participation. They designed a double-blind, randomized controlled trial crossover study and enrolled 27 healthy subjects between 25-65 years of age, then divided them into two groups. Two participants dropped out prior to the start of the study, and one did so after.

One group received a placebo for 14 days while the other received 10 mg of escitalopram for seven days and then 20 mg for another seven days. Both groups received 25 mg of psilocybin on day 14. After a two-day washout period, the groups switched, with the second group taking a placebo and the first group taking escitalopram, with psilocybin administered at the end. There was no change in reported adverse events. Brain-derived neurotrophic factor levels and 5HT2A gene expression were measured and showed significant increases, but they were unaffected by co-administration.

Electrocardiograms were taken 1 and 2.5 hours after administration and showed no change in QTc, although the longest QTc in the group was someone co-administered psilocybin and escitalopram. Escitalopram co-administration attenuated blood pressure increases and pupil dilation, with a nonsignificant trend toward decrease in heart rate. The study also looked at alterations in consciousness using 5D-ASC and 3D-OAV and mystical experiences via SOCP questionnaire. Co-administration showed decreased acute untoward effects seen with psilocybin, such as “anxious ego dissolution,” perceived “bad drug effects,” and anxiety. But did not reduce the positive mood effects associated with psilocybin administration.º

HOW PSilocYBIN WORKS
Psychedelics appear to dysregulate cortical brain activity, enhancing various global connectivity. This is referred to by Dr. Robin Carhart-Harris (one of the leading researchers in studying brain effects to psychedelics) and her research group as network “disintegration” and “desegregation.” These brain effects, when studied during a psychedelic experience, seem to correlate with what patients experience as “ego-dissolution” and other key aspects to the psychedelic experience. In fact, these brain changes during the experience were found to correlate with the post-experience acute personality domain of “openness.”

In 2017, Dr. Carhart-Harris’ lab used functional MRI (fMRI) to analyze brain activity in patients with treatment-resistant depression who received psilocybin...
Participants received psilocybin 10 mg followed by 25 mg one week later, and fMRI was used both pre-treatment at baseline and one day following the treatment. The study specifically mentioned the concept of the “default mode network” (DMN) in the brain as it relates to depression and analyzed the brain activity in this area. The DMN is active in periods of self-directed thought and introspection, and dysfunction within the DMN may contribute to rumination and self-preoccupation in depressed patients.

Research in this area of the brain referred to as the DMN has suggested that increased DMN activity may be a marker of depressed mood and rumination. Brain activity one day after the psilocybin treatment was different than previous research has shown during the psychedelic state. Specifically, the previously observed decrease in DMN activity (in prior studies) under psilocybin was different post-treatment, with an increased DMN activity observed one day post-treatment. They also noted that the findings suggested a correlation in antidepressant action of electroconvulsive therapy and psilocybin in which DMN activity decreases acutely and increases (or normalizes) post-treatment, accompanied by improvements in depressive symptoms — referred to as a “reset.” This same study also found decreased blood flow in the amygdala post-psilocybin treatment correlated with a reduction in depressed mood. The study comparing escitalopram to psilocybin confirmed this finding, showing decreased DMN activity with psilocybin but no change seen with escitalopram. While the DMN is shown to decrease post-psilocybin, the functional connectivity between the executive network (EN) and salience network (SN), are increased. EN and SN are associated with higher cognitive flexibility and cognitive control as well as switching between internal vs. external attention. Psilocybin’s main targets, 5HT2a receptors, have a higher density among these SN and EN networks and explain the specific phenomenon seen with treatment.

A study by Roseman et al analyzed fMRI data on amygdala activity in a previous study measuring responses to psilocybin in those with treatment-resistant depression. Those experiencing untreated depression have been found to have a hypersensitive amygdala response to negative stimuli. SSRIs decrease the amygdala response to negative stimuli. In contrast, the study by Roseman et al found that treatment with psilocybin increased amygdala response to fearful, neutral, and happy stimuli, with significant differences between fearful vs. neutral stimuli one day following psilocybin administration. The amygdala is thought to be sensitive to emotional extremes, both positive and negative. Some data suggest that SSRIs blunt the amygdala’s response to both positive and negative stimuli, often described by patients as feeling “flat.” These fMRI data suggest it may be that psilocybin with therapy led to acceptance of all stimuli via confrontation and subsequent catharsis as opposed to SSRIs, which may reinforce emotional avoidance and disconnection.

Adding to this research will be an important next step to further clarify and compare how the “Default Mode Network” relates to depressive symptoms and treatment response to the variety of treatment modalities used for depression. Meditation also is linked to decreased DMN activity. Dr. Judson Brewer’s research team has looked at the brain with fMRI in both experienced meditators and meditation-naive people as they performed several different meditations. They found that the main nodes of the DMN were relatively deactivated in experienced meditators across all meditation types.

**FUTURE PROMISE AND CHALLENGES**

The use of psilocybin shows immense promise. Recent trials have shown that it can be as effective as the current first-line pharmacotherapy for depression and that psilocybin shows potential for those who have not responded to current conventional treatment.

Controlled trials to date have not shown any major adverse events. In fact, data suggest it can be used effectively with SSRIs without causing safety issues or compromising effectiveness of either therapy. Finally, the therapeutic actions have been shown to be quite durable months after administration. An open-label study enrolling those with treatment-resistant depression, with matched healthy controls receiving psilocybin, was able to identify likely responders using machine learning to differentiate based on speech, showing a 75% precision compared to 41% without. If it can be replicated, this shows promise for better identifying those who would benefit from treatment with psilocybin.

While there have been mostly positive data, questions remain unanswered. Trials, while well-designed, have been relatively small, consisting of fewer than 100 people. Psilocybin has been tested only in a very specific population that does not have other major mental health or medical comorbidities. Fogg et al also highlight how the racial and demographic disparities seen in healthcare overall are also present in psychedelic research. The vast majority of participants in these trials are Caucasian, missing potentially important genetic and cultural differences in how non-white groups process and react to psilocybin administration. This may lead to future suboptimal treatment among these groups.

In addition, psilocybin has only been studied with comprehensive psychological support that may not be available in the primary care setting. That said, one or two more intensive sessions may be preferable for some, as opposed to having to take a daily pill indefinitely.
Research with larger numbers and more diverse participant populations are required to confirm effectiveness and generalizability.

The main barrier to psilocybin research is its current legal status as a schedule 1 drug in the United States (defined as having high potential for abuse, no currently accepted medical treatment use, and lacking accepted safety standards for use under medical supervision). This makes investigation very difficult, with only the most well-funded and well-equipped labs able to study psilocybin. In addition, there is very little monetary incentive among pharmaceutical companies to pursue a substance that only requires one or two administrations for effectiveness and cannot be patented because of the wide availability and relatively uncomplicated purification process of the necessary mushrooms. For this reason, funding likely will need to be public as opposed to industry-based.

REFERENCES
Upon completion of this educational activity, participants should be able to:

- Present evidence-based clinical analyses of commonly used alternative therapies.
- Make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice.
- Describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

CME QUESTIONS

1. Psilocybin is what kind of medication?
   a. Schedule 1
   b. Schedule 2
   c. Schedule 3
   d. Schedule 4

2. Psilocybin activates what type of neurotransmitter receptors?
   a. Dopamine
   b. Glutamate
   c. Serotonin
   d. Norepinephrine

CME OBJECTIVES

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