

Oregon Psilocybin Advisory Board Rapid Evidence Review and Recommendations

July 30, 2021

Authors: The Oregon Psilocybin Evidence Review Writing Group*

*Writing group members:

Atheir I. Abbas, MD, PhD
Assistant Professor
Department of Behavioral Neuroscience
Department of Psychiatry
Oregon Health & Science University

Angela Carter, ND
Massage Therapist and Midwife
Chair, OHSU Transgender Health Program Community Advisory Board
Supervisor, Fireside Project

Thomas Jeanne, MD, MPH
Deputy State Health Officer
Oregon Health Authority
Public Health Division

Rachel Knox, MD, MBA
Endocannabinologist & Health Equity Consultant
Doctors Knox, Inc., ACHEM

P. Todd Korthuis, MD, MPH
Professor
Department of Medicine
Department of Public Health (secondary)
Addiction Medicine Section Head
Oregon Health & Science University

Ali Hamade, PhD
Deputy State Epidemiologist
Oregon Health Authority
Public Health Division

Christopher Stauffer, MD
Assistant Professor
Department of Psychiatry
Oregon Health & Science University

Jessie Uehling, PhD
Assistant Professor
College of Agricultural Sciences
Department of Botany and Plant Pathology
Oregon State University

Acknowledgements:

The authors would like to thank Tracy Dana for assistance with the rapid review literature search, and Sarann Bielavitz for reference formatting and copyediting.

Summary

High quality phase 1 and 2 clinical trials suggest that psilocybin is efficacious in reducing depression and anxiety, including in life-threatening conditions. The effect sizes of psilocybin treatment trials are large, though limited diversity of clinical trials participants limits generalizability. In all of these trials, psilocybin is administered in the context of counseling support in the weeks before and after dosing. The FDA has designated psilocybin a breakthrough therapy for treatment of depression, indicating that preliminary clinical evidence suggests it may represent a significant improvement over existing therapies. Initial research also suggests that psilocybin may be efficacious in reducing problematic alcohol and tobacco use. Across studies, psilocybin increases spiritual well-being which may mediate other observed benefits. Study participants also commonly rate their psilocybin experiences as highly meaningful.

Transient effects including nausea, vomiting, headache, increases in heart rate, increases in blood pressure, QT interval prolongation, grief, anxiety, fear, feelings of isolation, preoccupation with death, transient thought disorder, and transient paranoia may occur in a dose-dependent manner after use of psilocybin in supervised settings. Rare severe or longer-term adverse effects such as sustained worsening of depression and anxiety have been reported but their link to psilocybin treatment is unclear. Lifetime history of unsupervised psilocybin use is associated with decreased risk of mental health symptoms in population-based surveys. Well-established screening practices are used to exclude people thought to be at risk for adverse effects of psilocybin, but few psilocybin-specific tools are available to identify persons most likely to benefit or be harmed by psilocybin.

Published clinical trials have administered biosynthesized psilocybin, but mushroom consumption has been the dominant form of psilocybin used in traditional and unsupervised settings. *Psilocybe cubensis* is the best characterized mushroom species for production, though psilocybin and psilocin concentrations vary widely by dried weight of mushrooms. There are established technologies for analyzing commercial mushroom products to quantify psilocybin concentration and potential contaminants.

1. Introduction

Psychedelics have been used for millennia by indigenous cultures.^{1,2,3} Indigenous people with documented usage of psychedelic psilocybin-containing mushroom species include the Nahuatl, Mayans, Olmec, Mazatecs, Chinantecs, Mixes, Zapotecs, Chatinos, Colima, Purepechas and Totonacs of Mexico⁴ and some of the peoples of Central and South America.⁵ Of particular note, Mazatec healers, including Maria Sabina, utilized psilocybin-containing mushrooms (e.g., los niños santos, or teonanacotl) to understand disease processes and paths to holistic health. In traditional ceremonies, or veladas, both the provider and recipient use psilocybin-containing mushrooms, with singing and chanting to invoke spiritual beings who seek to dispel evil influences and replace them with beneficial ones.⁶ In the United States, interest and research focused on psilocybin has waxed and waned, but there has been a sharp increase that is at least in part the result of newer well-designed phase 1 and 2 trials suggesting it may have unique therapeutic properties for mental health conditions.

In 2020, Oregonians voted to pass Measure 109, which directs the Oregon Health Authority (OHA) to establish rules and regulations to support the provision of psilocybin services. Measure 109 also requires the Psilocybin Advisory Board to provide a focused summary of available scientific and other evidence and recommendations to the OHA, as outlined in Section 11 of Measure 109, to support the development of an Oregon psilocybin services framework:

Measure 109, Section 11 (3):

On or before June 30, 2021, and from time to time after such date, the board shall submit its findings and recommendations to the Oregon Health Authority on available medical, psychological, and scientific studies, research, and other information relating to the safety and efficacy of psilocybin in treating mental health conditions, including but not limited to addiction, depression, anxiety disorders, and end-of-life psychological distress.

The intent of this rapid review is to highlight particularly pertinent, high quality published works, rather than provide an exhaustive systematic review of the published literature. In its focus on published scientific evidence, the report excludes meaningful and significant experiences, knowledge, and wisdom from indigenous peoples and other communities and institutions not represented in scientific literature. The Oregon Psilocybin Advisory Board will augment this report with critical information from these communities before the full implementation of Measure 109.

2. Methods

The Psilocybin Advisory Board Research Subcommittee searched, reviewed, and summarized the available literature on the efficacy and safety of psilocybin to address key questions, which the full board approved on April 28, 2021. The Research Subcommittee conducted the rapid review over eight weeks using the World Health Organization's rapid review methodology to systematically summarize evidence that informs public policy in a short period of time.⁷ An experienced research librarian searched Ovid Medline, PsycINFO, and the Cochrane Library for articles published from inception through May 6, 2021 in Spanish, Russian, German, Danish, English, and Dutch. Specific search terms included psilocybin, psilocin (the main active metabolite of psilocybin), mushroom, randomized controlled trials, systematic review, meta-analysis, and risk assessment. Full search strategies are available in Appendix 5.

The search identified 632 citations. Research subcommittee members reviewed all abstracts and identified 273 relevant articles for full text review (163 articles for Key Questions 1 & 2 and 110 articles for Key Question 4). One relevant publication was identified for Key Question 3. We excluded commentaries and articles that did not involve human subjects, psilocybin, or clinical outcomes.

Published systematic reviews and randomized trials were prioritized for evidence synthesis. Research Subcommittee members supplemented the literature search with additional pertinent peer-reviewed publications when no randomized trials were available and to provide contextual information.

The Oregon Health Authority sought external expert peer review prior to the report's release on July 30, 2021. A public comment period is scheduled for August 2021.

3. Key Questions Summary

The Psilocybin Advisory Board approved the following key questions (KQ) to guide the evidence review:

KQ1. What are the potential benefits and risks* of psilocybin in controlled settings in persons seeking services for improving condition-specific symptoms and quality of life in the following categories?

- a. Depression
- b. Anxiety Disorders and Obsessive-Compulsive Disorder (OCD)
- c. Trauma-related Disorders, including racial trauma
- d. Substance use Disorders
- e. Palliative care
- f. Spirituality
- g. Other conditions

KQ2. What are the potential benefits and risks* of unsupervised psilocybin use?

KQ 1 & 2 Sub-question: How do the potential benefits and risks of psilocybin differ by population subgroups, including but not limited to dosage, psilocybin source, age, setting, co-ingestion, or personal characteristics?

KQ3. What are provider or patient risk assessment tools that can identify persons likely to benefit or be harmed by psilocybin-assisted therapy?

KQ4. What are the relative potential benefits and risks* of different sources of psilocybin?

*includes interpersonal, medical, and psychological risks

4. Evidence Synthesis

KQ1. What are the potential benefits and risks of psilocybin in controlled settings in persons seeking treatment for improving condition-specific symptoms and quality of life in the following categories?

Potential benefits, including interpersonal, medical, and psychological benefits:

Castro Santos & Marques⁸ published a systematic review of clinical evidence on psilocybin for the treatment of psychiatric disorders. They identified nine publications making up seven independent clinical trials: three for anxiety and depression related to life-threatening cancer^{9,10,11} (N=92); two for treatment-resistant depression¹² (N=20) and an earlier iteration of the same trial¹³ (N=12); two for tobacco use disorder¹⁴ (N=15), and a long-term follow-up with the same cohort;¹⁵ one for alcohol use disorder¹⁶ (N=10); and one for obsessive-compulsive disorder¹⁷ (N=9). The authors concluded that the

results of these studies suggest “substantial therapeutic potential” and call for further research to confirm results and explore underlying mechanisms. Furthermore, Goldberg *et al.*, 2020¹⁸ demonstrated statistically significant large effect sizes of psilocybin therapy on depression and anxiety in a meta-analysis of four of these clinical trials⁹⁻¹² (N=117). We identified three additional trials that confirm and advance the above findings¹⁹⁻²¹ as well as a trial for a non-psychiatric indication, migraine headaches.²² All eleven of these clinical trials are described in further detail below.

a. Depression

In an open-label, dose-escalating pilot trial of patients with treatment-resistant moderate-to-severe Major Depressive Disorder (n=12), depression measured on the Quick Inventory of Depressive Symptoms was reduced at 3 months post-treatment.¹³ Sixty-seven percent achieved remission of major depressive disorder at 1 week, and 42% maintained remission at 3 months. The protocol included four hours of preparatory sessions and post-psilocybin “debriefing.” This study was considered at high risk of bias due to small sample size, no placebo control/blinding, and no correction for multiple comparisons.

In a randomized crossover trial of two doses of psilocybin (20 mg/70 kg and 30 mg/70 kg, 1.6 weeks apart) with a wait-list control, participants with moderate-to-severe major depressive disorder (n= 24) experienced reductions in GRID-Hamilton Depression (GRID-HAMD) rating scales that favored the immediate treatment arm with large effect sizes at week 5 (Cohen’s $d=2.5$, $p<.001$) and week 8 ($d=2.6$, $p<.001$).²⁰ Fifty-four percent achieved remission of Major Depressive Disorder at four weeks, with moderate risk of bias due to lack of placebo control and blinding. The protocol included 8 hours of preparatory therapy and 2-3 hours of integrative therapy sessions.

In a double-blind, randomized trial of two doses of psilocybin (25 mg) versus escitalopram 10-20 mg/day for 6 weeks for treatment of Major Depressive Disorder (n=59), participants in both arms experienced decreases in Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16) measure of depressive symptoms at 6 weeks with no statistically significant difference between the psilocybin group and the escitalopram group at 6 weeks.²¹ The protocol consisted of 3 hours of preparatory therapy, two in-person integration therapy sessions, and 6 additional integration phone calls.

In an open-label, proof-of-concept trial (psilocybin 0.3 - 0.36 mg/kg) in men who have sex with men who were long-term AIDS survivors (n=18) with moderate-to-severe “demoralization” (i.e., “poor coping and a sense of helplessness, hopelessness, and a loss of meaning and purpose in life”),²³ which has a stronger association to suicidality than *DSM* Major Depressive Disorder, participants experienced reductions in the self-reported Demoralization Scale-II at the end of treatment and at 3 months (standardized effect size $\eta_p^2=.047$, 90% CI 0.21-0.60). At end-of-treatment and 3 months, 88.9% and 66.7% of participants, respectively, experienced sustained clinically significant reductions in demoralization.¹⁹ The protocol consisted of 1.5 hours of individual plus 6 hours of group preparatory therapy sessions and 2 hours of individual plus 6-9 hours of group integrative therapy sessions. Additional research trials examining the efficacy of psilocybin on cancer-related depression are described below in the palliative care section.

Additional multisite Phase 2 clinical trials are currently in progress for treatment-resistant depression (NCT03775200, n=216), and major depressive disorder (NCT03866174, n=80). Additional ongoing trials of psilocybin for depression include: NCT04670081 (n=144), NCT03554174, NCT03715127, NCT03380442, NCT04630964, NCT04123314 (depression in early Alzheimer’s disease/mild cognitive impairment), NCT04433845 (depression in bipolar II disorder), and NCT04620759 (depression in alcohol use disorder)

b. Anxiety Disorders and Obsessive Compulsive Disorder

A small, within-subjects, randomized dose escalation study of psilocybin treatment for Obsessive Compulsive Disorder¹⁷ (n=9) documented reductions in the Yale-Brown Obsessive-Compulsive Scale up to 24 hours after psilocybin administration. There was no associated preparatory or integrative therapy. This study has a high risk of bias due to its small sample size and short follow-up period. Additional trials examining the efficacy of psilocybin on cancer-related anxiety are described in the palliative care section.

Additional ongoing clinical trials of psilocybin for OCD include: NCT03300947, NCT03356483, NCT04882839

c. Trauma-related disorders and racial trauma

A high-quality systematic review of psychoactive drugs for the treatment of Post-Traumatic Stress Disorder (PTSD) identified no trials of psilocybin for treatment of PTSD.²⁴

There were no trials for use of psilocybin for racial trauma. Published clinical trials of psilocybin included fewer than 10% of participants from under-represented minority groups. A cross-sectional internet-based survey²⁵ of Black, Indigenous, and people of color in North America who reported a positive experience with psychedelics in the past (n=313), 37% of whom had used psilocybin, asked participants to rate Trauma Symptoms of Discrimination Scale (TSDS) scores before and after their previous psychedelic experiences. Respondents reported reductions in TSDS score following their use of psychedelics. The study has a high risk of bias due to cross-sectional design, potential selection bias, and potential recall bias.

d. Substance Use Disorders

An open-label, uncontrolled, dose-escalation trial combined psilocybin (20 mg/70 kg, 30 mg/70 kg, and an optional third dose of 20–30 mg/70 kg) with cognitive behavioral therapy for smoking cessation (6 hours of preparatory counseling sessions and up to 10.5 hours of integrative counseling sessions).¹⁴ Participants with tobacco use disorder (n=15) smoked an average of 19 cigarettes/day (range 15–25) and had an average of 6 unsuccessful previous quit attempts (range 2–12). Eighty percent of participants had confirmed tobacco abstinence at six months. In a follow-up study, 67% were confirmed smoking abstinent at 12 months.¹⁵

An open-label, within-subjects, dose-escalation trial of two dosing sessions of psilocybin (0.3 mg/kg and 0.3–0.4 mg/kg 8 weeks apart) in participants with *DSM-IV* Alcohol Dependence not currently in treatment (n=10) assessed change in drinking days and heavy-drinking days.¹⁶ The protocol included 7 sessions of Motivational Enhancement Therapy in addition to 3 psilocybin preparatory sessions and 2 psilocybin integration sessions. Psilocybin treatment was associated with large reductions in the percentage of drinking days ($d=1.19$, $p=.007$) and percentage of heavy drinking days ($d=1.38$, $p=.004$) in weeks 25–36 compared with baseline.

Additional ongoing clinical trials of psilocybin for substance use disorders include:

- Alcohol Use Disorder: NCT02061293 (n=135), NCT04141501, NCT04410913, NCT04620759 (with Major Depressive Disorder)

- Tobacco Use Disorder: NCT01943994 (n=95)
- Cocaine Use Disorder: NCT02037126
- Opioid Use Disorder: NCT04161066 (in combination with buprenorphine)

e. Palliative care (pain, end-of-life, etc.)

A within-subjects, double-blind, placebo-controlled trial¹⁰ randomized participants (n=12) with advanced-stage cancer and *DSM-IV* acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety, to receive psilocybin (0.2 mg/kg) versus niacin (250 mg) as an active control. All participants received both psilocybin and placebo several weeks apart, along with unstructured support. Participants experienced no difference in State-Trait Anxiety Inventory score following placebo versus niacin. After dosing with either psilocybin or niacin, State-Trait Anxiety Inventory scores decreased at one and three-month follow-up, but differences were attenuated at six months. Depression, as measured by the Beck Depression Inventory, was improved at six months.

A double-blind, placebo-controlled crossover trial¹¹ tested psilocybin (0.3 mg/kg) versus niacin (250 mg) as an active control seven weeks apart in participants with a life-threatening cancer diagnosis and *DSM-IV* anxiety disorder (n=29). The protocol included six hours of preparatory therapy and 12 hours of integrative therapy, with additional support available from study therapists for 26 weeks after the final study session. Depression scores (Beck Depression Inventory and Hospital Anxiety and Depression Scale) and anxiety scores (State-Trait Anxiety Inventory and Hospital Anxiety and Depression Scale) improved following treatment and were sustained at 6.5 months with Cohen's *d* effect sizes of 0.82 to 1.29.

A double-blind, placebo-controlled crossover trial⁹ tested psilocybin (22 or 33 mg/70 kg) versus low-dose psilocybin (1 or 3 mg/70 kg; considered a placebo dose) in participants with a life-threatening cancer diagnosis and *DSM-IV* anxiety and/or mood disorder (n=51). Each participant received both doses of psilocybin approximately 5 weeks apart in a randomized order in addition to ~7.9 hours of preparatory therapy and ~7 hours of integrative therapy. Participants receiving high-dose psilocybin first experienced improvements in GRID-Hamilton Depression Rating Scale (GRID-HAM-D-17) and Hamilton Anxiety Rating Scale (HAM-A) (Cohen's *d*=1.30, *p*<.001 for depression; Cohen's *d*=1.23, *p*<.001 for anxiety). Improvements in depression and anxiety remained significant for all participants at 6-month follow-up compared to baseline. At 6-month follow-up, 71% and 63% remained in remission for depression and anxiety, respectively, in the high-dose-first group; while 59% and 50% remained in remission for depression and anxiety, respectively, in the low-dose-first group.

A meta-analysis²⁶ of the three cancer-related anxiety and depression clinical trials significantly favored psilocybin versus the control group regarding effects on depression (Beck Depression Inventory) and anxiety (State-Trait Anxiety Inventory).

Additional clinical trials are currently underway for depression in cancer patients (NCT04593563), and existential distress in palliative care (NCT04754061).

f. Spirituality

Psychedelics have been used for millennia by indigenous cultures for religious ceremonies and mystical rituals.¹⁻³ Indigenous people with documented usage of psychedelic psilocybin species include the Nahuatl, Mayans, Olmec, Mazatecs, Chinantecs, Mixes, Zapotecs, Chatinos, Colima, Purepechas and Totonacs of Mexico⁴ and indigenous peoples in parts of Central and South America.⁵

One of the proposed mechanisms for observed improvements in depression and anxiety symptoms in clinical trials is a sense of spiritual well-being that many people report during psilocybin treatment. Spiritual phenomenology or mystical experiences in these trials include self-reported experience of meaning beyond oneself and sense of interconnectedness. A landmark, high quality, double-blinded crossover randomized trial²⁷ of therapist-facilitated psilocybin (30 mg/70 kg) versus active control (methylphenidate 40mg/70kg) in healthy, psychedelic-naïve volunteers assessed measures of mystical experience using the Mysticism Scale²⁸ 7 hours and 60 days after ingestion. Volunteers received four preparatory sessions with their therapist before four integration sessions after the day of medication administration. At two months, participants reported experiences of substantial personal meaning and spiritual significance associated with psilocybin exposure. Sixty-seven percent of participants rated their psilocybin experience as the single most or top five most meaningful experience of their lives.

A systematic review²⁹ of psychedelic treatment outcomes identified 10 randomized trials that assessed long-term changes in spirituality after psilocybin use. Nine of these 10 trials demonstrated increases in ratings of spiritual well-being from two to 16 months following psilocybin administration. Four of seven trials reporting openness to experiences documented lasting changes in openness.³⁰⁻³² One trial reported sustained increases in meditation frequency³¹ and one trial documented increases in mindfulness.³²

g. Other Conditions:

We identified one within-subjects pilot randomized trial²² of psilocybin versus placebo in people with migraine headaches (n=10). Twenty percent of participants reported at least a 50% reduction following placebo, whereas 50% of participants reported a 50% reduction in weekly migraine days following psilocybin.

Trials are currently in progress to assess the efficacy of psilocybin for treatment of migraine headache (NCT03341689, NCT04218539), cluster headache (NCT04280055, NCT02981173), post-concussion headache (NCT03806985), short-lasting unilateral neuralgiform headache attacks (NCT04905121), anorexia nervosa (NCT04052568, NCT04505189, NCT04661514), and body dysmorphic disorder (NCT04656301).

Risks, including interpersonal, medical, and psychological risks:

Like all interventions, psilocybin is associated with other effects that are generally reported in the scientific literature as adverse effects or adverse events. We have in some instances chosen to use the adjective "adverse" to describe these effects and in others have chosen not to qualify the effects. This choice does not imply certainty regarding whether or not they are adverse effects. We also emphasize that many of these effects have not been definitively linked to any actual harms and some (e.g., anxiety) might be positively correlated with therapeutic benefit.

Psilocybin is associated with risks that fall into two main categories: physical and psychological. The best characterization of these transient effects is in clinical trials, many of which are described above, in which they are quantified, and frequency and/or severity of the adverse effects is compared to individuals who have received placebo or an active comparator treatment. These effects typically are seen during the administration period. Most effects appear to be dose-dependent—the higher the dose, the more common or intense the effect.³³⁻³⁵ Examples of transient adverse physical effects include nausea, vomiting, headache, increases in heart rate, increases in blood pressure, and QT interval prolongation (a change in electrical conduction in the heart).^{8,33} Psilocybin at a range of doses did not increase body temperature.³⁶ Examples of transient psychological effects include grief, anxiety or fear, feelings of insanity, feelings of isolation, preoccupation with death, transient thought disorder, and

transient paranoia.^{8,20,37} Some of the transient adverse effects listed above can co-occur with transient and lasting benefits.²⁰

Dahmane et al³³ found in a small group of volunteers that age and body weight had no effect on psilocin area under the curve (AUC)—a measure of total drug exposure, and maximum plasma concentration (C_{max}) and suggested that body weight-adjusted dosing is not necessary. The authors suggested 25 mg of psilocybin as a clinical dose at which no clinically significant change in QT interval occurs, while higher doses can result in worsening QTc prolongation. These dose considerations do not account for repeated psilocybin microdosing, a practice that might require further study.

Scientific research to date suggests that long-term adverse effects due to psilocybin and other psychedelics are rare, with the vast majority of clinical trials reporting no long-term adverse effects.^{11,29,38} Individuals with depression³⁹ and individuals with substance use disorders⁴⁰ have specifically noted a subjective lack of long-term adverse effects. A small subset of individuals experienced less transient adverse effects such as “emotional instability” that resolved within weeks to months.⁴¹ Anxiety and depression that persist well beyond the administration period have been reported in at least two individuals.^{41,42} In a head-to-head comparison of psilocybin versus the SSRI escitalopram, the frequency of adverse events and benefits of psilocybin were comparable to those of escitalopram.²¹

Serotonin syndrome is a toxicity related to consuming one or more drugs that affect serotonin transporters or receptors. Psilocybin acts on serotonin receptors. The risk for this syndrome varies considerably from drug to drug and is highest with combinations of serotonin drugs.⁴³ Serotonin syndrome has not been reported in clinical studies with psilocybin and only one article detailing three case reports was found.⁴⁴ Hallucinogen Persisting Perception Disorder (HPPD) has been associated with unsupervised psychedelic use, primarily LSD and cannabis.⁴⁵ One case report describes an individual who experienced HPDD after psilocybin and cannabis use.⁴⁶ This syndrome has not been reported after supervised clinical use. Psilocybin use in human research settings⁴⁷ and in the community⁴⁸ has not been associated with compulsive, repetitive use.

It should be noted that much of the research describing transient negative effects is of higher quality, often quantified in the setting of a randomized, controlled clinical trial and in some cases with a placebo or active drug comparator. This strengthens the linkage of these adverse effects to psilocybin and the quantification of their frequency and severity. Much of the research literature regarding more serious adverse events comprises low-quality case reports or descriptions of one or two individuals experiencing these adverse events in the context of a clinical trial. As a result, these events are difficult to definitively link to psilocybin, either because they are rare or because no actual link exists.

Many psychedelic experts have emphasized the importance of the context (“set and setting”) of psilocybin administration with respect to some transient negative effects. However, even in tightly controlled research settings, transient psychological manifestations such as anxiety and fear are common.²⁷ Pooled data from 23 placebo-controlled studies suggests that psilocybin dose and subject characteristics are the two most critical determinants of the psilocybin experience.⁴⁹ Some warn against administering psychedelics to those having personal or family history of psychotic disorders or other severe psychiatric disorders.³ In a comparison of the effects of psychedelics (not just psilocybin) and the symptoms of schizophrenia, Leptourgos et al.⁵⁰ found that subjects using psychedelics can typically recognize distortions in their experience of reality, in contrast to the lack of insight into distortions of reality encountered in schizophrenic psychosis.

Consumption of whole mushrooms may carry additional potential risks. Individuals with fungal allergies are at risk for adverse reactions from whole fungal products. Consuming whole mushroom products

poses unique risks, as species of psilocybin-producing fungi vary in the presence and concentration of other bioactive indole alkaloids with structural homology to psilocybin such as baeocystin.⁵¹⁻⁵⁴ There is variability in presence and abundance of phenylethylalanines in mushrooms which are structural relatives to amphetamines and may induce tachycardia, nausea, and anxiety.⁵⁵ Other safety considerations during mushroom production include unintentional ingestion due to insufficient personal protective equipment and occupational hazards associated with fungal cultivation and or molecular/biochemical labs. Adverse reactions have also been described when combining psilocybin mushrooms with alcohol, cannabis, cocaine, MDMA.⁵⁶

Additional information related to KQ1

Please note that more detailed summaries of many of the clinical trials cited above are contained within this document in Appendix 1.

KQ2. What are the potential benefits and risks of unsupervised psilocybin use?

No randomized trials assess the potential benefits and risks of unsupervised psilocybin use. Limited data from observational studies of people regarding unsupervised use suggest that the majority of people using unsupervised psilocybin mushrooms experience subjective benefits and minimal risks. Retrospective studies suggest that the individuals who have consumed psilocybin in the community rarely experience long-term adverse consequences. A review⁵⁷ of 6000 psilocybin exposures reported to the National Poison Center between 2000 and 2016 indicated that most calls were from adolescents and young men and were mostly associated with mild and moderate adverse events. A thorough literature review^{58,59} spanning many decades resulted in rare case reports of severe morbidity or mortality associated with unmonitored psilocybin use in the community. Retrospective studies note few fatalities in which psilocybin was believed to be the only drug used, with the few deaths reported usually resulting from events such as drowning or motor vehicle crashes.⁵⁷ Circumstances in most cases were poorly characterized.

In a nationally representative U.S. household survey,⁶⁰ any lifetime use of psilocybin was associated with decreased adjusted odds of inpatient mental health hospitalization (adjusted odds ratio (aOR)=0.7 [0.5–0.8]), medications for mental health treatment (aOR=0.8 [0.7–0.9]), serious psychological distress (aOR=0.9 [0.8–1.0]), and diagnosis of depression (aOR=0.8 [0.7–1.0]) In a separate analysis⁶¹ of these data, lifetime psychedelic use, including psilocybin, was associated with reduced odds of past-month psychological distress (weighted odds ratio (OR)=0.81 (0.72–0.91)), past-year suicidal thinking (weighted OR=0.86 (0.78–0.94)), past-year suicidal planning (weighted OR=0.71 (0.54–0.94)), and past-year suicide attempt (weighted OR=0.64 (0.46–0.89)), whereas lifetime illicit use of other drugs was largely associated with an increased likelihood of these outcomes. Similarly, any lifetime use of classical psychedelics including psilocybin was associated with a reduced odds of past year larceny/theft (aOR=0.73 (0.65–0.83)), past year assault (aOR = 0.88 (0.80-0.97)), past year arrest for a property crime (aOR=0.78 (0.65–0.95)), and past year arrest for a violent crime (aOR=0.82 (0.70–0.97)), whereas other drug use increased the odds of these outcomes.⁶²

Observational studies seeking to assess risks of unsupervised use generally had high risk of bias due to lack of comparison groups or population-based estimates, and cross-sectional study designs. In 346 self-reported psilocybin “bad trips”, females were more represented and the episodes were associated with thought disorder.⁶³ The use of multiple doses of psilocybin in the same session or combining it with other substances was linked to the occurrence of long-term negative outcomes, while the use of

mushrooms in single high doses was linked to self-reported emergencies involving a need for assistance from parents or emergency responders.⁶³ In a web-based survey⁶⁴ of people using psilocybin mushrooms (n=1993), participants reporting challenging experiences (i.e., “bad trips”) while taking psilocybin had greater odds of testing positive for neuroticism on the Ten-Item Personality Inventory.

Sub-question for KQ 1 & 2: How do the potential benefits and risks of psilocybin differ by population subgroups including but not limited to dosage, psilocybin source, age, setting, co-ingestion, or personal characteristics?

No clinical trials have been conducted specifically to assess the potential benefits and risks of psilocybin in population subgroups. Reported demographic data about psilocybin indicate that majority of participants are white, college-educated, cis-gender males with few medical comorbidities. Consistent with Phase 1 and 2 clinical trials research on psilocybin treatment, most published psilocybin trials exclude patients with comorbid psychiatric and medical conditions. We are consequently unable to comment on differences in psilocybin response by race/ethnicity, gender, or medical subgroups. This limits the generalizability of currently available clinical trials.

Potential benefits and risks synthetic versus mushroom-based psilocybin sources are addressed in key question 4. There are no head-to-head clinical trials comparing synthetic psilocybin to psilocybin-containing mushrooms.

KQ3. What are provider or patient risk assessment tools that can identify persons likely to potentially benefit or experience increased risk of adverse events by psilocybin-assisted therapy?

There are no scientifically validated risk assessment tools for identifying persons with increased likelihood of benefit or harms from psilocybin-assisted services in clinical practice. We identified one study⁶⁵ that used a natural speech analytics/machine-learning algorithm to analyze structured interview questions and identify speech patterns that predicted the likelihood of psilocybin efficacy for treatment resistant depression. The algorithm improved identification of people likely to experience relief of depressive symptoms with psilocybin treatment. The study was conducted in the context of the psilocybin pilot trial for treatment resistant described above.¹³ Such an algorithm could become clinically useful if further tested, validated, and commercialized for clinical use.

Participants considered at increased risk of mental or physical harm from psilocybin have typically been excluded from clinical trials. Examples include individuals with schizophrenia or heart conditions. Appendices 2 and 3 contain sample screening considerations and instruments along with background information; many of these considerations are directly related to scientifically established risks or potential risks described in KQ1 and KQ2.

KQ4. What are the relative potential benefits and risks of different sources of psilocybin?

a. Fungal physiology, genetics, and identification

i. Structure and synthesis of psilocybin

Psilocybin and the dephosphorylated psychotropic agent psilocin are bioactive indole alkaloids originally derived from fungi. Psilocybin and psilocin and closely related fungal secondary metabolites resulting from coordinated activities of genes which are spatially clustered in fungal genomes.⁶⁶ The

psilocybin production or Psy genes occupy an ~11–22 kilobase genomic region including four genes for synthesis and transport.^{53,67-73}

ii. Identity and species of fungi producing psilocybin

Psilocybin and psilocin production has been documented in species of the fungal genera *Psilocybe*, *Conocybe*, *Gymnopilus*, *Panaeolus*, *Pluteus*, and *Stropharia*.^{66,74} In total, there are over 200 species in over six genera of fungi producing psilocybin and psilocin.^{4,75,76} Some of these species (*P. azurescens*, *P. stuntzii*, *P. alennii* and other species that grow on decaying wood) are believed to produce chemicals of unknown structure that cause temporary paralysis (a.k.a. “wood lovers’ paralysis”). While this phenomenon is not yet documented in the primary literature, extreme care should be taken to avoid adverse reactions by consumption of these species.

The wide majority of currently cultivated *Psilocybe* fungi are *P. cubensis*. While species level DNA-based, barcode sequences of the internal transcribed spacer region (ITS) of ribosomal DNA (rDNA) are available in public data repositories such as the National Center for Biotechnology (NCBI) GenBank, accuracy of species-level identification is unclear. Currently there are assembled genomes or raw whole genome and transcriptome data in NCBI databases of *Psilocybe cubensis* (GCA_017499595.1), *P. cf. subviscida* (GCA_013368295.1) and *P. cyanescens* (GCA_002938375.1). The generation of fungal genetic and genomic resources for psilocybin-producing fungi is crucial for their accurate identification.

iii. Identification of psilocybin producing fungi

Fungi can be reliably identified to the species level using DNA sequencing by analyzing either genes (short DNA segments) or whole genome sequences (the total DNA in an organism). Further information can be used in concert with molecular DNA data to confidently assign fungal identity including quantifying microscopic morphological observations,^{77,78} noting species, generic, or familial level characteristics such as spore color in deposit, the presence or absence of tissues such as veils, overall mushroom color, size and stature, morphological patterns of cap or pileal margins,⁴ and the presence or absence of characteristic blue staining.^{66,79} The majority of fungal species that produce psilocybin and psilocin have very visually similar relatives with deadly toxins; misidentification can lead to death.⁷⁵ Potential harms of ingesting misidentified fungi include gastrointestinal distress, cellular destruction, liver and kidney damage, autonomic and central nervous system malfunction, and death.^{75,80} Accurate identification of fungi to species requires molecular DNA sequencing combined with expert evaluation of salient micro- and macromorphological features.

b. Psilocybin production, extraction, and quantification

i. Diversity of psilocybin products

The potential sources for obtaining psilocybin products include (1) *in vivo* cultivation of mushrooms or other naturally occurring fungal tissues such as hyphae or sclerotia; (2) production of psilocybin artificially in cell culture using genetic model organisms^{81,82} or (3) *in vitro* chemical biosynthesis.^{70,83} The majority of published or in progress clinical trials utilize synthetic psilocybin.²⁰ Psilocybin products in use differ by region and include a long history of whole mushrooms in Mexico and Central and South America,^{4,84,85} and truffles or sclerotia in Europe.⁵² In addition to these biological products, it has become possible more recently to isolate and purify psilocybin from fungal tissues *en masse* or from cell cultures^{81,82} and to synthesize psilocybin *in vitro*.^{70,83} Accounting for solvents used in extractions and carryover of potentially harmful chemicals or pathogenic microbes (bacteria, viruses, parasites, fungi) from cultivation substrates, especially in compost or dung, will be paramount to ensuring

consumer safety. Creating genetically modified microbes that can take residence in the mammalian gut such as *Escherichia coli* or *Saccharomyces cerevisiae* may also carry unique risks.

ii. Psilocybin concentration by product

It has been estimated that fungal tissues differ greatly in psilocybin and psilocin content ranging from ~0.01-2.00% by dry weight.^{51,86} Ingesting 1–4 grams of dried, whole mushrooms, 4–10 mg of pure psilocybin, or 50–300 µg/kg body weight have been considered a dose.^{36,55} The notable variability in psilocybin content from species to species and even between mushrooms in the same fruiting flush^{52,86,87} coupled with a historical focus on grams of dry weight fungi for ingestion⁴ have led to lack of consensus regarding psilocybin dose quantification. Understanding the relationship between psilocybin concentration and client dosing will be essential to ensuring safe and effective psilocybin treatments.

iii. Psilocybin extraction and quantification in products

Accurate and reliable quantification of psilocybin and psilocin from fungal tissues or extracts relies on chromatography approaches. Separation and quantification of compounds can be achieved using amino-type polar phase or silica columns combined with reversed-phase liquid chromatography (HPLC)⁸⁸⁻⁹¹ or with fluorescence (FL) detection.⁸⁸ Products can then be identified via comparison to internal standards, such as 5-methoxytryptamin.⁸⁷ Similar chromatographic or mass spec methods can be used to differentiate between fungi that have been counterfeit (impregnated with other psychedelics such as LSD) with these methods and Thin Layer Chromatography (TLC).⁹²

Extraction of psilocybin and psilocin from dried fungal tissues is possible using methanol,⁹³ and other polar solvents such as water, water-alcohol mixtures, and buffer solutions.^{94,95} Sonication, maceration, and rotation may affect extraction yields.⁹⁴ Qualitative detection of psilocybin and psilocin can be achieved leveraging TLC separations and visualization with Ehrlich's reagent.⁹¹ Quantitative psilocybin and psilocin detection methods involve gas chromatography (GC), high-performance liquid chromatography (HPLC), or ultra-high-performance liquid chromatography (UPLC/UHPLC) methods.⁹⁵

Separation of psilocybin and psilocin from fungal tissue homogenate can be carried out using HPLC columns which differentially move cellular contents based on their molecular polarity and result in retention time metrics that are used to identify compounds in complex samples. Normal and reverse phase HPLC differ in the polarity of their stationary and mobile phases and can be adapted to isolate psilocybin and psilocin accordingly.⁹⁵ In a related approach called hydrophilic interaction liquid chromatography (HILIC) a hydrophilic stationary phase is combined with reversed mobile phases and results in longer psilocybin and psilocin retention times. Utilizing larger or longer columns and combining columns can differentiate between psilocybin, psilocin, and other related highly polar compounds based on their retention times.⁹⁶⁻⁹⁸

Detection of psilocybin and psilocin can be achieved by combining HPLC systems with either an ultra-violet/visible light spectroscopy detector (HPLC-UV/Vis) or diode array detectors (DAD). Psilocybin concentration data can be derived from these analyses by quantifying the amount of specific wavelength UV or visible light absorbed by a molecule. A second approach for detection of psilocybin, psilocin, and related compounds is by coupling HPLC systems with mass spectrometers (HPLC-MS). Molecules of interest are first filtered and then collided with an inert gas in a collision cell to yield daughter ions as fragments of the initial mass. The resulting molecular fingerprints can be used to precisely identify psilocybin, psilocin, and potential contaminants in samples.^{94-96,98}

Quantification of psilocybin, psilocin, and other compounds is achieved by comparing experimental samples to a calibration curve of data from pure analytes (psilocybin or psilocin) prepared at a range of

known concentrations. To avoid quantification artifacts related to chemical interactions, an internal standard such as deuterated psilocybin, psilocybin-d4,⁹⁹ or synthetic indolealkylamine derivatives and structural isomers^{100,101} can be included in experimental samples.

Potential psilocybin product contaminants include (1) residual solvents and/or disinfectants used for sterilization or involved in the extraction process, (2) toxic metals, pesticides, antibiotics, herbicides, animal husbandry medications, and bioaccumulated from contaminated growth substrates, (3) microbiological concerns in the form of both other fungi and bacteria, and (4) insecticides, antibiotics, or other pesticides which may be applied directly to fungi in an attempt to limit the presence of flies and mites

Mushrooms and fungal tissues are ephemeral structures prone to microbial, insect-related and arachnid-related decay. Common mushroom contaminants that can be screened for include species of the fungal genera *Trichoderma* (green mold), *Aspergillus*, *Dactylium*, *Lecanicillium*, *Mucor*, *Rhizopus*, *Mycogone*, *Neurospora*, and *Penicillium*.¹⁰² Bacteria that affect mushrooms and fungal cultures include species of the genera *Pseudomonas* and *Ewingella* and others.¹⁰² Insect and arachnid pathogens of mushrooms include species of the genera *Lycoriella*, *Megaselia*, *Heteropeza*, *Mycophila*, *Leptocera*, *Tyrophagus*, *Caloglyphus*, *Linopodes*, *Tarsonemus*, and *Pygmephorus*.¹⁰²

The presence and quantity of contaminants including residual solvents from extractions and disinfectants from cultivation¹⁰²⁻¹⁰⁵ can be evaluated using GC-MS, HPLC-MS, or HPLC-UV/Vis. Bioaccumulated heavy metals can be detected and quantified using atomic absorption spectroscopy (AAS), atomic fluorescence spectroscopy (AFS), x-ray fluorescence (XRF), inductively coupled plasma atomic emission spectroscopy (ICP-AES), inductively coupled plasma optical emission spectroscopy (ICP-OES), and inductively coupled plasma mass spectrometry (ICP-MS) or quadrupole ICP-MS.¹⁰⁶⁻¹¹⁸ Residual pesticides in mushrooms or hyphae can be detected using GC-MS, GC-MS/MS, HPLC-MS, HPLC-MS/MS, UPLC-MS, UPLC-MS/MS, and hybrid quadrupole-Orbitrap HPLC systems.¹¹⁹⁻¹²²

Additional information related to KQ4

Please note that additional information related to the detection and/or quantification of psilocybin in the human body and potential risks related to consumption of psilocybin containing mushrooms is contained within this document in Appendix 4.

Rapid Review Limitations

The above rapid review findings should be interpreted in light of several potential limitations. First, clinical trials of psilocybin services are in early phases, with small sample sizes and focus on safety measures that excluded participants with common comorbid medical and psychiatric conditions, consistent with early-phase research. Second, available clinical trials and observational studies participants were nearly all White, college-educated, cis-gender men. Both of these important limitations of the scientific literature impact generalizability of efficacy and safety results to groups of people who were not included in these studies. Third, the authors acknowledge the limitations of the Western research model and how it might inequitably stratify evidence (i.e. evidence inequity). This rapid review excludes meaningful experiences, knowledge, and wisdom from indigenous peoples and other communities and institutions not represented in the scientific literature. Finally, rapid review methodology necessarily limits the scope and depth of literature review to address key public policy questions on a compressed timeline. We did not attempt to survey unpublished literature, indigenous knowledge, grey literature (information produced outside of conventional publishing and distribution channels), or interview key stakeholders who may have provided additional valuable information.

Recommendations

1. To end evidence inequity, Oregon Health Authority (OHA) should gather additional information from individuals, communities, and institutions not represented in Western scientific literature (e.g., those administering psilocybin in cultures with longstanding practices and others with experience administering psilocybin in the community) to aid in developing best practices for a psilocybin services framework that maximizes equity and potential benefits and minimizes risks
2. The OHA should consider strength of evidence and risk of bias in developing a psilocybin treatment framework, particularly given the early stage of most psilocybin treatment trials.
3. OHA should consider commissioning an ongoing review (a.k.a. “living review”) mechanism to periodically summarize updates in the field of psilocybin research as they arise, given the rapidly evolving evidence base for psilocybin potential benefits and risks.
4. OHA should consider how consumers and providers of psilocybin services are informed of the potential negative effects that can occur during and after psilocybin administration (e.g., citizen education initiatives and informed consent process for consumers; incorporation of common acute and rare long-term adverse events into training, licensing, and ongoing continuing education processes for providers).
5. Because there is evidence of dose dependence of the potential benefits and risks of psilocybin, OHA should support the development of guidance regarding optimal dosing parameters to minimize these negative effects and consider how this knowledge should be disseminated to psilocybin providers and consumers (e.g., during provider training and licensing and/or via product monitoring and control).
6. OHA should consider the role of screening processes to identify individuals at higher than usual risk of negative physical and psychological effects of psilocybin and how to use this information to promote safety while preserving equitable access.
7. Given the limited generalizability of currently available clinical trials, OHA should explore the feasibility of developing a voluntary process and outcome measures for ongoing monitoring of psilocybin services implementation in Oregon, including consensual assessment of implementation in key population subgroups (e.g., by race/ethnicity, gender, and comorbid medical conditions), indications for psilocybin services, psilocybin exposure (e.g., amount and source type of psilocybin), and condition-specific outcome measures to help inform safety and equitable access to psilocybin services. Declining to share information should not affect access to psilocybin services, and the optional nature of the data sharing should be prominently emphasized during the informed consent process.
8. OHA should consider the range of research on cultivating and characterizing psilocybin-containing mushrooms (e.g., genotyping to confirm identity, methods for measuring psilocybin concentration) in developing a regulatory framework.
9. Because of toxicity concerns, OHA should initially consider prioritizing cultivation of *Psilocybe cubensis* and use of grain-based substrates for cultivation rather than dung or wood, and revisit cultivation of other species as more information becomes available.
10. OHA should explore feasibility and capacity of employing modern DNA sequencing-based techniques to identify fungi and fungal tissues for use in production licensing and quality control.

11. OHA should facilitate the development of screening requirements for possible mushroom contaminants. These may include the following:
- Residual solvents and/or disinfectants used in the extraction or sterilization processes
 - Toxic metals, pesticides, antibiotics, herbicides, livestock medications, and other potential bioaccumulation contaminants from growth substrates or direct application
 - Pathogenic microbes (bacteria, viruses, parasites, other fungi) and microbially produced toxins

Appendix 1. Detailed Psilocybin Research Trial Information

1. Depression & Demoralization

a. **Carhart-Harris et al. (2016)**¹³ - ISRCTN14426797

Design: open-label, dose-escalating

Dosing: 1: psilocybin 10 mg, 2: psilocybin 25 mg; two psilocybin sessions 7 days apart

Psychotherapy protocol: 4 hours of preparatory therapy + “debriefing”

Participants: n=12; moderate-severe treatment-resistant major depressive disorder

Primary Outcome Measures: Quick Inventory of Depressive Symptoms (QIDS)

Primary Outcome: Depression was significantly reduced from baseline up to the final follow-up at 3 months ($p=.003$) post-treatment. 67% achieved remission of major depressive disorder at 1 week, and 42% maintained remission at 3 months.

Secondary Outcomes: Significant reductions were also seen in the Beck Depression Inventory ($p=.002$), State-Trait Anxiety Inventory-Trait ($p=.004$), and the Snaith-Hamilton Pleasure Scale, which measures anhedonia ($p=.002$).

Long-term Follow-up & Exploratory Outcomes: Subsequently, an additional 8 participants were enrolled in this study. In the full sample ($n=20$), QIDS was reduced at 5 weeks (Cohen’s $d=2.3$), 3 months ($d=1.5$), and 6 months ($d=1.4$, all $p<.001$); Beck Depression Inventory was reduced at 3 months ($p<.001$) and 6 months ($p<.001$); State-Trait Anxiety-Trait was reduced at 3 months ($p<.001$) and 6 months ($p<.001$); and Snaith-Hamilton Pleasure Scale was reduced at 3 months ($p=.005$). Neuroticism scores significantly decreased and Extraversion and Openness increased using the Revised NEO Personality Inventory.³⁰ Increased amygdala responses to emotional stimuli were seen on fMRI.¹²³ Features of the psilocybin-occasioned mystical experience.¹²³ Thematic qualitative analysis was used to describe participants’ experiences based on transcripts of semi-structured interviews.³⁹

Limitations: small sample size, no placebo control/blinding, exploratory analyses were not pre-registered, no correction for multiple comparisons

b. **Davis et al. (2021)**²⁰ - NCT03181529

Design: randomized, delayed-treatment waitlist control

Dosing: 1: psilocybin 20 mg/70 kg, 2: psilocybin 30 mg/70 kg; two psilocybin sessions 1.6 weeks apart; counterbalanced crossover of immediate treatment arm with delayed treatment control arm; delayed treatment arm received psilocybin after 8 weeks

Psychotherapy protocol: 8 hours of preparatory therapy and 2-3 hours of integrative therapy

Participants: n=24; moderate-severe major depressive disorder

Primary Outcome Measures: GRID-Hamilton Depression rating scale (GRID-HAMD)

Primary Outcome: Reduction in GRID-HAMD favored the immediate treatment arm with large effects sizes at week 5 (Cohen's $d=2.5$, $p<.001$) and week 8 ($d=2.6$, $p<.001$). 58% at week 1 and 54% at week 4 were in remission.

Secondary Outcomes: Reduction in the Quick Inventory of Depression Symptoms ($d=3.4$, $p<.001$), Beck Depression Inventory-II ($d=3.6$, $p<.001$), Patient Health Questionnaire-9 ($d=3.9$, $p<.001$), Hamilton Anxiety Scale ($d=2.8$, $p<.001$), State-Trait Anxiety Inventory-State ($d=2.9$, $p<.001$), and State-Trait Anxiety Inventory-Trait ($d=1.9$, $p<.001$). No significant change in the Columbia-Suicide Severity Rating Scale. Psilocybin-occasioned mystical-type, personally meaningful, and insightful experiences were associated with decreased in depression at 4 weeks.

Limitations: 92% Caucasian, 96% heterosexual, and 92% college-educated participants; 870 individuals pre-screened and 70 underwent in-person screening (limits in generalizability, risk of selection bias); short 8-week follow-up, no placebo control/blinding (though clinical raters were blinded to treatment condition)

c. **Carhart-Harris et al. (2021)**²¹ - NCT03429075

Design: double-blind, randomized, controlled

Dosing: Psilocybin Condition: 1: psilocybin 25 mg + daily placebo x 3 weeks, 2: psilocybin 25 mg + daily placebo x 3 weeks

Escitalopram Condition: 1: psilocybin 1 mg + daily escitalopram 10 mg x 3weeks, 2: psilocybin 1 mg + daily escitalopram 20 mg x 3 weeks

Psychotherapy protocol: 3 hours of preparatory therapy, 2 in-person integration sessions, and 6 additional integration calls

Participants: n=59; moderate-severe major depressive disorder

Primary Outcome Measure: Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16), change from baseline

Primary Outcome: There was no significant difference between the psilocybin group and the escitalopram group in the primary outcome measure ($p=.17$).

Secondary Outcomes: There was no significant difference in QIDS-SR-16 scores at 6 weeks. 57% were in remission in the psilocybin group and 28% were in remission in the escitalopram group. The Hamilton Depression (HAM-D-17), the Beck Depression Inventory-1A, and the Montgomery and Asberg Depression Rating Scale all showed significantly greater reduction in the psilocybin group versus escitalopram. Significantly greater reduction in the Spielberger's Trait Anxiety Inventory, avoidance, anhedonia, and suicidality, and greater improvement in work and social functioning, flourishing, and well-being, were also seen in the psilocybin

group. Aside from higher anxiety and dry mouth in the escitalopram group, there were no significant differences between adverse events between the two treatments over the 6-week study.

Limitations: For all outcomes, confidence intervals were not corrected for multiple comparisons; thus, “no clinical conclusions can be drawn from these data”. 88% Caucasian, 76% college-educated, 66% male; 1000 individuals pre-screened and 103 underwent in-person screening (limits in generalizability, risk of selection bias)

d. **Anderson et al. (2020)¹⁹** - NCT02950467

Design: open-label, proof-of-concept (preparatory and integrative group therapy)

Dosing: psilocybin 0.3-0.36 mg/kg

Psychotherapy protocol: 1.5 hours of individual + 6 hours of group preparatory psychotherapy and 2 hours of individual + 6-9 hours of group integrative psychotherapy (psilocybin session individual)

Participants: n=18; gay, male, older, long-term AIDS survivors with moderate-severe demoralization (i.e., “poor coping and a sense of helplessness, hopelessness, and a loss of meaning and purpose in life”, stronger association to suicidality than *DSM* major depressive disorder)

Primary Outcome Measure: Demoralization Scale-II

Primary Outcome: Significant reduction in demoralization occurred from baseline to 3 months (standardized effect size $\eta_p^2=.047$, 90% CI 0.21-0.60). At end-of-treatment and 3 months, 88.9% and 66.7% of participants, respectively, experienced a clinically significant reduction in demoralization.

Secondary Outcomes: Significant reductions occurred for symptoms of PTSD ($\eta_p^2=0.27$, 90% CI 0.05-0.43), complicated grief ($\eta_p^2=0.45$, 90% CI 0.19-0.58), and alcohol use ($\eta_p^2=0.40$, 90% CI 0.03-0.62).

Exploratory Outcomes: Attachment anxiety was significantly reduced at 3 months ($d_m=0.45$, $p=.045$). Baseline attachment anxiety predicted psilocybin-occasioned mystical-type experiences ($p=.029$) and baseline attachment avoidance predicted psilocybin-related challenging experiences ($p=.006$).¹²⁴

Limitations: 78% Caucasian, 100% male and gay-identified, 72% college-educated (limits in generalizability); no placebo control/blinding, small sample size

- Ongoing clinical trials of psilocybin for depression:
- Treatment-resistant depression: NCT03775200 (n=216), NCT04670081 (n=144)
- Major Depressive Disorder: NCT03866174 (n=80), NCT03554174, NCT03715127, NCT03380442, NCT04630964

- Co-morbid depression: NCT04123314 (early Alzheimer’s disease, mild cognitive impairment), NCT04433845 (bipolar II disorder), NCT04620759 (alcohol use disorder)

2. Anxiety Disorders

A 2018 systematic review of 10 systematic reviews of trials assessing the effect of psychedelics on mood and anxiety found moderate-to-high level of evidence for the use of psilocybin for treatment of depression and anxiety.¹²⁵ Three randomized trials included in these systematic reviews found that psilocybin reduced anxiety of patients with life-threatening diseases, including advanced-stage cancer.⁹⁻¹¹

a. **Moreno et al. (2006)**¹⁷

Design: within-subjects, dose-escalating with random insertion of very low dose

Dosing: 1: psilocybin 0.1 mg/kg, 2: psilocybin 0.2 mg/kg, 3: psilocybin 0.3 mg/kg (in this order, with psilocybin 0.025 mg/kg randomly inserted as an active placebo); the four psilocybin sessions were each separated by at least 1 week

Psychotherapy protocol: none

Participants: n=9; treatment-resistant obsessive-compulsive disorder (OCD)

Primary Outcome Measures: Yale-Brown Obsessive Compulsive Scale (YBOCS), Visual Analog Scale of overall OCD symptom severity

Outcomes: Repeated-measures analysis of variance for reduction in YBOCS values at 0, 4, 8, and 24 hours post-ingestion revealed a significant effect of time for psilocybin 0.1 mg/kg ($p=.004$) and psilocybin 0.2 mg/kg ($p=.006$), but not for psilocybin 0.025 mg/kg ($p=.128$) or psilocybin 0.3 mg/kg ($p=.406$). A significant effect of time was found for reduction in Visual Analog Scale of overall OCD symptom severity for psilocybin 0.1 mg/kg ($p=.010$), but not for the other doses.

Limitations: Small sample size; fixed order open-label with stronger than anticipated response to very low dose “active placebo”; assessments didn’t extend beyond 24 hours after psilocybin ingestion; no psychotherapy and inpatient hospital setting

Ongoing clinical trials:

- OCD: NCT03300947, NCT03356483, NCT04882839

3. Cancer-related Depression and Anxiety

a. **Grob et al. (2011)**¹⁰ - NCT00302744

Design: double-blind, placebo-controlled

Dosing: psilocybin 0.2 mg/kg versus niacin 250 mg; counterbalanced crossover with each participant receiving both psilocybin and placebo several weeks apart

Psychotherapy protocol: support available as needed through final follow-up

Participants: n=12; advanced-stage cancer; *DSM-IV* diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety

Primary Outcome Measures: BDI = Beck Depression Inventory, STAI = State-Trait Anxiety Inventory

Outcomes: There were no statistically significant effects of psilocybin versus niacin on depression or anxiety at the primary endpoint of 2 weeks after first dose. After participants had received both psilocybin and niacin, six monthly follow-up assessments demonstrated reductions in depression, significant only at 6-month follow-up ($t_7=2.71$, $p=.03$), and anxiety, significant only at the 1-month ($t_1=4.36$, $p=.001$) and 3-month ($t_3=2.55$, $p=.03$) follow-up points.

Limitations: Phase 1 safety and feasibility study, modest psilocybin dose compared to other trials, 4 of 12 participants did not complete the 6-month follow-up assessment, no structured psychotherapy protocol, no double-blinded results after the 2-week endpoint

b. **Ross et al. (2016)¹¹** - NCT00957359

Design: double-blind, placebo-controlled

Dosing: psilocybin 0.3 mg/kg versus niacin 250 mg; counterbalanced crossover with each participant receiving both psilocybin and niacin 7 weeks apart

Psychotherapy protocol: 6 hours of preparatory therapy and 12 hours total of integrative therapy, with additional support available from study therapists for 26 weeks after the final study session

Participants: n=29; life-threatening cancer diagnosis; *DSM-IV* diagnosis of adjustment disorder or generalized anxiety disorder

Primary Outcome Measures: BDI = Beck Depression Inventory, HADS = Hospital Anxiety and Depression Scale, STAI = State-Trait Anxiety Inventory

Primary Outcomes: There were statistically significant effects of psilocybin versus niacin up until the 7-week crossover point for depression (BDI: $p\leq.05$; HADS-Depression: $p\leq.01$) and anxiety (STAI-State: $p\leq.01$; STAI-Trait: $p\leq.001$; HADS-Anxiety: $p\leq.01$) with large effect sizes (Cohen's $d=.82-1.29$).

Secondary Outcomes: Psilocybin was associated with significant reduction in cancer-related demoralization and hopelessness and increase in quality of life. Psilocybin was not associated with significant changes in the Death Anxiety Scale. 52% and 70% of participants rated the psilocybin experience within the top 5 most spiritually significant and personally meaningful experiences of their lives, respectively. The strength of total psilocybin-occasioned mystical-type experience (MEQ30) correlated with greater change in depression and anxiety for most of the primary outcome measures.

Long-term Follow-up & Exploratory Outcomes: Long-term follow-up of, on average,

3.2 years (n=15) and 4.5 years (n=14) indicated statistically significant sustained reductions relative to baseline on all primary measures of anxiety and depression.¹²⁶ (An exploratory analysis of a subset of participants from this study (n=11) demonstrated that psilocybin was associated with within-group reductions in suicidal ideation that persisted at 6.5-month follow-up and reductions in Loss of Meaning that were evident at 4.5-year follow-up.¹²⁷ Transcripts from semi-structured interviews of a subset of participants were used to highlight themes (n=13)¹²⁸ and produce comprehensive summaries of their experiences (n=4).¹²⁹

Limitations: 90% Caucasian participants; blinded assessment period only 7 weeks

c. **Griffiths et al. (2016)⁹** - NCT00465595

Design: double-blind, placebo-controlled

Dosing: psilocybin 22 or 33 mg/70 kg versus low-dose psilocybin 1 or 3 mg/70 kg; counterbalanced crossover with each participant receiving both doses of psilocybin approximately 5 weeks apart

Psychotherapy protocol: ~7.9 hours of preparatory therapy and ~7 hours total of integrative therapy

Participants: n=51; potentially life-threatening cancer diagnosis, “DSM-IV diagnosis that includes anxiety and/or mood symptoms”

Primary Outcome Measures: 17-item GRID-Hamilton Depression Rating Scale (GRID-HAM-D-17) and Hamilton Anxiety Rating Scale (HAM-A)

Primary Outcomes: After the first psilocybin session, there were significant reductions for the high-dose, versus low-dose, psilocybin treatment arm in both depression (Cohen’s $d=1.30$, $p<.001$) and anxiety ($d=1.23$, $p<.001$) ratings. After participants had received both doses, there were no significant differences between treatment groups. Reduction in depression and anxiety remained significant for all participants at 6-month follow-up compared to baseline. At 6-month follow-up, 71% and 63% remained in remission for depression and anxiety, respectively, in the high dose first group; while 59% and 50% remained in remission for depression and anxiety, respectively, in the low dose first group.

Secondary Outcomes: After the first psilocybin session, there were significant reductions for the high-dose, versus low-dose, psilocybin treatment arm in secondary outcomes for depression and anxiety: Beck Depression Inventory ($d=0.81$, $p<.01$), Hospital Anxiety and Depression Scale-Depression ($d=0.56$, $p<.05$), State-Trait Anxiety Inventory-Trait ($d=0.60$, $p<.05$), Profile of Mood States-total mood disturbance ($d=0.70$, $p<.01$), and Brief Symptom Inventory ($d=0.78$, $p<.01$). There were significant increases in McGill Quality of Life-overall quality of life ($d=0.65$, $p<.05$), McGill Quality of Life-meaningful existence ($d=0.65$, $p<.05$), Life Attitude Profile-Revised-Death Acceptance ($d=0.97$, $p<.05$), and Life Orientation Test-Revised-optimism ($d=0.75$, $p<.05$). There were no significant differences reported for Hospital Anxiety and Depression Scale-Anxiety, Hospital Anxiety and Depression Scale-Total, State-Trait Anxiety Inventory-State, Death Transcendence, Purpose in Life Test, or Life Attitude Profile-Revised-Coherence.

Limitations: 94% Caucasian and 98% college-educated participants; changed psilocybin dosing mid-study; assessment period before crossover limited to 5 weeks; no correction for multiple comparisons

A meta-analysis of the above three cancer-related anxiety and depression clinical trials significantly favored psilocybin versus the control group regarding effects on depression (BDI) and anxiety (STAI) (Vargas et al., 2020).²⁶

Ongoing clinical trials:

- NCT04593563 (depression in cancer patients), NCT04754061 (existential distress in palliative care)

4. Substance Use Disorders

a. Johnson et al. (2014)¹⁴

Design: open-label, dose-escalating

Dosing: 1: psilocybin 20 mg/70 kg, 2: psilocybin 30 mg/70 kg, 3: psilocybin 20-30 mg/70 kg; 3rd dose optional

Psychotherapy protocol: cognitive-behavioral therapy for smoking cessation + psilocybin preparation/integration: 6 hours of preparatory therapy and 9.5-10.5 hours of integrative therapy, target quit date set to coincide with first psilocybin session at week 5

Participants: n=15; smoked on average 19 cigarettes/day (range 15-25), an average of 6 unsuccessful previous quit attempts (range 2-12), current desire to quit smoking

Primary Outcome Measures: smoking timeline follow-back, urine cotinine (detects smoking over past 6 days)

Primary Outcomes: 80% of participants were confirmed as smoking abstinent at 6 Months

Secondary Outcomes: Significant differences were seen across timepoints for the Questionnaire of Smoking Urges ($p < .001$), the Smoking Abstinence Self-Efficacy subscales confidence ($p < .001$) and temptation ($p < .001$), and the Wisconsin Smoking Withdrawal Scale ($p = .009$).

Long-term Follow-up & Exploratory Outcomes: At 12-month follow-up (n=15), 67% were confirmed smoking abstinent.¹⁵ 86.7% rated their psilocybin experiences among the top 5 most personally meaningful and spiritually significant experiences of their lives, and abstainers scored significantly higher on some measures of the psilocybin-occasioned mystical experience.¹⁵ At 16- to 57-month follow-up (n=12), 60% of the original sample were confirmed as smoking abstinent.¹⁵ Participants (n=10) who chose overtone-based music versus Western classical music showed a slight benefit in smoking abstinence (66.7% versus 50%), and psilocybin-occasioned mystical-type experience scores tended to be higher in overtone-based sessions (Strickland, 2020).¹³⁰

Analyses of retrospective, semi-structured, follow-up interviews (n=12) identified perceived mechanisms and key themes from these sessions.⁴⁰

Limitations: 93% Caucasian, 66.67% male, 100% college-educated participants; 322 individuals pre-screened and 27 underwent in-person screening

b. Bogenschutz et al. (2015)¹⁶ - NCT01534494

Design: within-subjects, open-label, dose-escalating

Dosing: 1: psilocybin 0.3 mg/kg, 2: psilocybin 0.3-0.4 mg/kg; 2 psilocybin sessions 8 weeks apart

Psychotherapy protocol: 7 total sessions of Motivational Enhancement Therapy, 3 psilocybin preparation sessions, and 2 psilocybin debriefing sessions

Participants: n=10; DSM-IV alcohol dependence (average 15.1 years) with ≥ 2 heavy drinking days in the past 30 days, current concern about drinking, not in any concurrent treatment for alcohol use, and no alcohol withdrawal requiring medical treatment during the study

Primary Outcome Measures: Percent drinking days and percent heavy drinking days

Primary Outcomes: Reduction in percent drinking days ($d=1.19$, $p=.007$) and percent heavy drinking days ($d=1.38$, $p=.004$) during weeks 25-36 compared to baseline

Secondary Outcomes: Significant changes at week 36 compared to baseline were seen for the Short Inventory of Problems-interpersonal ($p<.01$) and -intrapersonal ($p<.05$), and the Penn. Alcohol Craving Scale ($p<.001$). There were no significant changes for the Short Inventory of Problems-physical/impulse control/responsibility, the Alcohol Abstinence Self-Efficacy scale, the Stages of Change Readiness and Treatment Eagerness Scale, or the Profile of Mood States. Qualitative content analysis of key themes (n=10)¹³¹ (and descriptions of treatment experiences and persisting¹³² effects (n=3) were also published.

Limitations: proof-of-concept, small sample size, no placebo control/blinding, lack of biological verification of alcohol use

Ongoing clinical trials:

- Alcohol Use Disorder: NCT02061293 (n=135), NCT04141501, NCT04410913, NCT04620759 (with Major Depressive Disorder)
- Tobacco Use Disorder: NCT01943994 (n=95)
- Use Disorder: NCT02037126
- Opioid Use Disorder: NCT04161066 (in combination with buprenorphine)

Appendix 2. Sample screening considerations

1. Physical Considerations

i. Cardiac: Due to the potential increases in blood pressure and tachyarrhythmias after consumption of psilocybin, people with uncontrolled hypertension, aneurysms, heart disease, or arrhythmias such as Wolff-Parkinson-White Syndrome¹³³ may be at increased risk for injury. Psilocybin and psilocin have been demonstrated to increase QTc interval by a mean of 2.1 (6.6) milliseconds.³³ People with long QT syndrome or other irregularities of heart rhythm and people taking medications that prolong QTc interval may be at risk for exacerbation of arrhythmias and potential injury.

ii. Endocrine: Psilocybin's effect on blood glucose has only been studied in animal models. There is potential for mild hyperglycemia with psilocybin use.¹³⁴ People who take psilocybin may be at risk for transient episodes of hyperglycemia. Blood sugar monitoring in recipients with diabetes or other blood sugar dysregulation issues may be prudent to avoid hyperglycemia.

iii. Polypharmacy: Concomitant use of certain medications or drugs with psilocybin carries a variety of risks depending on the pharmacokinetics of each drug class, interaction with receptors, impacts on metabolism, and epigenetic factors. DrugBank lists 436 potential Psilocybin/Drug interactions. Psilocybin is metabolized to the active form, psilosin by first pass hydrolysis by Alkaline phosphatase. Psilocin is then primarily glucuronidated by UGT1A10, and also oxidized by monoamine oxidase, Ceruloplasmin, Cytochrome oxidase, and aldehyde dehydrogenase, and other minor pathways.¹³⁵ Any medications that impact these metabolic pathways could change the rate of psilocybin and psilocin metabolism, and thus possibly change the intensity and duration of a psilocybin experience. People using drugs such as oral contraceptive pills (Naz et al. 2016), the 4-anilinoquinazoline class of kinase inhibitors (Miners et al. 2017), Cinacalcet (Belozeroff 2016), Disulfiram (Veverka 1997), Monoamine Oxidase Inhibitors, and others may experience differences in intensity and duration in psilocybin effects due to changes in the metabolism of psilocybin.

Drugs that bind directly to 5-HT receptors or transporters may interfere with psilocybin binding. Examples include SSRI's, SNRI's, tricyclic antidepressants, buspirone, antipsychotics, and some muscle relaxers. Drugs such as antipsychotics that inhibit 5-HT_{2A} receptors, likely the main site of action of psilocybin, may also have an impact on the intensity and duration of psilocybin effects (Honda Nishida Ono 2003).

As noted above, psilocybin may prolong QTc interval. Drugs that prolong QTc interval may act synergistically with psilocybin putting those combining the two at risk for arrhythmia and injury.

iv. Gastrointestinal: Psilocybin can cause transient nausea and vomiting. This may be a consideration for individuals with eating disorder or gastrointestinal disease.

v. Allergy: Most fungi including the psilocybin containing fungi contain chitin in their cell walls, which is known to cause allergy in some individuals. Mushrooms may also contain multiple other antigens that cause allergic reactions.¹³⁶ People with a known mushroom allergy are at risk for allergic reactions and anaphylaxis with the use of psilocybin containing mushrooms. However, synthetic psilocybin products with no mushroom extractives may still be possible for safe use, depending on the nature of the allergy.

vi. Ability to Provide Informed Consent: A number of brain disorders affect the ability to provide informed consent.

vii. Pregnancy: Psilocybin use in pregnancy has not been studied.

viii. Renal: There is one confirmed case and some other scientific and anecdotal evidence of potential for acute kidney injury after psilocybin ingestion in some individuals.^{137,138}

ix. End of life care: End of life care is psychologically nuanced and often complicated by polypharmacy, mobility concerns, and organ system dysfunction.

2. Mental Health Considerations

i. Psychotic disorders: Psilocybin acts at least partly through 5-HT_{2A} receptors, the blockade of which reduces psychotic symptoms. It is widely assumed that individuals with a history of psychotic disorder such as schizophrenia are at high risk of precipitation or exacerbation of psychosis, although this has not been studied or quantified. Individuals with history of psychotic disorder are excluded from clinical trials studying psilocybin.

ii. Mania or Likelihood of Manic Induction: Gard, et al. found 15 cases of manic induction in the literature, advising caution with use of psilocybin in bipolar disorder while also proposing to study the effect of psilocybin on bipolar disorder symptoms in a clinical trial (not yet peer reviewed).¹³⁹

iii. Suicidality: Evidence to date suggests that psilocybin may be efficacious for depression and anxiety^{12,18} but psilocybin has not been studied in acutely suicidal individuals. A systematic review of psilocybin and suicidality indicated potential benefit in decreasing suicidality among patients receiving psilocybin.¹⁴⁰

Appendix 3. Sample screening instruments

i. Screening for Psychosis, Mania, Schizophrenia, and Dissociative States (Seiler et al. 2020)¹⁴¹

Brief Psychiatric Rating Scale (BPRS) <https://www.smchealth.org/sites/main/files/file-attachments/bprsform.pdf?1497977629>

Positive and Negative Syndrome Scale PANSS
<https://www.psychdb.com/media/psychosis/panss.pdf>

Scale for the Assessment of Positive Symptoms (SAPS)
<https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/GetPdf.cgi?id=phd000837.1>

Psychotic Symptom Rating Scale (PSYRATS)
<https://core.ac.uk/download/pdf/204498869.pdf>

Clinician-Administered Rating Scale for Mania (CARS-M)
https://www.neurotransmitter.net/CARS_M.pdf

ii. Bipolar screening

Hypomania Checklist (HCL-32) - Self Report
<http://www.oacbdd.org/clientuploads/Docs/2010/Spring%20Handouts/Session%20220b.pdf>

Mood Disorder Questionnaire (MDQ) https://www.ohsu.edu/sites/default/files/2019-06/cms-quality-bipolar_disorder_mdq_screener.pdf

Composite International Diagnostic Interview (CIDI)
https://www.hcp.med.harvard.edu/ncs/ftplib/CIDI_3.0_Bipolar_Screening_Scales_final.pdf

iii. Screening for Dissociative states

Dissociative Experiences Scale (DES)
<https://www.hebpsy.net/files/ruZXkl5YGeKcvt6dBZpS.pdf>

iv. Screening for Suicidality

ASQ Suicide Risk Screening tool
https://www.nimh.nih.gov/research/research-conducted-at-nimh/asq-toolkit-materials/asq-tool/screening_tool_asq_nimh_toolkit_155867.pdf

v. Screening Tools to Assess Benefit

PTSD Checklist for DSM-5 (PCL-5)
<https://www.ptsd.va.gov/professional/assessment/adult-sr/ptsd-checklist.asp>

Patient Health Questionnaire (PHQ-9)
<https://patient.info/doctor/patient-health-questionnaire-phq-9>

Depression anxiety and stress scale

(DASS21; Lovibond & Lovibond, 1995)¹⁴²

<https://maic.qld.gov.au/wp-content/uploads/2016/07/DASS-21.pdf>

A study by Carrillo et al in 2018 found that a low-cost and effective machine learning algorithm applied to recipient speech patterns during intake can assess for the likelihood of psilocybin effectiveness in managing treatment resistant depression.⁶⁵

GAD-7 (General Anxiety Disorder-7)

<https://www.mdcalc.com/gad-7-general-anxiety-disorder-7>

Demoralization scale

Kissane DW, Wein S, Love A, Lee XQ, Kee PL, Clarke DM. The Demoralization Scale: A Report of its Development and Preliminary Validation. *Journal of Palliative Care*. 2004;20(4):269-276.
doi:10.1177/082585970402000402

Psychological Insight Questionnaire

(PIQ; Davis et al., 2021¹⁴³; Davis et al., in press)

vi. Research Tools for tracking changes

The Oregon psilocybin program provides a rich opportunity to grow the body of knowledge about the impacts and benefits of psilocybin through voluntary surveys and symptom tracking pre-and post- use. In addition to using the above screening tools, the following may inform screening guidelines.

Well-Being Inventory

<https://www.ptsd.va.gov/professional/assessment/documents/WellBeingAssessment.pdf>

Well-Being Inventory Manual

<https://www.ptsd.va.gov/professional/assessment/documents/WellBeingInventoryManual.pdf>

Mystical Experiences Questionnaire (MEQ; (Barrett et al., 2015; MacLean et al, 2011)

<https://www.ocf.berkeley.edu/~jfkihstrom/ConsciousnessWeb/Psychedelics/States-of-Consciousness-Questionnaire-and-Pahnke.pdf>

Challenging Experiences Questionnaire

Facilitator Experiences Questionnaire (FEQ)

Currently under research at the BAND lab at UCSF

Appendix 4. Additional information regarding mushroom products

Psilocybin detection in the human body

Psilocybin can be detected in the body by analyzing psilocybin content in urine,¹⁴⁴⁻¹⁴⁶ hair,¹⁴⁷ or in blood plasma.¹⁴⁸ Methods for detection include enzyme-linked immunosorbent assays (ELISAs) via monoclonal antibodies that bind psilocybin or psilocin,¹⁴⁹ liquid or gas chromatography,^{86,88,150} and mass spectrometry.¹⁴⁷ It is possible to differentiate between psilocybin, psilocin, and related molecules using hydrophilic interaction liquid chromatography (HILIC).^{150,151}

Potential risks of related to consumption of psilocybin containing mushrooms.

Adverse physiological reactions to consuming psilocybin mushrooms include short lived anxiety and panic,^{152,153} tachycardia, hypertension or hyperreflexia,¹⁵⁴ Mydriasis,¹⁵⁴ nausea and vomiting,¹⁵⁴ paresthesia and feelings of depersonalization,¹⁵⁴ renal complications¹³⁸ and gastrointestinal complications¹⁵⁵ and hallucinatory sensations.¹⁵⁶ Adverse reactions have been described by combining psilocybin mushrooms with alcohol, cannabis, cocaine, and MDMA.⁵⁶ Individuals with fungal allergies are at risk for adverse reactions with whole fungal products. Consuming whole mushroom products pose unique risks, as species of psilocybin producing fungi vary in the presence and concentration of other bioactive indole alkaloids with structural homology to psilocybin such as baeocystin.⁵¹⁻⁵⁴ There is variability in presence and abundance of phenylethylalanines in mushrooms which are structural relatives to amphetamines and may induce tachycardia, nausea, and anxiety (**Beck et al. 1982**). Other safety considerations during mushroom production include unintentional ingestion due to insufficient personal protective equipment, occupational hazards associated with fungal cultivation and or molecular/biochemical labs.

Appendix 5. Search Strategies

Psilocybin search strategies and literature search results

Database: Ovid MEDLINE(R) ALL 1946 to May 05, 2021

- 1 Psilocybin/
- 2 (psilocybin or psilocin).ti,ab,kf.
- 3 1 or 2
- 4 (random* or control* or trial or systematic or "meta analysis" or metaanalysis or medline).ti,ab,kf.
- 5 3 and 4
- 6 limit 3 to randomized controlled trial
- 7 limit 3 to (meta analysis or "systematic review")
- 8 or/5-7
- 9 exp risk/
- 10 (risk and (assess* or predict*)).ti,ab,kf.
- 11 3 and (9 or 10)
- 12 mushroom*.ti,ab,kf.
- 13 3 and 12
- 14 8 or 11 or 13

Database: APA PsycInfo 1806 to April Week 4 2021

- 1 Psilocybin/
- 2 (psilocybin or psilocin).ti,ab.
- 3 1 or 2
- 4 (random* or control* or trial or systematic or "meta analysis" or metaanalysis or medline).ti,ab.
- 5 3 and 4
- 6 (risk and (assess* or predict*)).ti,ab.
- 7 exp risk assessment/ or exp risk factors/ or exp risk management/
- 8 3 and (6 or 7)
- 9 mushroom*.ti,ab.
- 10 3 and 9
- 11 5 or 8 or 10

Database: EBM Reviews - Cochrane Central Register of Controlled Trials April 2021

- 1 Psilocybin/
- 2 (psilocybin or psilocin).ti,ab.
- 3 1 or 2
- 4 conference abstract.pt.
- 5 "journal: conference abstract".pt.
- 6 "journal: conference review".pt.
- 7 "http://.www.who.int/trialsearch*".so.
- 8 "https://clinicaltrials.gov*".so.
- 9 4 or 5 or 6 or 7 or 8
- 10 3 not 9

Literature search results – number of citations

KQ	MEDLINE	PsycInfo	CCRCT
1 & 2	256	177	108
3	19	15	--
4	241	81	--
Total	461	248	108

Deduplicated total: 632

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