CLACKAMAS COUNTY BOARD OF COUNTY COMMISSIONERS

Policy Session Worksheet

Presentation Date: July 6, 2022 **Approx. Start Time:** 11:30 AM **Approx. Length:** 30 min

Presentation Title: Oregon Ballot Measure 109 (Psilocybin)

Department: County Counsel

Presenters: Nate Boderman – Assistant County Counsel

Other Invitees: Dr. Sarah Present – County Health Officer, Stephen Madkour – County Counsel, Jack Stinson – Legal Intern.

WHAT ACTION ARE YOU REQUESTING FROM THE BOARD?

Today's policy session will update the Board on the status of the state rulemaking related to regulation of psilocybin, to respond to certain questions directed to staff by individual commissioners, and to get Board direction on whether to direct staff move forward with drafting an ordinance referring to the voters for the November, 2022 general election a ban on psilocybin product manufacturers and/or psilocybin service centers within the unincorporated areas of Clackamas County.

EXECUTIVE SUMMARY:

Measure 109 and State Rulemaking

In 2020, Oregon voters passed Measure 109, which allows the manufacturing, delivery, and administration of psilocybin, a hallucinogenic chemical found in certain mushrooms.[1] Measure 109 directs the Oregon Health Authority ("OHA") to license and regulate activities related to the manufacturing, delivery, sale, and purchase of psilocybin products, as well as the provision of psilocybin services. Ballot Measure 109 has been codified as ORS 475A.

Measure 109 created the Oregon Psilocybin Advisory Board ("OPAB"), which has been meeting and making recommendations to OHA. While Measure 109 contains certain requirements and regulations which serve to establish the framework for the production of psilocybin and the administration of psilocybin services in Oregon, OHA has been delegated authority to adopt administrative rules to ensure the program can be implemented and operational on the date that OHA is to begin accepting applications for licensure, which is January 2, 2023.

OHA recently adopted the first set of administrative rules, effective May 20, 2022, which relate to psilocybin products, testing, and training programs. See Attachment B. OHA anticipates that it will adopt the remaining administrative rules by December 30, 2022, which is the final business day before OHA is required to begin accepting applications for licensure.[2]

OHA has summarized key implementation dates related to the Oregon Psilocybin Services Act as follows:

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[1] In Clackamas County, Measure 109 passed with 52.4% of the vote (128,890 votes in favor vs. 117,098 votes opposed).

[2] On June 17, 2022, OHA updated local governments on its efforts to implement the requirements of Measure 109. Materials from this meeting are included with this report as Attachment A.

• November 24, 2021: Preliminary recommendations from OPAB
• December 2021: Public Listening Sessions
• January 1, 2022: Community Interest Survey
• May 13, 2022: Effective Date for Expedited Rules.
• June 1, 2022: OHA begins accepting applications for training programs
• June 30, 2022: Recommendations for Remaining Rules
• July 2022: Public Listening Sessions
• September 2022: RAC for Remaining Rules
• November 1-21, 2022: Public Comment for Remaining Rules
• December 30, 2022: Effective Date for Remaining Rules
• January 2, 2023: OHA begins accepting applications for licensure

(Attachment A, pg. 10).

Answering Commissioner Questions

In advance of this session, individual Commissioners have asked questions of staff related to psilocybin generally, existing regulations, and Measure 109. Each of the three questions received are addressed below.

- What kind of evaluations have been done to prove the medical efficacy of psilocybin?

The Oregon Psilocybin Advisory Board has published its review of psilocybin clinical trials completed to date. This review was the first assignment given to the research subcommittee. The Oregon Psilocybin Advisory Board Rapid Evidence Review and Recommendations report, dated July 30, 2021, is included with this report as Attachment C.

- Are companies involved with psilocybin going to be able to use banking facilities, or will they be forced to operate with cash only?

Similar to marijuana, psilocybin is classified as a Schedule 1 drug and is illegal at the federal level. Because of this, banks subject to federal regulation will likely avoid the risks associated with psilocybin in the same manner as was done with marijuana. Accordingly, all signs point to these businesses operating as cash only for the time being.

- Will certified medical personnel dispense the substance?

No. The individual dispensing the substance will be trained and certified but will not be required to hold any medical license or credential, although medical personnel can become a facilitator if they choose and they are authorized by their licensing board. ORS 475A.325(2)(d) requires that facilitators must have at least a high school diploma or its equivalent, but ORS 475A.325(3) then prohibits any requirement that facilitators have a degree from any other “institution of higher education.”

OHA expedited a portion of its rulemaking related to training to ensure those rules would be in place, and individuals would have the opportunity to receive the requisite training, by the time OHA began accepting license applications. Those training requirements adopted by the OHA can be found in the attached Exhibit C and at OAR 333-333-3005 through 333-333-3090. For example, OAR 333-333-3050 sets forth the core training program requirements, and mandates at least 120 hours of instruction. To facilitate psilocybin sessions at a certified service center, and individual MUST have completed the state mandated training. It is worth noting that Oregon’s psilocybin program does not authorize direct to consumer sales in any form.

Local Government Opt-Out (ORS 475A.718)

The effect of Measure 109 will be to have OHA issue licenses to qualifying applicants in cities and counties statewide as soon as January 2, 2023. Measure 109 does, however, provide local

jurisdictions the option of adopting an ordinance, to be referred to the voters, that prohibits or allows psilocybin product manufacturers, psilocybin service centers, or both in those areas subject to the jurisdiction of the local government.[3] ORS 475A.718(2) provides that if the county were to adopt such an ordinance, it would need to be submitted to the electors for approval at the next statewide general election (which occurs in November of even-numbered years).

In order to be eligible for the November, 2022 election, the deadline for the County to file with the elections official the adopted ordinance would be August 19. Adopting such an ordinance would follow the County's normal adoption process as set forth in state law, which typically requires multiple readings of the proposed ordinance, each accompanied by public hearings. To provide enough time to allow for notice and to complete the required public hearing process, the Board should decide as soon as possible whether to direct staff to proceed with scheduling the necessary public hearings. The League of Oregon Cities has created a model ordinance and sample ballot measure language that could provide a starting point for any such effort to pursue an opt-out, as described above and in ORS 475A.718. These materials are attached to this report at Attachment D.

In addition to a model ordinance that would potentially implement a permanent ban on psilocybin product manufacturers and/or psilocybin service centers, the attached materials also include a model ordinance that could be used to implement a limited 2-year ban. Staff is aware that some jurisdictions are considering such a limited duration ban in response to the timing of state rulemaking and the reality that the final rules related to psilocybin manufacturing and service centers likely will not be completed until after such time that an ordinance banning such uses must be passed and referred to the voters. A 2-year ban, if passed by the voters, would allow time for state rulemaking to be completed and for the OHA program to be fully implemented before licenses would issue in a local jurisdiction in which such a limited-duration ban has passed. This additional time would, in theory, allow such a local jurisdiction to be able to evaluate what local rules, if any, were necessary to supplement the state's rules, or to observe how the program had been operating in other jurisdictions and to consider whether a full ban would be appropriate to refer to the voters in 2024.

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[3] These provisions are codified at ORS 475A.718 and provide as follows:

475A.718 Adoption of ordinances; referral to electors for approval. (1) The governing body of a city or county may adopt ordinances to be referred to the electors of the city or county as described in subsection (2) of this section that prohibit or allow the establishment of any one or more of the following in the area subject to the jurisdiction of the city or in the unincorporated area subject to the jurisdiction of the county:

(a) Psilocybin product manufacturers that hold a license issued under ORS 475A.290;

(b) Psilocybin service center operators that hold a license issued under ORS 475A.305; or

(c) Any combination of the entities described in this subsection.

(2) If the governing body of a city or county adopts an ordinance under this section, the governing body shall submit the measure of the ordinance to the electors of the city or county for approval at the next statewide general election.

(3) If the governing body of a city or county adopts an ordinance under this section, the governing body must provide the text of the ordinance to the Oregon Health Authority.

(4) Upon receiving notice of a prohibition under subsection (3) of this section, the authority shall discontinue licensing those premises to which the prohibition applies until the date of the next statewide general election.

(5) If an allowance is approved at the next statewide general election under subsection (2) of this section, the authority shall begin licensing the premises to which the allowance applies on the first business day of the January immediately following the date of the next statewide general election.

(6) Notwithstanding any other provisions of law, a city or county that adopts an ordinance under this section that prohibits the establishment of an entity described in subsection (1) of this section may not impose a tax or fee on the manufacturing or sale of psilocybin products.

Local Government Time, Place and Manner Regulations

Measure 109 contains some limited provisions pertaining to land use regulation of psilocybin manufacturing and service centers. For instance, ORS 475A.305 restricts service centers from being located within 1,000 feet of a school and ORS 475A.270 requires license applicants with OHA request a land use compatibility statement ("LUCS") from the local government demonstrating that the requested license is for a land use that is allowable within the zoning designation where the land is located.

State regulations contained in ORS 475A and in any rules adopted by OHA will apply to licensed psilocybin manufacturing and service center facilities. ORS 475A.530 authorizes local governments to adopt reasonable time, place and manner regulations to supplement the state regulations that would otherwise apply.[4] As noted above, because final rules related to psilocybin manufacturing and service center facilities will likely not be adopted by OHA until immediately before OHA will begin accepting license applications, the Board may wish to consider additional local regulations in the event that the draft OHA rules are not as robust as the Board would like. Given the timing challenges described above, the Board would likely need to begin considering these types of local regulations regardless of whether it refers any type of opt-out to the voters in November, since a rejection of such an opt-out would leave little time for the Board to adopt local time, place and manner regulations prior to OHA beginning to accept license applications on January 2, 2023. Staff recommends the Board consider these options as part of a follow up session within the next month or two, which will allow staff time to prioritize any efforts related to an opt-out (assuming the Board decides to move forward with such an effort), and to allow staff time to review any draft rules that may be published by OHA in the interim related to psilocybin manufacturing and service center facilities.

FINANCIAL IMPLICATIONS (current year and ongoing):

Is this item in your current budget? ☐ YES ☒ NO

What is the cost? $ Unknown What is the funding source? N/A

STRATEGIC PLAN ALIGNMENT:

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[4] **475A.530 Local time, place and manner regulations.** (1) For purposes of this section, "reasonable regulations" includes:

(a) Reasonable conditions on the manner in which a psilocybin product manufacturer that holds a license issued under ORS 475A.290 may manufacture psilocybin products;

(b) Reasonable conditions on the manner in which a psilocybin service center operator that holds a license issued under ORS 475A.305 may provide psilocybin services;

(c) Reasonable limitations on the hours during which a premises for which a license has been issued under ORS 475A.210 to 475A.722 may operate;

(d) Reasonable requirements related to the public's access to a premises for which a license has been issued under ORS 475A.210 to 475A.722; and

(e) Reasonable limitations on where a premises for which a license may be issued under ORS 475A.210 to 475A.722 may be located.

(2) Notwithstanding ORS 30.935, 215.253 (1) or 633.738, the governing body of a city or county may adopt ordinances that impose reasonable regulations on the operation of businesses located at premises for which a license has been issued under ORS 475A.210 to 475A.722 if the premises are located in the area subject to the jurisdiction of the city or county, except that the governing body of a city or county may not adopt an ordinance that prohibits a premises for which a license has been issued under ORS 475A.305 from being located within a distance that is greater than 1,000 feet of another premises for which a license has been issued under ORS 475A.305.

- **How does this item align with your Department's Strategic Business Plan goals?** This item aligns with the Department's purpose of providing research, consultation, strategy, and implantation compliance services to the County, and its elected officials, so they can conduct their operations in a manner that comports with local, state, and federal regulations and laws.

- **How does this item align with the County's Performance Clackamas goals?** The proposal aligns with the Performance Clackamas goal to "Build Public Trust through Good Government" by responding to a state mandate and by considering regulations related to a use that is not currently addressed within in our code.

LEGAL/POLICY REQUIREMENTS:

The legal requirements related to a potential opt-out, as well as the ability to adopt reasonable time, place and manner regulations are discussed in detail above.

PUBLIC/GOVERNMENTAL PARTICIPATION:

Measure 109 was a statewide ballot initiative which passed in Oregon. Within Clackamas County specifically, Measure 109 passed with 52.4% of the vote (128,890 votes in favor vs. 117,098 votes opposed).

If the Board decides to refer an ordinance to the voters to implement a permanent or limited-duration ban on psilocybin product manufacturers and/or psilocybin service centers, public notice will be provided and public hearings will be held, as required by law, related to the adoption of any such ordinance. The ordinance would then be placed on the November, 2022 ballot for consideration by the voters of Clackamas County.

OPTIONS:

1.) Direct staff to schedule a public hearing and draft an ordinance referring to the voters for the November, 2022 general election a permanent ban on psilocybin product manufacturers and/or psilocybin service centers within the unincorporated areas of Clackamas County.

2.) Direct staff to schedule a public hearing and draft an ordinance referring to the voters for the November, 2022 general election a limited-duration ban on psilocybin product manufacturers and/or psilocybin service centers within the unincorporated areas of Clackamas County.

3.) Take no action regarding the opt-out provisions in ORS 475A.718.

RECOMMENDATION:

As this decision represents a policy-based decision by the Board, staff expresses no opinion as to a preferred option. Staff will be able to implement any of the options identified above.

ATTACHMENTS:

Attachment A: Local Government Partners Webinar – Introduction to the Oregon Psilocybin Services Act (June 17, 2022)
Attachment B: Oregon Administrative Rule Chapter 333, Division 333 (Effective May 20, 2022)
Attachment C: Oregon Psilocybin Advisory Board Rapid Evidence Review and Recommendations (July 30, 2021)
Attachment D: League of Oregon Cities has created a model ordinance and sample ballot measure language (June, 2022)

SUBMITTED BY:
Division Director/Head Approval _____

Department Director/Head Approval _____

County Administrator Approval _____

For information on this issue or copies of attachments, please contact Nate Boderman @ 503-655-8364

PUBLIC HEALTH DIVISION
Oregon Psilocybin Services

Oregon Psilocybin Services Section

Oregon Psilocybin Services is a new section housed within the Oregon Health Authority Public Health Division's Center for Health Protection.

The OPS team has been designed around three program areas:

- **Policy and Engagement**
- **Licensing**
  - **Local Government and Law Enforcement Liaison position**
- **Compliance**

Each program will center on health equity, including outreach to partners and communities and working to ensure access to services.

Ballot Measure 109: The Oregon Psilocybin Services Act

In November of 2020, Ballot Measure 109, the Oregon Psilocybin Services Act was passed by voters in Oregon. The ballot measure is now codified as ORS 475A.

M109 created a license and regulatory framework for production of psilocybin and facilitation of psilocybin services for adults 21 years of age and older and created the Oregon Psilocybin Advisory Board that makes recommendations to OHA.

M109 does not:

- Create a consumer market for psilocybin
- Allow for export or import of psilocybin
- Allow licensees to interact with unregulated markets

License Types

Manufacturer License

- Cultivates fungi and manufactures psilocybin products
- Cannot cultivate outdoors
- Premise must have defined boundaries
- Cannot exceed production quantities established in rule
- Product tracking system required to track manufacturing, sale and transfer of psilocybin products to prevent diversion, ensure accurate accounting, ensure accurate reporting of lab testing results

Laboratory License

- All psilocybin products must be tested by a licensed lab prior to sale.
- Labs must be accredited by the Oregon Environmental Laboratory Accreditation Program
- Testing results must be entered in the product tracking system

License Types (cont'd)

Facilitator License

- Supervises sessions where clients consume psilocybin.
- Must complete **OHA approved training program** as a condition of licensure.
- Must pass exam approved or administered by OHA

Service Center License

- Cannot be located within 1000 feet of a school
- Must have defined boundaries
- Transfers psylocibin products to client for use during administration session

Psilocybin Services

Psilocybin will only be administered to persons 21 years or older in licensed service center settings under the supervision of trained and licensed facilitators.

Psilocybin Services may include:

- Preparation Session
- Administration Session
- Integration Session (optional)

Product tracking system required to track manufacturing, sale and transfer of psilocybin products to:

- Prevent diversion
- Ensure accurate accounting
- Ensure accurate reporting of lab testing results

Local Government Issues

Local Government Opt-Out:

- Local governments (cities and counties) may adopt ordinances that prohibit Manufacturers and Service Centers
- Ordinances must be referred to voters at the next general election

Local Government Time Place and Manner Regulations

- Local governments may adopt reasonable regulations on hours, location, and operation of licenses

Land Use Compatibility Statements (LUCS)

- Applicants for Service Center and Manufacturer licenses are required to request a LUCS from their local government before submitting a license application

Site Requirements

Service Centers:

- GIS mapping tool for school proximity
- Cannot be located on public land; must have defined boundaries
- Cannot be located within a residence
- Cannot be located in an area within city limits that is zoned exclusively for residential use

Manufacturers:

- Cannot be located on public land; must have defined boundaries
- Outdoor cultivation is prohibited
- Landlord must consent to use

TPM:

- OPS will not track local time place and manner regulations

License and Application Fees, Taxes

License and Application Fees

- License and application fees will be set in rule later this year
- Oregon Psilocybin Services will be a fee-based program and fees must cover the costs associated with the agency's work

Taxes

- Service Centers collect a 15% tax on the sale of psylocibin products payable to Oregon Department of Revenue
- Local taxes and fees are prohibited
- Psilocybin services are not taxed

OHA Key Dates

- **November 24, 2021:** Preliminary recommendations from OPAB
- **December 2021:** Public Listening Sessions
- **January 1, 2022:** Community Interest Survey
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Thank You!

Please visit our website:

https://www.oregon.gov/psilocybin

Oregon Health Authority

Public Health Division - Chapter 333

Division 333
PSILOCYBIN

333-333-1010
Definitions

For purposes of chapter 333, division 333 the following definitions apply:

(1) "Adulterant" means chemicals, drugs, plants or substances that alter the potency, intoxicating effect, duration of effect, toxicity or potential for excessive use when added to psilocybin products. Adulterant does not include naturally occurring substances contained in food items such as, but not limited to chocolate.

(2) "Authority" means the Oregon Health Authority.

(3) "Batch" means a quantity of whole fungi from a harvest lot, or a quantity of psilocybin product from a process lot.

(4) "Capsule" means a small soluble pill, tablet or container that contains liquid or powdered psilocybin product and is intended for human consumption.

(5) "Chemical synthesis" means the production of psilocybin using precursor ingredients rather than cultivation of fruiting bodies and mycelium.

(6) "Edible psylocibin product" means psilocybin extract or homogenized fungi that has been incorporated into a food item or potable beverage.

(7) "Extraction" means:

(a) The process of separating psilocybin from fungi by using a solvent; and

(b) Manufacturing psilocybin extracts.

(8) "Fruiting bodies" means the spore producing organs of the fungi *Psilocybe cubensis*.

(9) "Fungi" means the fruiting bodies or mycelium of the fungi *Psilocybe cubensis*

(10) "Harvest lot" means a specifically identified quantity of fungi that is cultivated and dried under the same conditions and harvested within a 24-hour period at the same location within the licensed premises.

(11) "Homogenized fungi" means dried fruiting bodies or mycelium that have been mixed by powdering or other techniques which uniformly distribute psilocybin throughout the product. Homogenized products may contain inactive ingredients such as binders, dilutants and carrying agents.

(12) "Laboratory" means a laboratory licensed under ORS 475A.594.

(13) "Manufacturer" means a manufacturer licensed under ORS 475A.290.

(14) "Manure" means animal excreta, alone or in combinations with litter, such as straw and feathers used for animal bedding, for use as a soil amendment or substrate. Manure does not include stabilized compost produced through a controlled composting process.

(15) "Mycelium" means the fungal threads or hyphae of *Psilocybe cubensis*.

(16) "Pesticide" means any substance or mixture of substances included in ORS 634.006(8).

(17) "Process lot" means homogenized fungi, psylocibin extract or edible psilocybin product of the same type that was processed at the same time using the same processing method, ingredients, and standard operating procedures.

(18) "Psilocybin" means psilocybin or psilocin.

(19) "Psylocibin extract" means:

(a) A substance consisting entirely of solid or liquid psilocybin and may include other compounds which were simultaneously extracted from fruiting bodies or mycelium of *Psilocybe cubensis*; and

(b) A substance consisting of solid or liquid psilocybin and may include other compounds which were simultaneously extracted from fruiting bodies or mycelium of *Psilocybe cubensis* and inactive ingredients that are used to form capsules, tinctures and other oral preparations.

(20) "Psilocybin Tracking System" means the system for tracking psilocybin products required by ORS 475A.400.

(21) "Psilocybin product" means psilocybin-producing fungi, mycelium and mixtures or substances containing a detectable amount of psilocybin, including whole fungi, homogenized fungi, psilocybin extract and edible psilocybin products.

(22) "These rules" mean Oregon Administrative Rules, chapter 333, division 333.

(23) "Tincture" means a liquid containing psilocybin that consists of either:

(a) A non-potable solution of at least 25 percent non-denatured alcohol, that is exempt from the Liquor Control Act under ORS 471.035; or

(b) A non-potable solution comprised of glycerin, plant-based oil, syrup and other ingredients.

(24) "Whole fungi" means dried fruiting bodies of *Psilocybe cubensis*, or portions thereof, that have not been homogenized.

(25) "Wood chips" mean substrates consisting primarily of wood products that have not been composted.

Statutory/Other Authority: ORS 475A.235
Statutes/Other Implemented: ORS 475A.235
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-2010
Psilocybin Production

A manufacturer is prohibited from:

(1) Using manure in cultivation or production of psilocybin products.

(2) Using wood chips as a growing medium in cultivation or production of psilocybin products.

(3) Producing psilocybin by using genetically modified organisms such as bacteria.

(4) Producing psilocybin by chemical synthesis.

Statutory/Other Authority: ORS 475A.235
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.290
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-2020
General Manufacturer Requirements

(1) A manufacturer must:

(a) Use equipment, counters and surfaces for post-harvest processing that are food-grade and do not react adversely with any solvent being used.

(b) Construct and maintain counters and surface areas in a manner that reduces the potential development of microbials, molds and unintended fungi and that can be easily cleaned.

(c) Maintain the licensed premise in a manner that is free from conditions which may result in contamination of psilocybin products and that is suitable for safe and sanitary operations.

(d) Store all psilocybin products in a locked area when not in use, including psilocybin products that require refrigeration.

(e) Assign every process lot and harvest lot a unique identification number and enter this information into the Psilocybin Tracking System.

(2) A manufacturer may not produce, transfer or sell a psilocybin product that appeals to minors, including but not limited to:

(a) Products that are modeled after non-psilocybin products primarily consumed by and marketed to children; or

(b) Products in the shape of an animal, vehicle, person or character.

Statutory/Other Authority: ORS 475A.235
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.290
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-2030
Manufacturer Endorsements

(1) A manufacturer may only produce and sell psilocybin products if the manufacturer has received an endorsement from the Authority for that type of product. Endorsement types are:

(a) Fungi cultivation;

(b) Psilocybin extraction; and

(c) Edible psilocybin production.

(2) An applicant for a manufacturer license must request an endorsement upon submission of an initial application but may also request to add or remove an endorsement at any time following licensure.

(3) To apply for an endorsement, an applicant or licensee must submit a form prescribed by the Authority that identifies the proposed endorsement.

(4) Only one application and license fee are required regardless of how many endorsements an applicant or licensee requests or when the request is made.

(5) An individual manufacturer may hold multiple endorsements.

(6) The Authority may deny a manufacturer's request for an endorsement or revoke an existing endorsement if the manufacturer cannot or does not meet the requirements of these rules. If the Authority denies or revokes approval, the processor has a right to a hearing under ORS chapter 183.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.295
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.295
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-2040
Pesticides

Manufacturers are prohibited from applying pesticides to fungi or growing medium.

Statutory/Other Authority: ORS 475A.235
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.290
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-2050
Adulterants

(1) A licensee may not add to psilocybin products any chemical, drug, plant, or substance that has the effect of altering potency, intoxicating effect, duration of effect, toxicity or potential for excessive use, including but not limited to monoamine oxidase inhibitors (MAOI's), beverage alcohol or cannabis. A psilocybin product that has added chemicals, drugs, plants or substances that alter the potency, intoxicating effect, duration of effect, toxicity or addictiveness is considered adulterated.

(2) A licensee may not produce, store or transfer adulterated psilocybin products. In addition to the provisions of section (1) of this rule, a psilocybin product may be considered adulterated if:

(a) It bears or contains any poisonous or deleterious substance in a quantity rendering the psilocybin product a risk to human health;

(b) It bears or contains any added poisonous or deleterious substance exceeding a safe tolerance if such tolerance has been established;

(c) It consists in whole or in part of any unsanitary, putrid, or decomposed substance, or is otherwise unfit for human consumption;

(d) It is processed, prepared, packaged or held under improper time-temperature conditions or under conditions increasing the probability of contamination with excessive microorganisms or physical contaminants;

(e) It is processed, prepared, packaged, or held under unsanitary conditions increasing the probability of contamination or cross-contamination;

(f) It is held or packaged in containers composed, in whole or in part of any poisonous or deleterious substance rendering the contents potentially injurious to health;

(g) Any substance has been substituted wholly or in part;

(h) Damage or inferiority has been concealed in any manner; or

(i) Any substance has been added, mixed or packaged to make it appear a better or of greater value than it is.

(3) Psilocybin products that are intended for research and development and will not be made available for consumption must be labeled in bold, capital letters, no smaller than 12-point font, "NOT FOR CONSUMPTION" and may be stored in states that are unfit for human consumption.

Statutory/Other Authority: ORS 475A.235
Statutes/Other Implemented: ORS 475A.235
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-2060
Psilocybin Extract Manufacturing Requirements

(1) A manufacturer with a psilocybin extraction endorsement may use only water, vegetable glycerin, acetic acid, ethanol and methanol as solvents in extraction. All other solvents are prohibited.

(2) A manufacturer with a psilocybin extraction endorsement may not use denatured alcohol.

(3) A manufacturer with a psilocybin extraction endorsement may not apply pressure or heat over 140 degrees Fahrenheit when manufacturing psilocybin extracts.

(4) If using methanol or ethanol, a manufacturer must process psilocybin extracts in a room with equipment, including all electrical installations that meet the requirements of the Oregon Structural Specialty Code, related Oregon Specialty Codes and the Oregon Fire Code.

(5) If a manufacturer with a psilocybin extraction endorsement produces a psilocybin extract that will be used in an edible psilocybin product, the manufacturer's licensed premises must be licensed by the Oregon Department of Agriculture as a food establishment and must comply with applicable provisions of OAR chapter 603, division 21, division 24, division 25 and division 28.

Statutory/Other Authority: ORS 475A.235

Statutes/Other Implemented: ORS 475A.235
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-2070
Psilocybin Extract Manufacturing Safety Procedures

(1) A manufacturer with an extraction endorsement must:

(a) Work in an environment with proper ventilation, controlling all sources of ignition where flammable vapors may be present;

(b) Use only potable water in processing;

(c) Have an emergency eye-wash station, rinse kit and emergency shower in any room in which solvents other than water are used; and

(d) Make appropriate personal protective equipment available to employees.

(2) A manufacturer with a psilocybin extraction endorsement must create and maintain a comprehensive training program that includes the hazards presented by all solvents used at the licensed premises as described in the material safety data sheet for each solvent.

Statutory/Other Authority: ORS 475A.235
Statutes/Other Implemented: ORS 475A.235
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-2080
Psilocybin Edible Manufacturing Requirements

(1) A manufacturer with an edible psilocybin production endorsement may only process in a food establishment licensed by the Oregon Department of Agriculture (ODA) and must comply with the applicable provisions of OAR chapter 603, division 21, division 24, division 25 and division 28.

(2) A manufacturer with an edible psilocybin production endorsement may not use a psilocybin product to produce edible psilocybin products unless that psilocybin product was processed or cultivated in a food establishment licensed by the ODA in compliance with the applicable provisions of OAR chapter 603, division 21, division 24, division 25 and division 28.

Statutory/Other Authority: ORS 475A.235
Statutes/Other Implemented: ORS 475A.235
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-2100
Psilocybin Manufacturing Records

A manufacturer with a psilocybin extraction, or edible psilocybin production endorsement must create and maintain standard policies and procedures that include but are not limited to:

(1) Instructions and ingredients for making each psilocybin product;

(2) The procedure for making each process lot homogenous;

(3) If applicable, the procedure for purging and disposing of any solvent or other unwanted product from a psilocybin extract;

(4) Procedures for conducting necessary safety checks prior to commencing production of psilocybin products;

(5) Procedures for cleaning all equipment, counters and surfaces;

(6) Procedures for preventing growth of pathogenic organisms and toxin formations;

(7) Proper handling and storage of any solvent or other chemical used in processing in accordance with material

safety data sheets and other applicable laws;

(8) Proper disposal of any waste produced during processing in accordance with applicable laws, rules and regulations;

(9) Appropriate use of any necessary safety or sanitary equipment; and

(10) Emergency procedures to be followed in case of fire, chemical spill or other emergencies.

Statutory/Other Authority: ORS 475A.235
Statutes/Other Implemented: ORS 475A.235
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-2110
Allowable Psilocybin Product Types

(1) A manufacturer with a fungi cultivation endorsement may produce and dry whole fungi, mycelium and homogenized fungi. A manufacturer with a fungi cultivation endorsement may produce fungi in aquatic environments in addition to any substrates and growing mediums allowed by these rules. A manufacturer with a fungi cultivation endorsement must completely dry all fungi before transferring to another licensee.

(2) A manufacturer with a psilocybin extraction endorsement may produce psylocibin extract.

(3) A manufacturer with an edible psilocybin production endorsement product may produce edible psilocybin products.

(4) A manufacturer may only produce those psilocybin products for which they hold an endorsement.

(5) Psilocybin products not included in this rule are prohibited and may not be manufactured, nor possessed by any licensee.

Statutory/Other Authority: ORS 475A.235
Statutes/Other Implemented: ORS 475A.235
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-2120
Psilocybin Product Delivery Methods

(1) A manufacturer must design and manufacture all psilocybin products to be consumed by a client orally or delivered via another enteral method

(2) A manufacturer is prohibited from designing or manufacturing psilocybin products that can be delivered to clients through any method other than orally or another enteral method. A manufacturer is prohibited from designing or manufacturing psilocybin products that include but not limited to, transdermal patches, inhalers, nasal sprays, suppositories and injections.

Statutory/Other Authority: ORS 475A.235
Statutes/Other Implemented: ORS 475A.235
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-3005
Psilocybin Training Definitions

As used in OAR 333-333-3010 through OAR 333-333-3090 the following definitions apply:

(1) "Adverse behavioral reaction" means client behavior that a facilitator reasonably believes may endanger the safety of the client, facilitator, or others.

(2) "Adverse medical reaction" means a client's physiological reaction occurring during an administration session that a facilitator reasonably believes may lead to medical harm. For example, a cardiac event or other health emergency.

(3) "Client information form" means the form required by ORS 475A.350.

(4) "Cultural equity" means values, policies, and practices that ensure all people, especially those who have been historically marginalized based on race, ethnicity, language, disability, age, gender, gender identity, sexual orientation, social class, intersections among these communities or identities, or other socially determined circumstances are considered in the development of social pathways to health equity.

(5) "Curriculum" means the topics, subjects, and activities that make up courses taught by a training program.

(6) "Facilitation" means the provision of services to clients by a licensed facilitator during preparation, administration, and integration sessions.

(7) "Health equity" means that Oregon will have established a health system that creates health equity when all people can reach their full health potential and well-being and are not disadvantaged by their race, ethnicity, language, disability, age, gender, gender identity, sexual orientation, social class, intersections among these communities or identities, or other socially determined circumstances. Achieving health equity requires the ongoing collaboration of all regions and sectors of the state, including tribal governments to address: the equitable distribution or redistribution of resources and power; and recognizing, reconciling and rectifying historical and contemporary injustices.

(8) "Intervention" means taking proactive steps to respond to the client's behavior, experience, or condition during an administration session.

(9) "Lead educator" means a person affiliated with a training program who is responsible for tracking the progress of students throughout the program.

(10) "Nondirective facilitation" means an approach to facilitation in which the facilitator maintains a consistent disposition with a client, while avoiding giving the client direct advice or directly interpreting a client's statements or behaviors.

(11) "Oregon Psilocybin Services Act" means ORS 475A.210 to ORS 475A.722.

(12) "Practicum site" means a designated service center that provides practicum training.

(13) "Practicum site supervisor" means an onsite practicum supervisor of assigned trainees, affiliated with a practicum site.

(14) "Program director" means a person authorized by a training program to track student progress, grant student enrollment and certify program completion.

(15) "Responsible referral and support" means supporting the personal needs, growth, and wellbeing of others, particularly those going through temporal crises such as houselessness, illness or marginalization.

(16) "Service Center" means a premises licensed under ORS 475A.305.

(17) "Scope of practice" means practice boundaries related to psilocybin facilitation and avoiding the unlicensed practice of other disciplines including but not limited to medicine or psychotherapy.

(18) "Synchronous learning" means that students learn from their instructor at the same time as their fellow students.

(19) "Training program applicant" means a program that has applied to offer training to psilocybin facilitators as described in ORS 475A.380.

(20) "Training program" means a program that has been approved to offer training to psilocybin facilitators as described in ORS 475A.380.

Statutory/Other Authority: ORS 475A.235
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.380
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-3010
Psilocybin Training Program Curriculum Approval Process

(1) A training program applicant must submit the following to the Authority to be considered for curriculum approval to train psilocybin facilitators:

(a) A completed application package, including a description of the proposed curriculum that shows the applicant

meets the requirements of OAR 333-333-3050, OAR 333-333-3060, OAR 333-333-3070 and OAR 333-333-3090; and

(b) A $500 non-refundable application evaluation fee paid in the form and manner specified by the Authority.

(2) The Authority will notify a training program applicant if their application is incomplete. The training program applicant will have 90 days from the date the notice is issued to submit a complete application. If the training program applicant does not complete their application within 90 days, the Authority will refuse to process the application. If the Authority refuses an application, the applicant may submit a new application, including a non-refundable application evaluation fee, for the program to be considered for approval.

(3) The Authority will evaluate training program applications to determine if the course meets the standards in OAR 333-333-3005 to OAR 333-333-3090.

(4) The Authority will notify the training program applicants in writing if the application is approved or denied.

(5) The Authority may deny a training program application for curriculum approval or revoke approval of a previously approved training program curriculum if:

(a) The training program application does not meet the requirements OAR 333-333-3005 to OAR 333-333-3090; or

(b) The program instructors, staff or representatives have made false or misleading statements to the Authority, students or the public.

(6) If the Authority denies an application or revokes a curriculum approval, the Authority will provide notice of the denial and the training program has a right to a hearing under ORS chapter 183.

(7) Training program curriculum approval has a term of five years from the date of initial approval. If the requirements of OAR 333-333-3005 to OAR 333-333-3090 change substantively during the term, the Authority may require training programs to resubmit an application for approval.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.380
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.380
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-3020
Psilocybin Training Program Application Requirements

For curriculum to be approved, training program applicants must:

(1) Demonstrate that its proposed course modules contain the content required by OAR 333-333-3060;

(2) Demonstrate that its proposed hours of instruction meet the requirements of OAR 333-333-3050;

(3) Demonstrate that its proposed practicum meets the requirements of OAR 333-333-3070;

(4) Identify all instructors, including at least two lead educators and list the instructors' qualifications to teach curriculum modules identified in these rules;

(5) Identify a program director who is responsible for tracking student progress and has authority to confer student enrollment and program completion; and

(6) Be located within the United States of America or U.S Territories or the freely associated states Republic of Martial Islands, Palau, and the Federated States of Micronesia.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.380
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.380
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-3030
Psilocybin Training Instructor Qualifications and Program Performance

(1) In order for curriculum to be approved, a training program must demonstrate that each instructor and person who trains instructors at a training program has sufficient experience, knowledge, skills and ability to competently train

students in their assigned subject matter.

(2) Sufficient experience, knowledge, skills and ability can be demonstrated via education, certifications, professional experience, personal narratives and references.

(3) Training programs shall treat personal narratives and references as confidential unless an instructor has consented to their publication.

(4) Each instructor at a training program must:

(a) Understand the objectives of the training program and be able to communicate effectively with students; and

(b) Demonstrate skill in instruction and student supervision.

(5) Training programs must notify the Authority of any material changes to the curriculum listed in their application that affect the requirements of OAR 333-333-3005 to OAR 333-333-3090 in a form and manner prescribed by the Authority.

(6) Training programs must notify the Authority of any changes of instructors, lead educators and program director in a form and manner prescribed by the Authority.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.380
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.380
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-3035
Psilocybin Training Curriculum Reapproval

(1) A training program that wishes for their curriculum to be reapproved upon expiration of their initial approval term must submit a completed reapproval application and a non-refundable $500 reapproval fee.

(2) The Authority must receive the reapproval application and fee at least 30 days prior to the date that the training program's approval is set to expire.

(3) If a training program files a reapproval application and fee at least 30 days prior to the date that the training program's approval is set to expire, the training program's curriculum approval remains valid while the Authority considers their reapproval application.

(4) If a training program does not file a reapproval application and fee at least 30 days prior to the date that the training program's approval is set to expire, the training program's curriculum approval will expire, and the training program must submit a new application.

(5) If the Authority approves reapproval, the reapproval is valid for five years.

(6) The Authority may deny the application for reapproval if:

(a) The training program has not complied with these rules; or

(b) The training program instructors, staff or representatives have made false or misleading statements to the Authority, students or the public.

(7) If the Authority denies reapproval, the Authority will provide notice of the denial and the program has a right to a hearing under ORS chapter 183.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.380
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.380
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-3040
Psilocybin Training Program Record Keeping

(1) Training programs shall maintain records for each class, including course syllabi, location, date and student attendance for every online and in-person class. These records must be maintained for five years. Training programs shall provide these records to current and former students upon request. Training programs shall provide these

records to the Authority upon request.

(2) Training programs shall maintain enrollment records, including the name of each student enrolled, their date of completion and examination results. These records must be maintained for five years.

(3) Training programs shall provide records required to be maintained under this rule to the Authority upon request, and in the manner requested.

(4) Except as required by sections (1) and (3) of this rule, student records shall not be released without the student's written consent.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.380
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.380
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-3050
Psilocybin Training Program Core Requirements

(1) Programs shall provide core training that consists of at least 120 hours of instruction.

(2) For training that is not conducted in person, at least 50 percent of the training shall be conveyed through online synchronous learning.

(3) Applicants for training programs must demonstrate that their curriculum consists of the following minimum hours of instruction, in the following areas consistent with the requirements of OAR 333-333-3060:

(a) Historical, Traditional, and Contemporary Practices and Applications: 12 hours.

(b) Cultural Equity in relation to Psilocybin Services: 12 hours.

(c) Safety, Ethics and Responsibilities: 12 hours.

(d) Psilocybin Pharmacology, Neuroscience, and Clinical Research: 4 hours.

(e) Core Facilitation Skills: 16 hours.

(f) Preparation and Orientation: 16 hours.

(g) Administration: 20 hours.

(h) Integration; 12 hours.

(i) Group Facilitation: 16 hours.

(4) Training programs must comply with the requirements specified in these rules to maintain approved status.

(5) The requirements listed in these rules are minimum requirements. Nothing in these rules prevents a training program from offering additional modules or hours of instruction.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.380
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.380
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-3060
Psilocybin Training Curriculum Modules

(1) "Historical, Traditional, and Contemporary Practices and Applications" module shall include:

(a) Current and historical use of plant and fungal medicines in indigenous and western cultures;

(b) The Controlled Substances Act and its effect on psilocybin research and drug policy; and

(c) Overview of historical and recent academic research.

(2) "Cultural Equity in relation to Psilocybin Services" module shall include the following subjects and their application during preparation, administration, and integration sessions:

(a) Cultural equity, its relationship to health equity and social determinants of health;

(b) Racial justice, including the impact of race and privilege on health outcomes and the impact of systemic racism on individuals and communities;

(c) The impact of drug policy on individuals and communities;

(d) History of systemic inequity, including systemic inequity in delivery of healthcare, mental health and behavioral health services;

(e) Intergenerational trauma; and

(f) Responsible Referral and Support

(3) "Safety, Ethics, Law and Responsibilities" module shall include the following subjects and their application during preparation, administration, and integration sessions:

(a) Awareness of facilitator's personal bias, including examination of facilitator's motives;

(b) Training on the Oregon Psilocybin Services Act and related laws, regulations, and professional standards for facilitators; including facilitator scope of practice and expectation of referral when scope of practice is exceeded.

(c) Training in ethical issues related to psilocybin facilitation, including:

(A) Oregon's Facilitator Code of Ethics;

(B) Ethical considerations relating to equity, privilege, bias and power;

(C) Awareness of increased vulnerability associated with altered states of consciousness;

(D) Appropriate use of touch and client consent to physical contact;

(E) Appropriate emotional and sexual boundaries between facilitators and clients both during provision of psilocybin services and at other times, potential harm to clients and consequences for facilitators of breaching those boundaries;

(F) Historical and contemporary abuse of power associated with psychedelics, including sexual, emotional and physical abuse, and implications for facilitators;

(G) Financial conflicts of interest and duties to clients; and

(H) Reasonable expectations regarding client outcomes.

(d) Accurate record keeping and client confidentiality.

(e) Awareness of new research related to safety and ethics of providing psilocybin services and resources for professional development following program completion.

(f) Appropriate measures to mitigate risks associated with psilocybin services, including harm reduction, de-escalation, and conflict resolution.

(4) "Psilocybin Pharmacology, Neuroscience, and Clinical Research" module shall include:

(a) Pharmacodynamics and pharmacokinetics of psilocybin;

(b) Drug and supplement interaction;

(c) The metabolism of psilocybin and psilocybin products including concentration of psilocybin and psilocin in available psilocybin products;

(d) The primary effects and mechanisms of action of psilocybin on the brain, including connectivity in the brain and activation of serotonin receptors;

(e) Key areas of psilocybin research; and

(f) Models of substance use, addiction, and recovery.

(5) "Core Facilitation Skills" module shall include the following subjects and their application during preparation, administration, and integration sessions:

(a) Client communication, empathy and rapport, including a nondirective facilitation approach, cultural attunement and a nonjudgmental disposition;

(b) Response to psychological distress and creating a safe space for difficult emotional experiences;

(c) Physical reactions and side effects of psilocybin;

(d) Trauma informed care, including physiology of trauma, vicarious trauma, empathic stress and compassion fatigue;

(e) Active monitoring of client-facilitator boundaries specifically boundaries related to consent and touch;

(f) Identification and facilitation of a variety of subjective psilocybin experiences, including experiences relating to physiological sensations, cognitive, emotional and mystical states, and traumatic memories;

(g) Appropriate modes of intervention, understanding when intervention is necessary, and when a client may need a higher level of care;

(h) Recognizing and addressing adverse behavioral reactions and adverse medical reactions; and

(i) Identification of the unique health, psychological and socio-cultural presented by persons with terminal illness; and awareness of the appropriate knowledge, skills and approach needed to provide safe facilitation to such persons in a manner consistent with client goals, values, heritage, and spiritual practices.

(6) "Preparation and Orientation" module shall include:

(a) Informed consent;

(b) Client information form and intake interview, including discussion of client's reasons for seeking psilocybin services;

(c) Using the client information form to assist clients in identifying benefits of referral to specialized treatment services;

(d) Facilitator role and the limits of facilitator's scope of practice;

(e) Trauma informed communication skills;

(f) Identification of client safety concerns, including medical history, contra-indicated medication and psychological instability;

(g) Appropriate strategies to discuss client safety concerns, including but not limited to identification of client's support system;

(h) Determination of whether a client should participate in an administration session;

(i) Client directed safety planning to address identified safety concerns;

(j) Boundaries between the facilitator and the client including use of touch;

(k) Understanding of how racial and cultural dynamics affect interactions between client and facilitator; and

(l) Historical and indigenous modalities of preparation.

(7) "Administration" module shall include:

(a) Dosing strategies and considerations, including:

(A) Experiential differences relating to differing dosages;

(B) Physiological considerations in relation to dosage;

(C) Delivery mechanisms of psilocybin; and

(D) Use of secondary doses.

(b) Effectively working with challenging behaviors during an administration session, including:

(A) Unexpected client disclosures;

(B) Substance-induced psychosis; and

(C) Suicidality.

(c) Traumatic stress and its manifestation during a psilocybin experience and appropriate facilitator response, including:

(A) Trauma's relationship to the body;

(B) Repressed trauma emerging during a psilocybin experience;

(C) Trauma and traumatic stress resulting from systemic oppression;

(D) Safety for trauma resolution and risks associated with re-traumatization; and

(E) Protocols for ensuring facilitator safety and responding to emergencies.

(d) "Set and Setting" including environmental considerations for administration session such as lighting sound and temperature; and

(e) Completion of administration session.

(8) "Integration" module shall include:

(a) Identification of appropriate resources that may assist client with integration, including resources for:

(A) Interpreting feelings and emotions experienced during administration session;

(B) Facilitation of positive internal and external changes;

(C) Enhancement of existing supportive relationship.

(b) Identification of client safety concerns;

(c) Facilitator scope of practice; and

(d) Discussion of appropriate intervals between administration sessions and related safety concerns.

(9) "Group Facilitation" module shall include:

(a) Skills required to facilitate psilocybin group sessions, including, but not limited to:

(A) Assessing client's compatibility with group format;

(B) Set and setting for group facilitation;

(C) Facilitating group communications and dynamics, including strategies for working with multiple facilitators;

(D) Group agreements, including confidentiality and safety; and

(E) Identifying when a client within a group requires individual support, removal from a group, or additional intervention.

(b) Group Preparation Sessions;

(c) Group Integration Sessions; and

(d) Regulatory requirements for group facilitation.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.380
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.380
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-3070
Psilocybin Facilitator Practicum Requirements

(1) Programs shall require students to complete practicum training that provides an opportunity to facilitate and observe the facilitation of non-ordinary states of consciousness.

(2) If a practicum site is available, practicum training shall include placement at a practicum site where students can observe and facilitate psilocybin services under the supervision of a practicum site supervisor.

(3) Any licensed Service Center can function as practicum site. If a training program uses a Service Center as a practicum site to satisfy the requirements of this rule, the training program shall notify the Authority in a form and manner prescribed by the Authority.

(4) A practicum site must obtain written client consent prior to allowing a client to be observed by practicum students and prior to sharing any client information with practicum students or a training program.

(5) The practicum site supervisor is primarily responsible for developing students' practicum skills and evaluating students' practicum performance, focusing on services with clients.

(6) If a practicum site is not reasonably available or accessible to students, a training program may identify alternative practicum in their application for approval that reasonably approximates training at a practicum site.

(7) Alternative practicum may include but is not limited to observation of taped facilitation sessions that were recorded with participants' consent, participating in psychedelic peer support organization, role playing, and experience with altered states of consciousness that are not drug-induced, for example breath work, meditation or spiritual journeys.

(8) Students shall complete a minimum of 40 hours of practicum training, including at least 30 hours of direct practice in which students directly observe clients receiving psilocybin services or directly participate in alternative practicum activity as described in section (7), and at least 10 hours of consultation relating to the student's direct practice.

(9) All practicum training must be conducted in person.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.380
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.380
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-3080
Accelerated Training Hours

(1) Programs may confer upon qualified students accelerated training hours not to exceed 40 percent of the total number of core training hours required by OAR 333-333-3050.

(2) Accelerated training hours may be awarded based on students' professional credentialing, prior training and education, or relevant experiences such as practicing in established plant or fungi-based healing traditions.

(3) Training programs that offer accelerated training hours must establish and document criteria for conferring accelerated hours to qualifying students.

(4) Student transcripts and other records shall document the number and type of accelerated training hours conferred to each student.

(5) Training programs may not offer accelerated training hours for the following modules:

(a) "Cultural Equity in relation to Psilocybin Services;"

(b) "Safety, Ethics and Responsibilities;"

(c) "Preparation and Orientation;"

(d) "Administration;" or

(e) "Integration."

(6) Training programs may not offer accelerated training hours for practicum.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.380
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.380
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-3090
Training Program Completion and Exams

(1) Training programs shall maintain a level of training for students such that students who successfully complete the

program's training could reasonably expect to possess the knowledge and skills required to practice as a facilitator.

(2) Training programs must administer a comprehensive skills-based exam and every student must receive a passing score, established by the training program, as a condition of completing the training program.

(3) The exam required by section (2) of this rule is in addition to the exam required by ORS 475A.330.

(4) A lead educator or program director must endorse each student as qualified to provide psilocybin services as a condition of completing the training program.

(5) Training programs shall provide every student written confirmation of program completion, including the endorsement described in section (4) of this rule, signed by a lead educator upon the student's successful completion of the program, that includes:

(a) Student's full name;

(b) Date of completion; and

(c) Name and location of the training program.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.380
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.380
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7010
Psilocybin Testing: Purpose

(1) The purpose of these rules is to establish minimum compliance testing standards for psilocybin products.

(2) A person licensed under ORS 475A.290, 475A.305, or 475A.325 may not transfer, accept or provide a psilocybin product unless it has been sampled and tested in accordance with these rules.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7020
Ordering Tests

(1) A manufacturer must provide to a laboratory, prior to the laboratory taking samples, the following information:

(a) The manufacturer's license number and endorsement type;

(b) The manufacturer's name, address and contact information;

(c) Type of psilocybin product;

(d) Batch numbers to be sampled;

(e) Harvest lot number associated with the batch number, if applicable;

(f) Process lot number associated with the batch number, if applicable;

(g) Total mass or volume of each batch to be sampled; and

(h) Identification of tests requested.

(2) If the manufacturer informs a laboratory that a psilocybin product is being re-sampled after a failed test, the manufacturer must provide the laboratory with documentation of the failed test.

(3) A manufacturer is responsible for ordering the compliance tests necessary to comply with these rules.

(4) A manufacturer may not order more than one compliance test for the same harvest lot, process lot or psilocybin product except as allowed under OAR 333-333-7120.

(5) A manufacturer violates these rules if they:

(a) Fail to provide information required in these rules to a laboratory.

(b) Submit false or misleading information to a laboratory.

(6) Tests ordered under these rules expire after one year. If a test has expired, the psilocybin product must be tested again before it can be sold to a client, transferred to another licensee, or converted to another product type.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7030
Speciation Testing

(1) A manufacturer must order a test for a batch taken from the first harvest lot recorded in a calendar year to ensure that the lot consists only of *Psilocybe cubensis*. This test must be performed prior to transferring the harvest lot to another licensee or converting the harvest lot to another product type.

(2) Following the test described in section (1) of this rule, a manufacturer must order tests for one batch harvested in each month that a harvest lot is recorded to ensure that the lot consists only of *Psilocybe cubensis*.

(3) A batch fails speciation testing if the test demonstrates that the fungi is a species other than *Psilocybe cubensis*.

(4) If a batch fails speciation testing, a manufacturer must order tests for every harvest lot for a period of 12 months following the failed test to ensure that batches consist only of *Psilocybe cubensis*. This test must be performed prior to transferring the harvest lot to another licensee or converting the harvest lot to another product type.

(5) In addition to the requirements of section (1) of this rule, a manufacturer must submit one or more batches from a harvest lot or process lot for speciation testing upon written request by the Authority.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7040
Potency Testing

(1) A manufacturer must order tests for every batch of finished psilocybin product from a harvest lot or process lot to determine the concentration (potency) of psilocybin and psilocin in the product.

(2) A process lot of homogenized fungi, psilocybin extract or edible psilocybin product fails potency testing if the amount of psilocybin or psilocin between samples taken from the batch exceeds 20 percent relative standard deviation between sample increments.

(3) In addition to the requirements of section (1) of this rule, a manufacturer must submit one or more batches from a harvest lot or process lot for potency testing upon written request by the Authority.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7050
Solvent Testing

(1) If methanol or acetic acid are used to manufacture psilocybin extract, a manufacturer must order tests for methanol or acetic acid for every process lot of psilocybin extract prior to selling or transferring the psilocybin extract or converting to another product type.

(2) A batch fails solvent testing if a laboratory detects the presence of methanol above 3000 µg/g or acetic acid above 5000 µg/g in any sample.

(3) If a sample from a batch fails solvent testing, the batch may be remediated using procedures that would reduce the concentration of solvents to less than the action level.

(4) A batch that is remediated in accordance with section (3) of this rule, must be re-sampled and re-tested for solvents in accordance with these rules.

(5) In addition to the requirements of section (1) of this rule, a manufacturer must submit one or more batches from a process lot for solvent testing upon written request by the Authority.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7060
Pesticide Testing

(1) A manufacturer must submit one or more batches from a harvest lot or process lot for pesticide testing upon written request by the Authority.

(2) A batch fails pesticide testing if the test detects the presence of a pesticide above action levels in any sample, including a field duplicate:

(a) During an initial test where no reanalysis is requested; or

(b) Upon reanalysis as described in OAR 333-333-7120.

(3) If a sample from a harvest lot or process lot fails pesticide testing, the batch may not be remediated and must be destroyed.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7070
Contaminant Testing

(1) A manufacturer must submit one or more batches from a harvest lot or process lot for contaminant testing upon written request by the Authority.

(2) A psilocybin product required to be tested for contaminants under these rules must be sampled using appropriate aseptic technique and tested for total coliform count.

(3) If the presence of any fecal coliforms is detected the sample must be assessed for Escherichia coli (E. Coli)

(4) A batch fails microbial contaminant testing if the presence of E. Coli at more than 100 colony forming units per gram is detected in a sample.

(5) A psilocybin product required to be tested for contaminants may also be tested for aflatoxins and other harmful mycotoxins.

(6) A psilocybin product fails testing for aflatoxins and other harmful mycotoxins if the tests detect mycotoxins at levels that are unsafe for human consumption.

(7) If a sample from a batch of psilocybin product fails contaminant testing, the batch may not be remediated and must be destroyed.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7080
Heavy Metals Testing

(1) A manufacturer must submit one or more batches from a harvest lot or process lot for heavy metal testing upon written request by the Authority.

(2) A harvest lot or process lot required to be tested for heavy metals may be tested for lead, cadmium, mercury and arsenic.

(3) A batch fails heavy metal testing if the presence of metals above the limits in section (4) of this rule are detected in any sample, including a field duplicate:

(a) During an initial test where no reanalysis is requested; or

(b) Upon reanalysis as described in OAR 333-333-7120.

(4) The limits for heavy metal testing are:

(a) Lead (Pb) above .5 µg/g.

(b) Cadmium (Cd) above .2 µg/g.

(c) Arsenic (As) above .2 µg/g.

(d) Mercury (Hg) above .1 µg/g.

(5) If a sample from a batch of psilocybin product fails heavy metal testing, the batch may not be remediated and must be destroyed.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7090
Psilocybin Batch Requirements

(1) A manufacturer must separate each harvest lot of dried whole fungi into batches no larger than one kilogram.

(2) A process lot for psilocybin extracts, homogenized fungi or edible psilocybin products is considered a batch.

(3) A manufacturer must assign each batch a unique batch number and that unique batch number must be:

(a) Documented and maintained in the manufacturer's records for at least three years and available to the Authority upon request;

(b) Provided to the individual responsible for taking samples; and

(c) Included in the batch labels required by OAR 333-333-7110.

(4) A manufacturer may not reuse a unique batch number.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7100
Psilocybin Product Sampling Requirements

(1) Whole fungi.

(a) Whole fungi may only be sampled after it is dried, regardless of whether the whole fungi will be processed into another product type.

(b) Sufficient sample increments must be taken to perform required tests and samples must be taken in a manner consistent with the laboratory's sampling policies and procedures.

(2) Other product types.

(a) Samples of psilocybin extracts, homogenized fungi, and edible psilocybin products intended for use by a client must be taken from the finished product.

(b) Sufficient sample increments from a batch must be taken to determine whether the batch is homogenous and must be taken in a manner consistent with the laboratory's sampling policies and procedures.

(c) A sufficient sample size must be taken for analysis of all requested tests and the quality control performed by the testing laboratory for these tests.

(3) Only individuals employed by a laboratory with an ORELAP accredited scope item for sampling under these rules may take samples.

(4) Sampling may be conducted at a manufacturer's licensed premises, or the manufacturer may transport the batch to a laboratory with an ORELAP accredited scope item for sampling under these rules.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7110
Requirements for Pre-Tested Psilocybin Products

(1) Following samples being taken from a harvest or process lot a manufacturer must:

(a) Label the batch with the following information:

(A) The harvest or process lot unique identification number;

(B) The name of the laboratory that took samples and the name of the laboratory responsible for testing, if different;

(C) The test batch or sample unique identification numbers supplied by the laboratory;

(D) The date the samples were taken: and

(E) In bold, capital letters, no smaller than 12-point font, "PRODUCT NOT TESTED."

(b) Store and secure the batch in a manner that prevents the product from being tampered with or transferred prior to test results being reported; and

(c) Be able to easily locate a batch stored and secured under subsection (1)(b) of this rule and provide that location to the Authority or a laboratory upon request.

(2) If the samples pass testing, the product may be sold or transferred in accordance with applicable rules.

(3) If the samples do not pass testing, the manufacturer must comply with OAR 333-333-7120.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7120
Failed Test Samples

(1) If a sample or a field duplicate sample (collectively referred to as "sample" for purposes of this rule) fails any initial test, the laboratory that did the testing may reanalyze the sample. The laboratory that did the initial test may not subcontract the reanalysis. If a primary sample or a field duplicate sample fails, both must be reanalyzed. If the sample passes, another laboratory must resample the batch and confirm that result for the batch to pass testing.

(a) If a manufacturer wishes to have a sample reanalyzed, the manufacturer must request a reanalysis within seven calendar days from the date the laboratory sent notice of the failed test to the manufacturer. The reanalysis must be completed by the laboratory within 30 days from the date the reanalysis was requested.

(b) If a manufacturer has requested a reanalysis in accordance with subsection (1)(a) of this rule and the sample passes, the manufacturer has seven calendar days from the date the laboratory sent notice of the passed test to request that another laboratory resample the batch and confirm the passed test result. The retesting must be

completed by the second laboratory within 30 days from the date the retesting was requested.

(c) A manufacturer must inform the Authority immediately, of the following, in a manner prescribed by the Authority:

(A) A request for reanalysis of a sample;

(B) The testing results of the reanalysis;

(C) A request for retesting; and

(D) The results of retesting.

(2) If a sample fails a test or a reanalysis under section (1) of this rule the batch:

(a) May be remediated in accordance with these rules; or

(b) If it is not or cannot be remediated under this rule, must be destroyed in a manner specified by the Authority.

(3) If a manufacturer is permitted to remediate under this rule, the manufacturer must provide notice to the Authority of the registrant's intent to remediate.

(4) A psilocybin extract that is permitted to undergo remediation cannot be further processed into a psilocybin product during the remediation process.

(5) Failed microbiological contaminant testing. If a sample from a batch psilocybin product fails microbial contaminant testing the batch may not be remediated and must be destroyed as ordered by the Authority.

(6) Failed solvent testing.

(a) If a sample from a batch fails solvent testing the batch may be remediated using procedures that would reduce the concentration of solvents to less than the action level.

(b) A batch that is remediated in accordance with subsection (a) of this section must be re-sampled and re-tested in accordance with these rules and must be tested if not otherwise required for that product under these rules, for solvents and pesticides.

(c) A batch that fails solvent testing that is not remediated or that if remediated fails testing must be destroyed in a manner specified by the Authority.

(7) Failed pesticide testing. If a sample from a batch of psilocybin product fails pesticide testing the batch may not be remediated and must be destroyed as ordered by the Authority

(8) Failed heavy metal testing. If a sample from a batch of psilocybin product fails heavy metal testing the batch may not be remediated and must be destroyed as ordered by the Authority

(9) Failed potency testing. A psilocybin product that fails potency testing under OAR 333-333-7040 may be re-mixed in an effort to meet the standards in OAR 333-333-7040. A psylocibin product that is re-mixed must be re-sampled and re-tested in accordance with these rules.

(10) If a sample fails a test after undergoing remediation as permitted under this rule the batch must be destroyed in a manner approved by the Authority.

(11) A manufacturer must inform a laboratory prior to samples being taken that the batch has failed a test and is being retested after undergoing remediation.

(12) A manufacturer must document all sampling, testing, remediation and destruction that are a result of failing a test under these rules.

(13) If a batch fails a test under these rules a manufacturer:

(a) Must store and segregate the batch in a secure area and label the batch clearly to indicate it has failed a test and the label must include a test batch number.

(b) May not remove the batch from the registered premises without permission from the Authority.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
PH 74-2022, adopt filed 05/19/2022, effective 05/20/2022

333-333-7150
Quality Control and Research and Development Testing

(1) A manufacturer may request that a laboratory conduct testing for the purpose of assuring quality control or research and development, except as provided in section (2) of this rule.

(2) A manufacturer may not request that a laboratory conduct pesticide testing on psilocybin products for the purpose quality control or for research and development. A pesticide test is always a compliance test.

(3) A manufacturer that submits a psilocybin product for quality control or research and development testing is not subject to OAR 333-333-7010 to OAR 333-333-7120.

(4) A laboratory result from a quality control or research and development test cannot be used as a compliance test result. A psilocybin product that has undergone a quality control or research and development test may not be transferred or sold without undergoing required compliance tests.

(5) Manufacturers must retain all quality control and research and development test results for at least two years and provide copies of such results upon request to the Authority.

Statutory/Other Authority: ORS 475A.235 & ORS 475A.590
Statutes/Other Implemented: ORS 475A.235 & ORS 475A.590
History:
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Oregon Psilocybin Advisory Board Rapid Evidence Review and Recommendations

July 30, 2021

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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 Nahuatls, Mayans, Olmec, Mazatecs, Chinantecs, Mixes, Zapotecs, Chatinos, Colima, Purepechas and Totonacs of Mexico[4] 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 ninos 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 & Marques[8] 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 depression[12] (N=20) and an earlier iteration of the same trial[13] (N=12); two for

tobacco use disorder[14] (N=15), and a long-term follow-up with the same cohort;[15] one for alcohol use disorder[16] (N=10); and one for obsessive-compulsive disorder[17] (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.*, 2020[18] demonstrated statistically significant large effect sizes of psilocybin therapy on depression and anxiety in a meta-analysis of four of these clinical trials[9-12] (N=117). We identified three additional trials that confirm and advance the above findings[19-21] 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 η_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 Disorder[17] (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 survey[25] 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 trial[10] 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 trial[11] 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 trial[9] 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-analysis[26] 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 Nahuatls, Mayans, Olmec, Mazatecs, Chinantecs, Mixes, Zapotecs, Chatinos, Colima, Purepechas and Totonacs of Mexico[4] 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 trial[27] 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 Scale[28] 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 review[29] 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 frequency[31] and one trial documented increases in mindfulness.[32]

g. Other Conditions:

We identified one within-subjects pilot randomized trial[22] 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 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 al.[33] 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 depression[39] and individuals with substance use disorders[40] 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 settings[47] and in the community[48] 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 phenylethylamines 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 review[57] 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 analysis[61] 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 survey[64] 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 study[65] 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 ingestion[4] 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 cultivation[102-105] 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 η_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 (η_p^2=0.27, 90% CI 0.05-0.43), complicated grief (η_p^2=0.45, 90% CI 0.19-0.58), and alcohol use (η_p^2=0.40, 90% CI 0.03-0.62).

Exploratory Outcomes: Attachment anxiety was significantly reduced at 3 months (d_{rm}=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_{11}=4.36, p=.001) and 3-month (t_{10}=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≤.05; HADS-Depression: p≤.01) and anxiety (STAI-State: p≤.01; STAI-Trait: p≤.001; HADS-Anxiety: p≤.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 persisting[132] 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 Syndrome[133] 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, 157] 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[158], the 4-anilinoquinazoline class of kinase inhibitors[159], Cinacalcet[160], Disulfiram[161], 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.[162]

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-HT2A 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/ftpdir/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., 2021[143]; 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/~jfkihlstrom/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 complications[138] and gastrointestinal complications[155] 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 phenylethylamines 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, 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

Rapid Review References

1. Schultes RE. Hallucinogens of plant origin. *Science.* 1969;163(3864):245-254.
2. Schultes RE, Hofmann A, Rätsch C. Plants of the Gods: their sacred. *Healing, and Hallucinogenic Powers (Healing Arts, Rochester, VT).* 2001.
3. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. *J Psychopharmacol.* 2008;22(6):603-620.
4. Guzmán G. The hallucinogenic mushrooms: diversity, traditions, use and abuse with special reference to the genus Psilocybe. In: *Fungi from different environments.* CRC Press; 2019:256-277.
5. Araujo AM, Carvalho F, Bastos Mde L, Guedes de Pinho P, Carvalho M. The hallucinogenic world of tryptamines: an updated review. *Arch Toxicol.* 2015;89(8):1151-1173.
6. Krippner S, Winkelman M. Maria Sabina: Wise lady of the mushrooms. *J Psychoactive Drugs.* 1983;15(3):225-228.
7. Tricco AC, Langlois EV, Straus SE, editors. Rapid reviews to strengthen health policy and systems: a practical guide. In. Geneva: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO; 2017.
8. Castro Santos H, Gama Marques J. What is the clinical evidence on psilocybin for the treatment of psychiatric disorders? A systematic review. *Porto biomed.* 2021;6(1):e128.
9. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *J Psychopharmacol.* 2016;30(12):1181-1197.
10. Grob CS, Danforth AL, Chopra GS, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch Gen Psychiatry.* 2011;68(1):71-78.
11. Ross S, Bossis A, Guss J, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol.* 2016;30(12):1165-1180.
12. Carhart-Harris R, Bolstridge M, Day C, et al. Psilocybin with psychological support for treatment-resistant depression: Six-month follow-up. *Psychopharmacology (Berl).* 2018;235(2):399-408.
13. Carhart-Harris RL, Bolstridge M, Rucker J, et al. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry.* 2016;3(7):619-627.
14. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *J Psychopharmacol.* 2014;28(11):983-992.
15. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. *The American Journal of Drug and Alcohol Abuse.* 2017;43(1):55-60.
16. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa P, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *Journal of psychopharmacology (oxford, england).* 2015;29(3):289-299.
17. Moreno FA, Wiegand CB, Taitano E, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *The Journal of Clinical Psychiatry.* 2006;67(11):1735-1740.
18. Goldberg SB, Pace BT, Nicholas CR, Raison CL, Hutson PR. The experimental effects of psilocybin on symptoms of anxiety and depression: A meta-analysis. *Psychiatry Res.* 2020;284:112749.
19. Anderson BT, Danforth A, Daroff PR, et al. Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study. *EClinicalMedicine.* 2020;27:100538.
20. Davis AK, Barrett FS, May DG, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA Psychiatry.* 2021;78(5):481-489.

21. Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of Psilocybin versus Escitalopram for Depression. *N Engl J Med.* 2021;384(15):1402-1411.
22. Schindler EAD, Sewell RA, Gottschalk CH, et al. Exploratory Controlled Study of the Migraine-Suppressing Effects of Psilocybin. *Neurother.* 2020;12:12.
23. Vehling S, Kissane DW, Lo C, et al. The association of demoralization with mental disorders and suicidal ideation in patients with cancer. *Cancer.* 2017;123(17):3394-3401.
24. Varker T, Watson L, Gibson K, Forbes D, O'Donnell ML. Efficacy of Psychoactive Drugs for the Treatment of Posttraumatic Stress Disorder: A Systematic Review of MDMA, Ketamine, LSD and Psilocybin. *J Psychoactive Drugs.* 2021;53(1):85-95.
25. Williams MT, Davis AK, Xin Y, et al. People of color in North America report improvements in racial trauma and mental health symptoms following psychedelic experiences. *Drugs: Education, Prevention and Policy.* 2021;28(3):215-226.
26. Vargas AS, Luis A, Barroso M, Gallardo E, Pereira L. Psilocybin as a New Approach to Treat Depression and Anxiety in the Context of Life-Threatening Diseases-A Systematic Review and Meta-Analysis of Clinical Trials. *Biomedicines.* 2020;8(9):05.
27. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl).* 2006;187(3):268-283; discussion 284-292.
28. Hood J, Ralph W, Ghorbani N, Watson PJ, et al. Dimensions of the mysticism scale: Confirming the three-factor structure in the United States and Iran. *J Sci Study Relig.* 2001;40(4):691-705.
29. Aday JS, Mitzkovitz CM, Bloesch EK, Davoli CC, Davis AK. Long-term effects of psychedelic drugs: A systematic review. *Neurosci Biobehav Rev.* 2020;113:179-189.
30. Erritzoe D, Roseman L, Nour MM, et al. Effects of psilocybin therapy on personality structure. *Acta Psychiatr Scand.* 2018;138(5):368-378.
31. Griffiths RR, Johnson MW, Richards WA, et al. Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. *J Psychopharmacol.* 2018;32(1):49-69.
32. Madsen MK, Fisher PM, Stenbæk DS, et al. A single psilocybin dose is associated with long-term increased mindfulness, preceded by a proportional change in neocortical 5-HT2A receptor binding. *Eur Neuropsychopharmacol.* 2020;33:71-80.
33. Dahmane E, Hutson PR, Gobburu JVS. Exposure-Response Analysis to Assess the Concentration-QTc Relationship of Psilocybin/Psilocin. *Clin.* 2021;10(1):78-85.
34. Barrett FS, Carbonaro TM, Hurwitz E, Johnson MW, Griffiths RR. Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: effects on cognition. *Psychopharmacology (Berl).* 2018;235(10):2915-2927.
35. Johnson MW, Sewell R, Griffiths RR. Psilocybin dose-dependently causes delayed, transient headaches in healthy volunteers. *Drug and Alcohol Dependence.* 2012;123(1-3):132-140.
36. Hasler F, Grimberg U, Benz MA, Huber T, Vollenweider FX. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. *Psychopharmacology (Berl).* 2004;172(2):145-156.
37. Carbonaro TM, Bradstreet MP, Barrett FS, et al. Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. *J Psychopharmacol.* 2016;30(12):1268-1278.
38. Galvao-Coelho NL, Marx W, Gonzalez M, et al. Classic serotonergic psychedelics for mood and depressive symptoms: a meta-analysis of mood disorder patients and healthy participants. *Psychopharmacology (Berl).* 2021;238(2):341-354.
39. Watts R, Day C, Krzanowski J, Nutt D, Carhart-Harris R. Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant depression. *Journal of Humanistic Psychology.* 2017;57(5):520-564.

40. Noorani T, Garcia-Romeu A, Swift TC, Griffiths RR, Johnson MW. Psychedelic therapy for smoking cessation: Qualitative analysis of participant accounts. *J Psychopharmacol.* 2018;32(7):756-769.
41. Studerus E, Kometer M, Hasler F, Vollenweider FX. Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. *J Psychopharmacol.* 2011;25(11):1434-1452.
42. Benjamin C. Persistent psychiatric symptoms after eating psilocybin mushrooms. *Br Med J.* 1979;1(6174):1319-1320.
43. Ken Gillman P. Triptans, serotonin agonists, and serotonin syndrome (serotonin toxicity): a review. *Headache: The Journal of Head and Face Pain.* 2010;50(2):264-272.
44. Suzuki K. [Three cases of acute serotonin syndrome due to psilocybin mushroom poisoning]. *Chudoku Kenkyu.* 2016;29(1):33-35.
45. Martinotti G, Santacroce R, Pettorruso M, et al. Hallucinogen persisting perception disorder: etiology, clinical features, and therapeutic perspectives. *Brain sciences.* 2018;8(3):47.
46. Espiard M-L, Lecardeur L, Abadie P, Halbecq I, Dollfus S. Hallucinogen persisting perception disorder after psilocybin consumption: a case study. *European psychiatry.* 2005;20(5-6):458-460.
47. Dittrich A, von Arx S, Staub S. Concerning the question of increased readiness to consume hallucinogens subsequent to experiments with hallucinogens. *Schweizerische Zeitschrift für Psychologie und ihre Anwendungen/Revue suisse de Psychologie pure et appliquée.* 1980.
48. Nichols DE. Psychedelics. *Pharmacol Rev.* 2016;68(2):264-355.
49. Studerus E, Gamma A, Kometer M, Vollenweider FX. Prediction of psilocybin response in healthy volunteers. *PLoS ONE.* 2012;7(2):e30800.
50. Leptourgos P, Fortier-Davy M, Carhart-Harris R, et al. Hallucinations Under Psychedelics and in the Schizophrenia Spectrum: An Interdisciplinary and Multiscale Comparison. *Schizophrenia Bulletin.* 2020;46(6):1396-1408.
51. Beug MW, Bigwood J. Psilocybin and psilocin levels in twenty species from seven genera of wild mushrooms in the Pacific Northwest, U.S.A. *J Ethnopharmacol.* 1982;5(3):271-285.
52. van Amsterdam J, Opperhuizen A, van den Brink W. Harm potential of magic mushroom use: a review. *Regul Toxicol Pharmacol.* 2011;59(3):423-429.
53. Fricke J, Sherwood A, Kargbo R, et al. Enzymatic Route toward 6-Methylated Baeocystin and Psilocybin. *Chembiochem.* 2019;20(22):2824-2829.
54. Sherwood AM, Halberstadt AL, Klein AK, et al. Synthesis and Biological Evaluation of Tryptamines Found in Hallucinogenic Mushrooms: Norbaeocystin, Baeocystin, Norpsilocin, and Aeruginascin. *J Nat Prod.* 2020;83(2):461-467.
55. Beck O, Helander A, Karlson-Stiber C, Stephansson N. Presence of phenylethylamine in hallucinogenic Psilocybe mushroom: possible role in adverse reactions. *J Anal Toxicol.* 1998;22(1):45-49.
56. Skryabin VY, Vinnikova M, Nenastieva A, Alekseyuk V. Hallucinogen persisting perception disorder: A literature review and three case reports. *J Addict Dis.* 2018;37(3-4):268-278.
57. Leonard JB, Anderson B, Klein-Schwartz W. Does getting high hurt? Characterization of cases of LSD and psilocybin-containing mushroom exposures to national poison centers between 2000 and 2016. *J Psychopharmacol.* 2018;32(12):1286-1294.
58. Muller K, Puschel K, Iwersen-Bergmann S. [Suicide under the influence of "magic mushrooms"]. *Arch Kriminol.* 2013;231(5-6):193-198.
59. Lim TH, Wasywich CA, Ruygrok PN. A fatal case of 'magic mushroom' ingestion in a heart transplant recipient. *Intern Med J.* 2012;42(11):1268-1269.
60. Johansen P-O, Krebs TS. Psychedelics not linked to mental health problems or suicidal behavior: A population study. *J Psychopharmacol.* 2015;29(3):270-279.

61. Hendricks PS, Thorne CB, Clark CB, Coombs DW, Johnson MW. Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. *J Psychopharmacol.* 2015;29(3):280-288.
62. Hendricks PS, Crawford MS, Cropsey KL, et al. The relationships of classic psychedelic use with criminal behavior in the United States adult population. *J Psychopharmacol.* 2018;32(1):37-48.
63. Bienemann B, Ruschel NS, Campos ML, Negreiros MA, Mograbi DC. Self-reported negative outcomes of psilocybin users: A quantitative textual analysis. *PLoS ONE.* 2020;15(2):e0229067.
64. Barrett FS, Johnson MW, Griffiths RR. Neuroticism is associated with challenging experiences with psilocybin mushrooms. *Pers Individ Dif.* 2017;117:155-160.
65. Carrillo F, Sigman M, Fernandez Slezak D, et al. Natural speech algorithm applied to baseline interview data can predict which patients will respond to psilocybin for treatment-resistant depression. *J Affect Disord.* 2018;230:84-86.
66. Reynolds HT, Vijayakumar V, Gluck-Thaler E, Korotkin HB, Matheny PB, Slot JC. Horizontal gene cluster transfer increased hallucinogenic mushroom diversity. Evol. 2018;2(2):88-101.
67. Blei F, Baldeweg F, Fricke J, Hoffmeister D. Biocatalytic Production of Psilocybin and Derivatives in Tryptophan Synthase-Enhanced Reactions. Chemistry. 2018;11:11.
68. Blei F, Fricke J, Wick J, Slot JC, Hoffmeister D. Iterative l-Tryptophan Methylation in Psilocybe Evolved by Subdomain Duplication. *Chembiochem.* 2018;19(20):2160-2166.
69. Fricke J, Blei F, Hoffmeister D. Enzymatic Synthesis of Psilocybin. *Angew Chem Int Ed Engl.* 2017;56(40):12352-12355.
70. Fricke J, Kargbo R, Regestein L, et al. Scalable Hybrid Synthetic/Biocatalytic Route to Psilocybin. *Chemistry.* 2020;26(37):8281-8285.
71. Torrens-Spence MP, Liu CT, Pluskal T, Chung YK, Weng JK. Monoamine Biosynthesis via a Noncanonical Calcium-Activatable Aromatic Amino Acid Decarboxylase in Psilocybin Mushroom. *ACS Chem Biol.* 2018;13(12):3343-3353.
72. Demmler R, Fricke J, Dorner S, Gressler M, Hoffmeister D. S-Adenosyl-l-Methionine Salvage Impacts Psilocybin Formation in "Magic" Mushrooms. *Chembiochem.* 2020;21(9):1364-1371.
73. Lenz C, Sherwood A, Kargbo R, Hoffmeister D. Taking Different Roads: l-Tryptophan as the Origin of Psilocybe Natural Products. *ChemPlusChem.* 2021;86(1):28-35.
74. Reingardiene D, Vilcinskaite J, Lazauskas R. [Hallucinogenic mushrooms]. *Medicina (Kaunas).* 2005;41(12):1067-1070.
75. Lincoff G, Mitchel DH. *Toxic and hallucinogenic mushroom poisoning. A handbook for physicians and mushroom hunters.* Van Nostrand Reinhold Company.; 1977.
76. Stamets P. *Psilocybin mushrooms of the world.* Ten Speed Press; 1996.
77. Schafer AT. [Microscopic study of powders of hallucinogenic mushrooms--Psilocybe sp]. *Arch Kriminol.* 2000;205(1-2):30-36.
78. Uehling JK, Henkel TW, Aime MC, Vilgalys R, Smith ME. New species and distribution records for Clavulina (Cantharellales, Basidiomycota) from the Guiana Shield, with a key to the lowland neotropical taxa. *Fungal biology.* 2012;116(12):1263-1274.
79. Lenz C, Wick J, Braga D, et al. Injury-Triggered Blueing Reactions of Psilocybe "Magic" Mushrooms. *Angew Chem Int Ed Engl.* 2020;59(4):1450-1454.
80. Franz M, Regele H, Kirchmair M, et al. Magic mushrooms: hope for a 'cheap high' resulting in end-stage renal failure. *Nephrol Dial Transplant.* 1996;11(11):2324-2327.
81. Adams AM, Kaplan NA, Wei Z, et al. In vivo production of psilocybin in E. coli. *Metab Eng.* 2019;56:111-119.
82. Milne N, Thomsen P, Molgaard Knudsen N, Rubaszka P, Kristensen M, Borodina I. Metabolic engineering of Saccharomyces cerevisiae for the de novo production of psilocybin and related tryptamine derivatives. *Metab Eng.* 2020;60:25-36.
83. Fricke J, Lenz C, Wick J, Blei F, Hoffmeister D. Production Options for Psilocybin: Making of the Magic. *Chemistry.* 2019;25(4):897-903.

84. Guzmán G. Hallucinogenic mushrooms in Mexico: An overview. *Economic Botany.* 2008;62(3):404-412.
85. Guzmán G. New taxonomical and ethnomycological observations on psilocybe ss (fungi, basidiomycota, agaricomycetidae, agaricales, strophariaceae) from Mexico, Africa and Spain. *Acta botánica mexicana.* 2012(100):79-106.
86. Kamata T, Nishikawa M, Katagi M, Tsuchihashi H. Liquid chromatography-mass spectrometric and liquid chromatography-tandem mass spectrometric determination of hallucinogenic indoles psilocin and psilocybin in "magic mushroom" samples. *J Forensic Sci.* 2005;50(2):336-340.
87. Stribrny J, Borovicka J, Sokol M. [Levels of psilocybin and psilocin in various types of mushrooms]. *Soud Lek.* 2003;48(3):45-49.
88. Saito K, Toyo'oka T, Kato M, Fukushima T, Shirota O, Goda Y. Determination of psilocybin in hallucinogenic mushrooms by reversed-phase liquid chromatography with fluorescence detection. *Talanta.* 2005;66(3):562-568.
89. Sottolano SM, Lurie IS. The quantitation of psilocybin in hallucinogenic mushrooms using high performance liquid chromatography. *J Forensic Sci.* 1983;28(4):929-935.
90. Christiansen AL, Rasmussen KE. Screening of hallucinogenic mushrooms with high-performance liquid chromatography and multiple detection. *J Chromatogr.* 1983;270:293-299.
91. Beug MW, Bigwood J. Quantitative analysis of psilocybin and psilocin in psilocybe baeocystis (Singer and Smith) by high-performance liquid chromatography and by thin-layer chromatography. *J Chromatogr.* 1981;207(3):379-385.
92. Stahl E, Brombeer J, Eskes D. [Narcotic mushrooms with LSD?]. *Arch Kriminol.* 1978;162(1-2):23-33.
93. Hofmann A, et al. Psilocybin und Psilocin, zwei psychotrope Wirkstoffe aus mexicanischen Rauschpilzen. *Helvetica Chimica Acta* 1959;42:1557–1572
94. Van Orden RC. *Determination of psilocybin and psilocin in hallucinogenic mushrooms by HPLC with diode array and MS detection.* State University of New York College of Environmental Science and Forestry; 2008.
95. Stebelska K. Assays for Detection of Fungal Hallucinogens Such as Psilocybin and Psilocin. In: *Neuropathology of Drug Addictions and Substance Misuse.* Elsevier; 2016:909-926.
96. Nagy J, Veress T. HPLC analysis of hallucinogenic mushroom alkaloids (psilocin and psilocybin) applying hydrophilic interaction chromatography (HILIC). *Journal of Forensic Research.* 2016;7(6):10.4172.
97. Rácz N, Nagy J, Jiang W, Veress T. Modeling retention behavior on analysis of hallucinogenic mushrooms using hydrophilic interaction liquid chromatography. *J Chromatogr Sci.* 2019;57(3):230-237.
98. Veress T, Rácz N, Nagy J, Jiang W. Determination of Psilocin and Psilocybin in Magic Mushrooms Using iHILIC®-Fusion and MS. In: ADVANSTAR COMMUNICATIONS INC 131 W 1ST STREET, DULUTH, MN 55802 USA; 2020.
99. Zhou L, Xiang P, Wen D, et al. Sensitive quantitative analysis of psilocin and psilocybin in hair samples from suspected users and their distribution in seized hallucinogenic mushrooms. *Forensic Toxicology.* 2021:1-10.
100. Anastos N, Lewis SW, Barnett NW, Sims DN. The determination of psilocin and psilocybin in hallucinogenic mushrooms by HPLC utilizing a dual reagent acidic potassium permanganate and tris(2,2'-bipyridyl)ruthenium(II) chemiluminescence detection system. *J Forensic Sci.* 2006;51(1):45-51.
101. Gambaro V, Roda G, Visconti GL, et al. Taxonomic Identification of Hallucinogenic Mushrooms Seized on the Illegal Market Using a DNA-Based Approach and LC/MS-MS Determination of Psilocybin and Psilocin. 2015.
102. Stamets P, Chilton J. The mushroom cultivator. *First Washington.* 1983.
103. Lambert EB. Principles and problems of mushroom culture. *The Botanical Review.* 1938;4(7):397.

104. Evans HJ, Hughes DT, Thomas PT. Chemically induced neoplasms in fungi. *Nature.* 1956;178(4540):949-951.
105. Moore D. Principles of mushroom developmental biology. *International Journal of Medicinal Mushrooms.* 2005;7(1&2).
106. Bressa G, Cima L, Costa P. Bioaccumulation of Hg in the mushroomPleurotus ostreatus. *Ecotoxicology and environmental safety.* 1988;16(2):85-89.
107. Gabriel J, Vosahlo J, Baldrian P. Biosorption of cadmium to mycelial pellets of wood-rotting fungi. *Biotechnology Techniques.* 1996;10(5):345-348.
108. Tüzen M, Özdemir M, Demirbaş A. Heavy metal bioaccumulation by cultivated Agaricus bisporus from artificially enriched substrates. *Zeitschrift für Lebensmitteluntersuchung und-Forschung A.* 1998;206(6):417-419.
109. Michelot D, Siobud E, Doré J-C, Viel C, Poirier F. Update on metal content profiles in mushrooms—toxicological implications and tentative approach to the mechanisms of bioaccumulation. *Toxicon.* 1998;36(12):1997-2012.
110. Falandysz J, Szymczyk K, Ichihashi H, et al. ICP/MS and ICP/AES elemental analysis (38 elements) of edible wild mushrooms growing in Poland. *Food Additives & Contaminants.* 2001;18(6):503-513.
111. Demirbaş A. Concentrations of 21 metals in 18 species of mushrooms growing in the East Black Sea region. *Food Chemistry.* 2001;75(4):453-457.
112. Demirbaş A. Heavy metal bioaccumulation by mushrooms from artificially fortified soils. *Food chemistry.* 2001;74(3):293-301.
113. Demirbaş A. Metal ion uptake by mushrooms from natural and artificially enriched soils. *Food Chemistry.* 2002;78(1):89-93.
114. García MÁ, Alonso J, Melgar MJ. Lead in edible mushrooms: levels and bioaccumulation factors. *Journal of Hazardous Materials.* 2009;167(1-3):777-783.
115. Gabriel J, Švec K, Kolihová D, Tlustoš P, Száková J. Translocation of mercury from substrate to fruit bodies of Panellus stipticus, Psilocybe cubensis, Schizophyllum commune and Stropharia rugosoannulata on oat flakes. *Ecotoxicology and environmental safety.* 2016;125:184-189.
116. Širić I, Humar M, Kasap A, Kos I, Mioč B, Pohleven F. Heavy metal bioaccumulation by wild edible saprophytic and ectomycorrhizal mushrooms. *Environmental science and pollution research.* 2016;23(18):18239-18252.
117. Tel-Cayan G, Ullah Z, Ozturk M, Yabanli M, Aydin F, Duru ME. Heavy metals, trace and major elements in 16 wild mushroom species determined by ICP-MS. 2018.
118. Sener S. Effect of Seagrass Mixed With Casing Soil for the Cultivation of Mushrooms and Study of Bioaccumulation of Heavy Metals. *Atomic S pectroscopy.* 2019;40:188.
119. Chang Q, Fan C, Chen H, Kang J, Wang M, Pang G. Determination of 187 pesticide residues in edible fungi by liquid chromatography-tandem mass spectrometry. *Analytical Methods.* 2014;6(12):4288-4304.
120. Gałgowska M, Pietrzak-Fiećko R. Pesticide contaminants in selected species of edible wild mushrooms from the north-eastern part of Poland Part B Pesticides, food contaminants, and agricultural wastes. 2017.
121. Du P, Wu X, Xu J, et al. Different residue behaviors of four pesticides in mushroom using two different application methods. *Environmental Science and Pollution Research.* 2018;25(9):8377-8387.
122. Tian F, Qiao C, Luo J, et al. Method development and validation of ten pyrethroid insecticides in edible mushrooms by Modified QuEChERS and gas chromatography-tandem mass spectrometry. *Sci.* 2020;10(1):1-10.
123. Roseman L, Demetriou L, Wall MB, Nutt DJ, Carhart-Harris RL. Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression. *Neuropharmacology.* 2018;142:263-269.

124. Stauffer CS, Anderson BT, Ortigo KM, Woolley J. Psilocybin-Assisted Group Therapy and Attachment: Observed Reduction in Attachment Anxiety and Influences of Attachment Insecurity on the Psilocybin Experience. *ACS pharmacol.* 2021;4(2):526-532.
125. Dos Santos RG, Bouso JC, Alcazar-Corcoles MA, Hallak JEC. Efficacy, tolerability, and safety of serotonergic psychedelics for the management of mood, anxiety, and substance-use disorders: a systematic review of systematic reviews. *Expert Rev Clin Pharmacol.* 2018;11(9):889-902.
126. Agin-Liebes GI, Malone T, Yalch MM, et al. Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. *J Psychopharmacol.* 2020;34(2):155-166.
127. Ross S, Agin-Liebes G, Lo S, et al. Acute and Sustained Reductions in Loss of Meaning and Suicidal Ideation Following Psilocybin-Assisted Psychotherapy for Psychiatric and Existential Distress in Life-Threatening Cancer. *ACS pharmacol.* 2021;4(2):553-562.
128. Swift TC, Belser AB, Agin-Liebes G, et al. Cancer at the dinner table: Experiences of psilocybin-assisted psychotherapy for the treatment of cancer-related distress. *Journal of Humanistic Psychology.* 2017;57(5):488-519.
129. Malone TC, Mennenga SE, Guss J, et al. Individual Experiences in Four Cancer Patients Following Psilocybin-Assisted Psychotherapy. *Front Pharmacol.* 2018;9:256.
130. Strickland JC, Garcia-Romeu A, Johnson MW. Set and Setting: A Randomized Study of Different Musical Genres in Supporting Psychedelic Therapy. *ACS pharmacol.* 2021;4(2):472-478.
131. Nielson EM, May DG, Forcehimes AA, Bogenschutz MP. The Psychedelic Debriefing in Alcohol Dependence Treatment: Illustrating Key Change Phenomena through Qualitative Content Analysis of Clinical Sessions. *Front Pharmacol.* 2018;9(132).
132. Bogenschutz MP, Podrebarac SK, Duane JH, et al. Clinical Interpretations of Patient Experience in a Trial of Psilocybin-Assisted Psychotherapy for Alcohol Use Disorder. *Front Pharmacol.* 2018;9:100.
133. Borowiak KS, Ciechanowski K, Waloszczyk P. Psilocybin mushroom (Psilocybe semilanceata) intoxication with myocardial infarction. *J Toxicol Clin Toxicol.* 1998;36(1-2):47-49.
134. Steiner J, Sulman F. Simultaneous studies of blood sugar, behavioural changes and EEG on the wake rabbit after administration of psilocybin. *Archives internationales de pharmacodynamie et de therapie.* 1963;145:301-308.
135. Tyls F, Palenicek T, Horacek J. Psilocybin--summary of knowledge and new perspectives. *Eur Neuropsychopharmacol.* 2014;24(3):342-356.
136. Koivikko A, Savolainen J. Mushroom allergy. *Allergy.* 1988;43(1):1-10.
137. Raff E, Halloran PF, Kjellstrand CM. Renal failure after eating "magic" mushrooms. *Cmaj.* 1992;147(9):1339-1341.
138. Austin E, Myron HS, Summerbell RK, Mackenzie C. Acute renal injury cause by confirmed Psilocybe cubensis mushroom ingestion. *Med Mycol Case Rep.* 2019;23:55-57.
139. Gard DE, Pleet MM, Bradley ER, et al. Evaluating the Risk of Psilocybin for the Treatment of Bipolar Depression: A Review of the Research Literature and Published Case Studies. *medRxiv.* 2021:2021.2004.2002.21254838.
140. Zeifman RJ, Singhal N, Breslow L, Weissman CR. On the Relationship between Classic Psychedelics and Suicidality: A Systematic Review. *ACS pharmacol.* 2021;4(2):436-451.
141. Seiler N, Nguyen T, Yung A, O'Donoghue B. Terminology and assessment tools of psychosis: A systematic narrative review. *Psychiatry and clinical neurosciences.* 2020;74(4):226-246.
142. Lovibond PF, Lovibond SH. The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour research and therapy.* 1995;33(3):335-343.

143. Davis AK, Barrett FS, So S, Gukasyan N, Swift TC, Griffiths RR. Development of the Psychological Insight Questionnaire among a sample of people who have consumed psilocybin or LSD. *J Psychopharmacol.* 2021;35(4):437-446.
144. Kamata T, Nishikawa M, Katagi M, Tsuchihashi H. Optimized glucuronide hydrolysis for the detection of psilocin in human urine samples. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2003;796(2):421-427.
145. Shoda T, Fukuhara K, Goda Y, Okuda H. Enzyme-assisted synthesis of the glucuronide conjugate of psilocin, an hallucinogenic component of magic mushrooms. *Drug Test Anal.* 2011;3(9):594-596.
146. Poliwoda A, Zielinska K, Wieczorek PP. Direct Analysis of Psilocin and Muscimol in Urine Samples Using Single Drop Microextraction Technique In-Line with Capillary Electrophoresis. *Molecules (Basel).* 2020;25(7):29.
147. Pichini S, Marchei E, Garcia-Algar O, Gomez A, Di Giovannandrea R, Pacifici R. Ultra-high-pressure liquid chromatography tandem mass spectrometry determination of hallucinogenic drugs in hair of psychedelic plants and mushrooms consumers. *J Pharm Biomed Anal.* 2014;100:284-289.
148. Sticht G, Kaferstein H. Detection of psilocin in body fluids. *Forensic Sci Int.* 2000;113(1-3):403-407.
149. Morita I, Oyama H, Kiguchi Y, et al. Immunochemical monitoring of psilocybin and psilocin to identify hallucinogenic mushrooms. *J Pharm Biomed Anal.* 2020;190:113485.
150. Racz N, Nagy J, Jiang W, Veress T. Modeling Retention Behavior on Analysis of Hallucinogenic Mushrooms Using Hydrophilic Interaction Liquid Chromatography. *J Chromatogr Sci.* 2019;57(3):230-237.
151. Gotvaldova K, Hajkova K, Borovicka J, Jurok R, Cihlarova P, Kuchar M. Stability of psilocybin and its four analogs in the biomass of the psychotropic mushroom Psilocybe cubensis. *Drug Test Anal.* 2021;13(2):439-446.
152. Musha M, Ishii A, Tanaka F, Kusano G. Poisoning by hallucinogenic mushroom hikageshibiretake (Psilocybe argentipes K. Yokoyama) indigenous to Japan. *Tohoku J Exp Med.* 1986;148(1):73-78.
153. Riley SC, Blackman G. Between prohibitions: patterns and meanings of magic mushroom use in the UK. *Subst Use Misuse.* 2008;43(1):55-71.
154. Peden NR, Pringle SD, Crooks J. The problem of psilocybin mushroom abuse. *Hum Toxicol.* 1982;1(4):417-424.
155. Forrester MB. Hallucinogenic mushroom misuse reported to Texas poison centers. *J Addict Dis.* 2020;38(4):482-488.
156. Satora L, Goszcz H, Ciszowski K. Poisonings resulting from the ingestion of magic mushrooms in Krakow. *Przegl Lek.* 2005;62(6):394-396.
157. Manevski N, Kurkela M, Hoglund C, et al. Glucuronidation of psilocin and 4-hydroxyindole by the human UDP-glucuronosyltransferases. *Drug Metab Dispos.* 2010;38(3):386-395.
158. Naz F, Jyoti S, Rahul, Akhtar N, Siddique YH. Effect of Oral Contraceptive Pills on the Blood Serum Enzymes and DNA Damage in Lymphocytes Among Users. *Indian J Clin Biochem.* 2016;31(3):294-301.
159. Miners et al., 2017 – Citation pending
160. Belozeroff V, Goodman WG, Ren L, Kalantar-Zadeh K. Cinacalcet lowers serum alkaline phosphatase in maintenance hemodialysis patients. *Clin J Am Soc Nephrol.* 2009;4(3):673-679.
161. Veverka KA, Johnson KL, Mays DC, Lipsky JJ, Naylor S. Inhibition of aldehyde dehydrogenase by disulfiram and its metabolite methyl diethylthiocarbamoyl-sulfoxide. *Biochem Pharmacol.* 1997;53(4):511-518.
162. Honda M, Nishida T, Ono H. Tricyclic analogs cyclobenzaprine, amitriptyline and cyproheptadine inhibit the spinal reflex transmission through 5-HT(2) receptors. *Eur J Pharmacol.* 2003;458(1-2):91-99.

MODEL

ATTACHMENT D

League of Oregon Cities

Model Psilocybin Ordinance & Ballot Measure

JUNE 2022

Cities and counties that desire to prohibit the establishment of psilocybin-related businesses may do so by referral at a statewide general election, meaning an election in November of an even-numbered year. Cities and counties should consult the secretary of state's referral manual and work with the city recorder, elections official, or similar official to determine the procedures necessary to refer an ordinance to the voters.

Once the governing body of a city or county adopts an ordinance, its city or county must submit the ordinance to the Oregon Health Authority (OHA). The OHA will then stop registering and licensing the prohibited businesses until the next statewide general election, when the voters will decide whether to approve or reject the ordinance. In other words, the governing body's adoption of an ordinance acts as a moratorium on new psilocybin-related businesses until the election.

In addition, it is important to note that once election officials file the referral with the county election office, the ballot measure is certified to the ballot. At that point, the restrictions on public employees engaging in political activity will apply. Consequently, cities should consult the secretary of state's manual *Restrictions on Political Campaigning by Public Employees* and their city attorney to ensure that public employees are complying with state elections law in their communications about the pending measure. The model ordinances and ballot measures below contain two versions. The first is a permanent ban of psilocybin-related businesses until the ordinance is repealed and the second acts as a two-year moratorium.

This document is not a substitute for legal advice. City and county councils considering prohibiting psilocybin-related activities should not rely solely on this sample. Any city or county council considering any form of regulation of psilocybin should consult with its city or county attorney regarding the advantages, disadvantages, risks and limitations of any given approach.

Legal counsel can also assist a city or county in preparing an ordinance that is consistent with local procedures, existing ordinances and charter, and advise on what process is needed to adopt the ordinance. The sample provided is intended to be a starting point, not an end point, for any jurisdiction considering prohibiting psilocybin-related activities.

PERMANENT BAN

ORDINANCE NO. _____

AN ORDINANCE DECLARING A BAN ON PSILOCYBIN SERVICE CENTERS AND THE MANUFACTURE OF PSILOCYBIN PRODUCTS

WHEREAS, in November 2020, Oregon voters approved Ballot Measure 109, known as the Oregon Psilocybin Service Act (codified at ORS 475A), which allows for the manufacture, delivery and administration of psilocybin at licensed facilities; and

WHEREAS, ORS 475A.235 provides that the Oregon Health Authority will regulate the manufacturing, transportation, delivery, sale and purchase of psilocybin products and the provision of psilocybin services in the state; and

WHEREAS, the Oregon Health Authority has initiated a rulemaking process to implement the state's psilocybin regulatory program and intends to begin accepting applications for psilocybin-related licenses on January 2, 2023; and

WHEREAS, as of June {date}, 2022, the Oregon Health Authority has not completed the rulemaking process for implementing the state's psilocybin regulatory program, and the City of {city} is uncertain how the manufacture, delivery and administration of psilocybin at licensed psilocybin facilities will operate within the city; and

WHEREAS, ORS 475A.718 provides that a city council may adopt an ordinance to be referred to the electors of the city prohibiting the establishment of state licensed psilocybin product manufacturers and/or psilocybin service centers in the area subject to the jurisdiction of the city; and

WHEREAS, the {city} City Council believes that prohibiting psilocybin product manufacturers and psilocybin service centers within the city's jurisdictional boundaries to enable the adoption of the state's psilocybin licensing and regulatory program and to allow the city to adopt reasonable time, place, and manner regulations on the operation of psilocybin facilities is in the best interest of the health, safety and welfare of the people of {city}; and

WHEREAS, the City Council seeks to refer to the voters of {city} the question of whether to establish a ban on state-licensed psilocybin product manufacturers and psilocybin service centers within the city's jurisdictional boundaries.

Now, therefore,

THE CITY OF {CITY} ORDAINS AS FOLLOWS:

Section 1. **Prohibition**.

The establishment of psilocybin product manufacturers licensed under ORS 275A.290 and psilocybin service centers licensed under ORS 475A.305 is prohibited in the City of {city}.

Section 2. Referral.

This ordinance is referred to the electors of the city of {city} for approval at the next statewide general election on November 8, 2022.

Section 3. Effective Date.

This ordinance takes effect and becomes operative 30 days after the day on which it is approved by a majority of voters.

First reading this ____ day of _____, 2022.

Second reading and passage by this Council this ____ day of _____, 2022.

Signed by the Mayor this ____ day of _____, 2022.

ATTEST:

_____
{NAME}, City Recorder

SIGNED:

_____
{NAME}, Mayor

BALLOT TITLE

A caption which reasonably identifies the subject of the measure.

10-word limit under ORS 250.035(1)(a)

Prohibits psilocybin-related businesses within {city}. [Prohibition sunsets after two years.]

QUESTION

A question which plainly phrases the chief purpose of the measure so that an affirmative response to the question corresponds to an affirmative vote on the measure.

20-word limit under ORS 250.035(1)(b)

Shall {city or county} prohibit {psilocybin-related businesses} in {city or county}?

SUMMARY

A concise and impartial statement summarizing the measure and its major effect.

17-word limit under ORS 250.035(1)(c)

State law allows operation manufacturer, distribution and possession of psilocybin and psilocin. State law provides that a {city or county} council may adopt an ordinance to be referred to the voters to prohibit the establishment of any of those registered or licensed activities.

Approval of this measure would prohibit the establishment of {psilocybin project manufacturers} and/or {psilocybin service center operators} within the area {subject to the jurisdiction of the city} or {in the unincorporated area subject to the jurisdiction of the county.}

****

EXPLANATORY STATEMENT

An impartial, simple and understandable statement explaining the measure and its effect for use in the county voters' pamphlet.

500-word limit under ORS 251.345 and OAR 165-022-0040(3)

Approval of this measure would prohibit the establishment {and operation} of psilocybin-related businesses within the {city or county}.

A {city or county} council may adopt an ordinance prohibiting the establishment of psilocybin related businesses within the {city or county}, but the council must refer the ordinance to the voters at a statewide general election. The {CITY or COUNTY} OF {NAME} {city or county} council has adopted an ordinance prohibiting the establishment of psilocybin-related businesses within the {city or county} and, as a result, has referred this measure to the voters.

If approved, this measure would prohibit psilocybin-related businesses within the {city or county}.

TWO-YEAR MORATORIAM

ORDINANCE NO. _____

AN ORDINANCE DECLARING A TEMPORARY BAN ON PSILOCYBIN SERVICE CENTERS AND THE MANUFACTURE OF PSILOCYBIN PRODUCTS

WHEREAS, in November 2020, Oregon voters approved Ballot Measure 109, known as the Oregon Psilocybin Service Act (codified at ORS 475A), which allows for the manufacture, delivery and administration of psilocybin at licensed facilities; and

WHEREAS, ORS 475A.235 provides that the Oregon Health Authority will regulate the manufacturing, transportation, delivery, sale and purchase of psilocybin products and the provision of psilocybin services in the state; and

WHEREAS, the Oregon Health Authority has initiated a rulemaking process to implement the state's psilocybin regulatory program and intends to begin accepting applications for psilocybin-related licenses on January 2, 2023; and

WHEREAS, as of June {date}, 2022, the Oregon Health Authority has not completed the rulemaking process for implementing the state's psilocybin regulatory program, and the City of {city} is uncertain how the manufacture, delivery and administration of psilocybin at licensed psilocybin facilities will operate within the city; and

WHEREAS, ORS 475A.718 provides that a city council may adopt an ordinance to be referred to the electors of the city prohibiting the establishment of state licensed psilocybin product manufacturers and/or psilocybin service centers in the area subject to the jurisdiction of the city; and

WHEREAS, the {city} City Council believes that prohibiting psilocybin product manufacturers and psilocybin service centers within the city's jurisdictional boundaries to enable the adoption of the state's psilocybin licensing and regulatory program and to allow the city to adopt reasonable time, place, and manner regulations on the operation of psilocybin facilities is in the best interest of the health, safety and welfare of the people of {city}; and

WHEREAS, the City Council seeks to refer to the voters of {city} the question of whether to establish a two-year temporary ban on state-licensed psilocybin product manufacturers and psilocybin service centers within the city's jurisdictional boundaries.

Now, therefore,

THE CITY OF {CITY} ORDAINS AS FOLLOWS:

Section 1. **Prohibition**.

The establishment of psilocybin product manufacturers licensed under ORS 275A.290 and psilocybin service centers licensed under ORS 475A.305 is prohibited in the city of {city}.

Section 2. Referral.

This ordinance is referred to the electors of the city of {city} for approval at the next statewide general election on November 8, 2022.

Section 3. Effective Date.

This ordinance takes effect and becomes operative 30 days after the day on which it is approved by a majority of voters.

Section 4. Sunset.

This ordinance is repealed on December 31, 2024.

First reading this ____ day of _____, 2022.

Second reading and passage by this Council this ____ day of _____, 2022.

Signed by the Mayor this ____ day of _____, 2022.

ATTEST:

_____
{NAME}, City Recorder

SIGNED:

_____
{NAME}, Mayor

BALLOT TITLE

A caption which reasonably identifies the subject of the measure.

10-word limit under ORS 250.035(1)(a)

Prohibits psilocybin-related businesses within {city}. [Prohibition sunsets after two years.]

QUESTION

A question which plainly phrases the chief purpose of the measure so that an affirmative response to the question corresponds to an affirmative vote on the measure.

20-word limit under ORS 250.035(1)(b)

Shall {city or county} prohibit {psilocybin-related businesses} in {city or county}?

SUMMARY

A concise and impartial statement summarizing the measure and its major effect.

17-word limit under ORS 250.035(1)(c)

State law allows operation manufacturer, distribution and possession of psilocybin and psilocin. State law provides that a {city or county} council may adopt an ordinance to be referred to the voters to prohibit the establishment of any of those registered or licensed activities.

Approval of this measure would prohibit the establishment of {psilocybin project manufacturers} and/or {psilocybin service center operators} within the area {subject to the jurisdiction of the city} or {in the unincorporated area subject to the jurisdiction of the county.}

****

EXPLANATORY STATEMENT

An impartial, simple and understandable statement explaining the measure and its effect for use in the county voters' pamphlet.

500-word limit under ORS 251.345 and OAR 165-022-0040(3)

Approval of this measure would prohibit the establishment {and operation} of psilocybin-related businesses within the {city or county}.

A {city or county} council may adopt an ordinance prohibiting the establishment of psilocybin related businesses within the {city or county}, but the council must refer the ordinance to the voters at a statewide general election. The {CITY or COUNTY} OF {NAME} {city or county} council has adopted an ordinance prohibiting the establishment of psilocybin-related businesses within the {city or county} and, as a result, has referred this measure to the voters.

If approved, this measure would prohibit psilocybin-related businesses within the {city or county} until December 31, 2024.