

Psilocybin Study Report to the Connecticut State Legislature

Connecticut Department of Mental Health and Addiction Services

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Table of Contents

| | |
|--|----|
| Executive Summary..... | 3 |
| Summary of Key Findings..... | 4 |
| Research Findings | 4 |
| Findings Related to the FDA and Drug Enforcement Agency (DEA) | 5 |
| Summary of Recommendations..... | 7 |
| Psilocybin Study Workgroup Report to the Connecticut State Legislature | 8 |
| Introduction | 8 |
| Overview of Psilocybin..... | 10 |
| Psilocybin and Safety | 11 |
| National Efforts Related to Psilocybin | 14 |
| Summary of Psilocybin Research | 15 |
| Psilocybin Assisted Therapy | 18 |
| Research and the Role of the Food and Drug Administration (FDA) | 19 |
| Psilocybin Study Membership List | 24 |
| References | 25 |
| Appendix 1 | 27 |
| Appendix 2 | 28 |

Executive Summary

During the 2021 legislative session, the Connecticut State Legislature directed the Department of Mental Health and Addiction Services (DMHAS) to submit a Report to the legislature regarding, “**whether the use of psilocybin by a person under the direction of a health care provider may be beneficial to the person’s physical or mental wellbeing**”. The Report and Executive Summary are intended to provide finding and recommendations regarding the clinically supervised use of psilocybin. The report is a majority report. Because the group possessed a diversity of opinions, there was not universal agreement for all findings and recommendations listed in this report.

Findings regarding the medical use of psilocybin include the following:

- Research demonstrates psilocybin to be a promising treatment for some behavioral health conditions, including substance use, depression, and palliative care for end-of-life anxiety and depression.
- Psilocybin-assisted therapy for mental health conditions is effective when administered in highly structured settings under the supervision of a healthcare professional or professionals, using a treatment model developed for psilocybin and psychedelic-assisted therapy.
- Research to date is limited regarding who may benefit from this form of treatment and who may be at risk of experiencing adverse effects from psilocybin use.
- There may be serious risks associated with the use of psilocybin, including suicidal behavior, self-harm, and suicidal ideation, when administration is unsupervised.
- Psilocybin does not currently have FDA approval and may not be approved until 2025 or later.

Recommendations for the state encompass the following steps:

- When Food and Drug Administration (FDA) approval is granted for the drug, legalize the medically supervised use for defined medical problems in licensed health settings under the supervision of health professionals
- Explore funding resources that could be used to “seed” research projects to help better understand the psychiatric conditions appropriate for psilocybin-assisted treatment
- Explore the feasibility of facilitating the development of an FDA-approved Expanded Access program in Connecticut

These recommendations are based on currently available research. Future research findings may impact the service delivery models that the FDA approves to administer psilocybin and the restrictions that the FDA may impose on service providers. This report’s recommendations are also made with the understanding that based on current research data, psilocybin for therapeutic purposes should not be taken in unsupervised settings, nor should it be a take-home medication. Research finds that effective psilocybin treatment follows a very specific model using careful screening practices, close supervision of study participants, specially trained health or mental health professionals, and a carefully delineated therapeutic process designed to safely dose and administer psilocybin. Adherence to this model has shown that the drug has promise for treating certain conditions, though more needs to be learned about psilocybin’s use.

Summary of Key Findings

Research Findings

- Current research is demonstrating that there are health benefits to the therapeutic use of psilocybin in medical settings under the supervision of health professionals. Research being conducted at a number of institutions such as Johns Hopkins, Yale University, New York University, University of California Los Angeles, and the Imperial College of London have studied the use of psilocybin in the areas of substance use, major depression, and palliative care for end-of-life anxiety and depression with positive results.
- Psilocybin has been therapeutically administered in highly structured settings under the supervision of a healthcare professional or professionals, using a treatment model developed for psilocybin/psychedelic-assisted therapy. The model requires careful screening as certain individuals can be seriously harmed by psilocybin use from a psychological or medical perspective. This treatment model does not support psilocybin's use as a take-home medication, nor does that model support adult use of psilocybin for non-medical purposes. While adverse events are rare in supervised settings, there are much greater risks to the use of psilocybin, especially in unsupervised settings.
- Numerous drug harm studies have found psilocybin to be safe using multiple sets of risk measures. Psilocybin is consistently determined to carry low risk of dependence, mortality, and abuse. One study found that legal drugs like alcohol were found to be far more harmful than psilocybin. It is also believed that psilocybin would be difficult to divert based on the treatment model used for its administration.
- Research has shown that psilocybin used in unsupervised settings has serious risk for adverse events including suicidal behavior, self-harm, and suicidal ideation. Johns Hopkins study showed that almost 40% of psilocybin users in unsupervised settings reported adverse events. This survey deliberately recruited individuals that reported having a bad trip as a precondition to participate in the study. While the survey's design has limitations, the findings underscore the importance of only considering the medically supervised psilocybin services once approved by the FDA.
- Research and the evidence for efficacy is more advanced in certain psychiatric categories or life events. This is especially true for depression and anxiety and depression associated with palliative care. While more limited, research has shown that psilocybin can be effective in treating substance use. Other areas such as Post-Traumatic Stress Disorder (PTSD), Obsessive Compulsive Disorder (OCD), Headache Disorders, are also being studied to a lesser degree and are showing positive results.
- The provision of therapeutic psilocybin services in the United States is illegal outside of research settings. However, individuals are accessing psilocybin "underground" through unauthorized means or legally in other countries. Oregon is the sole state in the United States to legalize the use of psilocybin but will not likely be administering psilocybin until quarter 2 of 2023. Oregon is currently involved in a two-year development period and is in the process of developing regulations, licensing criteria, addressing production of psilocybin, accessibility, and continuing research. The state has taken on all of these functions because they are moving forward without FDA approval.
- The research that has been conducted to date has some limitations in regards to who may benefit from this form of treatment. Most research has involved small sample sizes and have typically not

examined the effects of psilocybin on population subgroups. A review of psilocybin research by the Oregon Psilocybin Advisory Board found that most participants in current research studies involving psilocybin were white males. The report concluded that additional research inclusive of varied population subgroups was needed in order to be able to generalize these findings.

- Further research is necessary to better understand which conditions may be appropriate for this form of treatment. Researchers are examining a wide range of psychiatric, medical, and life conditions to determine if psilocybin is a beneficial form of treatment. Some researchers have cautioned that medical marijuana has been approved for use with certain conditions for which there is no evidence that marijuana is helpful. There are concerns that the same could occur with psilocybin without further research.
- No screening tools exist for determining who may or may not benefit from this form of treatment. Researchers utilize exclusionary criteria for potential study participants in order to manage potential safety concerns. These are based on certain medical or psychiatric conditions. For example, most studies screen out individuals with schizophrenia or a family history of schizophrenia and also exclude persons with uncontrolled hypertension and heart conditions. Further research needs to better understand who can be treated with psilocybin-assisted therapy.

Findings Related to the FDA and Drug Enforcement Agency (DEA)

- Psilocybin does not currently have FDA approval. The FDA requires that Phase 3 clinical trials be completed before it considers granting approval. There are no Phase 3 trials with psilocybin underway at this time. Several organizations, Usona Institute and Compass Pathways are positioning to begin Phase 3 clinical trials, possibly within the next year. There is some hope that psilocybin could receive FDA approval by 2025.
- The FDA has signaled the research field that it sees benefit associated with the therapeutic use of psilocybin through its recent awards of breakthrough therapy status to several organizations. This was originally done in 2018 for treatment resistant depression and again in 2019 for major depression. Two companies received that designation, Compass Pathways and the Usona Institute, and are now undertaking larger clinical studies as a result of that designation.
- FDA approval has been the typical vehicle for safely bringing new drugs to the market. It is important to follow the FDA approval process for a number of reasons. This ensures safety, providing legitimacy to this treatment approach. Equitable access to this treatment will likely depend on FDA approval since the medication and therapy is unlikely to be covered by insurers without FDA approval. A program operating outside of the FDA approval process will likely only be available to the wealthy.
- The FDA will most likely require what is called Risk Evaluation Management Strategies (REMS) as part of the approval process. REMS are a system of processes and procedures designed to ensure safety with new medications where serious safety concerns exist. It is believed that REMS for psilocybin would likely include stipulations regarding who can provide the treatment, the training they must complete, and requirements regarding where the treatment must occur. Any psilocybin services program will need to conform to FDA requirements. The FDA's REMS typically deal with medications and have not regulated medical practices. **It is the responsibility of the drug manufacturer to ensure that providers meet the requirements of the REMS, not the state.**

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- While not a focus of this workgroup, another psychedelic drug, 3,4-Methylenedioxy methamphetamine (MDMA) is likely to receive FDA approval before psilocybin. MDMA is viewed as an extremely effective treatment for post-traumatic stress disorder and has a Phase 3 clinical trial underway. The therapeutic process for MDMA and psilocybin are similar and it is expected that each will have similar REMS imposed by the FDA.
 - Access to research slots are very limited which means that patients with serious or life threatening conditions are unable to access a medical treatment like psilocybin-assisted therapy (PAT) prior to it being legalized. Some individuals are seeking treatment outside of the United States. The FDA has a process for what is called expanded access/compassionate use and this could be a potential option for obtaining care prior to full approval.
 - Psilocybin remains a Schedule 1 drug both on the federal level and on the state level. The current DEA designation means that the drug has high potential for abuse and no medical benefits even though research and the FDA's breakthrough therapy designation is showing the drug to have promise. If psilocybin is approved by the FDA, it will likely be necessary to reschedule the drug on the state and federal level.

Summary of Recommendations

Research conducted at various institutions demonstrates psilocybin to be a promising treatment for various psychological and medical conditions. While additional research is needed, it is clear that psilocybin can be helpful when administered in highly structured settings under the supervision of health professionals. While not an appropriate medication for everybody, it appears to be an additional tool for treating psychiatric or substance use disorders like depression, anxiety, and substance use issues. Further research is necessary and may demonstrate psilocybin's effectiveness for other psychiatric disorders or medical conditions.

It is recommended that the state only legalize a medical psilocybin services program upon FDA approval of the drug. It is anticipated that the FDA will most likely require what is called Risk Evaluation Management Strategies (REMS) as part of the approval process. The drug manufacturer bears responsibility for developing the REMS and ensuring that providers comply with it. The state's role is much more limited in this scenario. At the time approval is granted the state may need to legalize or reschedule the drug and add psilocybin to the state's Medicaid formulary but the level of advance preparation is minimized when REMS are required. The following recommendations are made with an acknowledgement that psilocybin shows promise but also requires further study.

This report's recommendations are the following:

- Legalize the medically supervised use of psilocybin that is administered in licensed health/behavioral health facilities when FDA approval is granted for the drug. Psilocybin treatment should follow the guidelines and regulations provided by the FDA following approval. At the time that FDA approves psilocybin, further guidance regarding optimal therapeutic models may become available. Based on current research data, psilocybin should not be considered a take-home medication and should only be administered in licensed settings utilizing health professionals and comprehensive screening practices.
- Explore funding resources that could be used to “seed” research projects. This could explore innovative public/private partnerships with foundations engaged in psilocybin research. Several researchers have underscored the need for smaller research projects with lower costs. However smaller Phase 1 or Phase 2 research projects could benefit and would help to better clarify the range of psychiatric conditions appropriate for this form of treatment.
- Explore the feasibility of facilitating the development of an FDA approved Compassionate Use/Expanded Access program in Connecticut. There is considerable complexity to creating such a program. The program would require the following: a researcher willing to oversee the program, develop the design, eligibility criteria, and therapeutic protocols, obtain Institutional Review Board (IRB) approval, submit to the FDA, identify who would supply the drug, secure a program location, and obtain funding for administrative costs and costs per participant. Such a program might also serve as a “pilot” program which might help position Connecticut to enter the psychedelic services arena. Similar to the recommendation above, private foundations or companies with an interest in psilocybin research may be amenable to helping fund such a project.

Psilocybin Study Workgroup Report to the Connecticut State Legislature

Introduction

The Connecticut General Assembly enacted legislation in Section 9 of Public Act 21-26 which directed the Department of Mental Health and Addiction Services (DMHAS) to conduct a study of the health benefits of psilocybin. Specifically, the public act requires the DMHAS to convene a working group, that includes members of the of the Public Health Committee and subject matter experts as determined by the Commissioner to study the health benefits of psilocybin. The study shall include an examination of whether the use of psilocybin by a person under the direction of a health care provider may be beneficial to the person's physical or mental wellbeing. The Public Act also defines the term, "psilocybin" as the chemical compound obtained from certain types of hallucinogenic mushrooms that grow naturally in regions of Europe, South America, Mexico and the United States. By January 1, 2022, the working group is required to submit a report on its findings and recommendations to Public Health Committee. Lastly, the working group shall terminate on the date that it submits such report or January 1, 2022, whichever is later. See Appendix 1 for the full public act language.

The legislation was restricted to psilocybin, so this report will only focus on this psychedelic substance. However, it is important to note that research is being conducted on other psychedelic drugs such as Methylenedioxymethamphetamine (MDMA), Lysergic Acid Diethylamide (LSD), and ayahuasca. MDMA is showing great promise for the treatment of post-traumatic stress disorder (PTSD). It is believed that the increased interest in psychedelics for the treatment of psychological conditions has grown out of an awareness that there is great need and many of our current treatments are not adequately addressing conditions like depression, post-traumatic stress disorder (PTSD), anxiety and depression associated with end-of-life care, addiction, and suicidality.

The report considers whether there are health benefits to the use of psilocybin under the supervision of a health professional. The entire focus of this report is one that examines the use of psilocybin from a strictly medical perspective. It considers whether the medical use of psilocybin can be used to “treat” specific medical or psychiatric disorders or the psychological impacts associated with life events such as terminal cancer. In fact, the report is clear that this is not to be considered a take-home medication as serious safety issues have been documented with unsupervised use.

This report will provide an overview of psilocybin, the current legal status, potential medical/therapeutic uses of psilocybin, current research and relevant findings and recommendations. The report will also examine national developments including recent legislation that was enacted in Oregon (SB 109) which charged the Oregon Health Department with creating a Psilocybin Services Program. This followed the passage of a referendum within the state. This is an important initiative because it will be the first sanctioned program in the United States offering therapeutic psilocybin services outside of the research lab. To date, authorized therapeutic psilocybin services are only being provided within the structure of research labs.

Workgroup Composition and Methods

The legislation directed DMHAS to develop a working group that would include members of the joint standing committee of the General Assembly having cognizance of matters relating to public health. The legislation did not further specify who should be included in the workgroup but DMHAS' Commissioner required the group to include subject matter experts. DMHAS made efforts to recruit a diverse group of participants that reflected a broad range of viewpoints related to the subject. The group included DMHAS staff, researchers involved in psilocybin research, state agency representatives from the Department of Public Health and Department of Consumer Protection, a DMHAS provider representative, and a citizen advocate. Attempts were made to keep the group representative while limiting size in order to allow for participation. The complete list of workgroup participants can be found at the end of this document.

The workgroup met for approximately three months. Meetings included a number of presentations by researchers and study participants who provided information about their discrete research or their experience as participants in various research trials. Several individuals received psilocybin/psychedelics legally outside of the United States. Attempts were made to have presentations that focused on topic areas where research was most advanced or related to the group charge. Where possible, efforts were made to utilize Connecticut researchers involved in psilocybin research. The group was fortunate in that Yale University researchers provided information on 3 clinical trials related to psilocybin. Topic areas for these Yale research presentations included Major Depression (Dr. Jordan Slowshower), Anxiety and Obsessive Compulsive Disorder (Dr. Christopher Pittenger), and Headache Disorders (Dr. Emmanuelle Schindler). Other presentations focused on Palliative Care (Dr. Anthony Bossis), Substance Use, and the use of psychedelics with Post Traumatic Stress disorder (Dr. Lynnette Averill). The workgroup also heard from a member of the Oregon Psilocybin Advisory Board (Dr. Atheir Abbas) who presented on their research review and the developing Psilocybin Services program in that state.

The workgroup was also fortunate to hear from five individuals who were involved in these clinical trials or received psilocybin or other psychedelics in treatments provided in other countries. Some of the individuals who presented to the group were forced to seek treatment in other countries due to limited research slots in the United States or to their inability to legally access psychedelics in this country. These individuals powerfully provided testimony regarding how their lives were changed as a result of receiving psilocybin or other psychedelics. Based on the presentations regarding research and individual statements, it was determined that the use of psilocybin therapy has helped these individuals. However, further research needs to continue in order for FDA approval to take place. The presentations, topic areas and links to the actual workgroup presentations can be found in Appendix 2.

Additionally, the working group researched other states to determine if the use of psilocybin was currently permitted. It was determined that only one state was in the process of implementing a psilocybin program, which would not begin until the first or second quarter of calendar year 2023. Outside of the work group, DMHAS staff met with other researchers or organizations involved in psilocybin/psychedelic research. This included meetings with Usona Institute, Multi-Disciplinary Association for Psychedelic Study (MAPS), researchers from Johns Hopkins, New York University, and Yale University, and various psilocybin advocacy groups or political action organizations. Several meetings were also held with the Oregon state official charged with developing their Psilocybin Services Program.

Discussions took place regarding the limitations put in place for a program in Connecticut when a medication is not currently approved for use by the FDA. FDA approval is the typical route that experimental drugs are brought to market. This ensures safety for consumers. FDA approval is also important for reimbursement purposes. That approval would hopefully open the door for the payment of medication and therapy costs by insurers, something that is critical for making the program accessible to all Connecticut residents.

Overview of Psilocybin

Psilocybin Defined

Psilocybin is a naturally occurring psychedelic compound produced by more than 200 species of mushrooms, collectively known as psilocybin mushrooms. The most potent are members of the genus *Psilocybe*, such as *P. azurescens*, *P. semilanceata*, and *P. cyanescens*, but psilocybin has also been isolated from about a dozen other genera. As a prodrug, psilocybin is quickly converted by the body to psilocin, which has mind-altering effects similar to those of LSD and mescaline. The effects generally include euphoria, visual and mental hallucinations, changes in perception, a distorted sense of time, and spiritual experiences, and can include possible adverse reactions such as nausea and panic attacks. (source **Definitions** <https://www.definitions.net/definition/psilocybin>).

Natural mushrooms are easy to grow and can be grown in a number of environments. While useful for developing ample supply, this has the potential to create problems because certain growing environments may contaminate the product. For example, mushrooms can be grown in dung which increases the risk for contamination. A recent report produced by an advisory group in Oregon recommended that a specific mushroom should be used in their developing Psilocybin Services Program due to the greater safety of its growing environment (The Oregon Psilocybin Evidence Review Writing Group, 2021).

Psilocybin can also be manufactured and produced as a synthetic. This has become more popular due to the increase of research related to the therapeutic effects of psilocybin. It has been reported that most, if not all research that is being conducted at this time is being conducted using synthetic psilocybin. This apparently is being done in order to ensure supply while controlling for potency, chemical consistency, and dosing. This is necessary because natural mushrooms can vary significantly in potency based on the species, length of grow time, and the individual grower creating difficulties for researchers that require a high degree of control for their rigorous studies.

A growing number of companies are now creating synthetic psilocybin. Compass Pathways, Usona Institute, ATAI Life sciences, and Psygen Labs are considered to be among the leaders in the production of synthetic psilocybin. Some companies, like Compass Pathways, are seeking patents for their psilocybin products in an effort to protect their competitive position. Some feel that these patents will drive up the costs of psilocybin, making the drug less accessible. (Goldhill, 2021)

Synthetic psilocybin is produced according to what is called “Good Manufacturing Practices (GMP).” GMP is a system of processes, procedures, and documentation that are designed to ensure that a drug is consistently produced and is of high quality. GMP is law in many countries including the U.S. These laws came about because of tragedies related to drug manufacturing. A major impetus related to the thalidomide tragedy where regulators were unaware of the drug's serious side effects which caused deformities in developing fetuses. This tragedy stimulated increased regulation in the United States. Guidelines associated with GMP address a range of issues that affect the safety and quality of a product.

Legal Status

The legal status of psilocybin has, historically, had an impact on research into the therapeutic uses of psilocybin. Several psychedelic drugs, such as psilocybin (psychedelic mushrooms) and MDMA (ecstasy), are Schedule I controlled substances under federal law, subject to various criminal penalties. Schedule I substances, the strictest designation, are generally those with the highest potential for abuse and no approved medical use. The scheduling is confusing since the FDA had awarded “breakthrough therapy” status to psilocybin which is an indication that the drug shows promise for treating certain conditions. In Connecticut, psilocybin and MDMA are both listed as Schedule I controlled substances. State law does not specifically provide for the approved medical use for these substances (Callahan, Jessica & Kirby, Michelle, 2020).

Psilocybin and Safety

Risk of Dependency, Overdose, or Mortality

Researchers have found psilocybin to be a substance with low risk of harm from dependency, overdose, or death to users. Evidence of psilocybin’s safety includes a 2010 study which examined harm caused by various drugs. That study found psilocybin-containing mushrooms to have low risk of detrimental effects (Nutt et al., 2010). Researchers evaluated multiple criteria to determine the substance’s safety to users, including drug-specific and related mortality, drug-specific and related damage, risk of dependence, and drug-specific and related impairment of mental functioning. They also assessed criteria measuring risk of social harm, including physical and psychological injury, risk of crime, environmental damage, family adversity, and overall economic cost to communities. Using these measures, the researchers assigned mushrooms an overall score of four on a scale of zero to 100, of which a score of zero represented no risk of harm. This analysis determined the substance to be safe, with low risk of harm to both individual users as well as populations at large. The study also found psilocybin-containing mushrooms to be the least harmful of the drugs assessed in the analysis, which included alcohol, cannabis, ketamine, and tobacco, among others. By contrast to psilocybin’s low harm score, alcohol generated an overall harm score of 72, while cannabis generated a 20.

The conclusions of this study support those of numerous drug harm studies that also found psilocybin to be safe using multiple sets of risk measures. Psilocybin is consistently determined to carry low risk of dependence, mortality, and abuse using both relative and actual scales. Major national surveys and databases regarding drug abuse also indicate low rates of abuse or treatment-seeking behavior, underscoring the fact that psilocybin misuse has not been significant enough to have needed a named substance use disorder. Moreover, the authors of one study of psilocybin using the eight evaluative factors in the Controlled Substances Act found that, “The characterization of psilocybin as a substance with high abuse potential is based largely on social lore, sensationalized media coverage, and misinformation and misunderstanding about the actual risk of dependence and harms during the 1960s.” Rather, they find that the scientific evidence confirms that the “actual risk of dependence and harm associated with psilocybin has been estimated to be among the lowest of all major substances of abuse and dependence over the past several decades by several expert analysis”. Using the Controlled Substances Act’s assessment criteria of risk, which include factors such as potential for abuse, history and current pattern of abuse, significance of abuse, risk to public health, and psychic or physiological dependence liability, researchers conclude that current findings do not support placement more restrictively than Schedule IV, the Drug Enforcement Administration’s rating for substances with low potential for abuse and low risk of dependence. (Other Schedule IV drugs include Ambien and Xanax.)

Potential for Diversion

When considering making a drug like psilocybin available it is important to assess the potential for diverting the drug for illicit uses. Research regarding the abuse potential of medically administered psilocybin has similarly found the potential of misuse-associated harm to be low, and the potential risk of diversion to be manageable by the medical model used to administer the substance (Johnson et al 2018). The authors find that potential of abuse can be managed by administering psilocybin in accordance with risk management approaches, such as limitations on the number of doses administered to individual patients, administration of the substance in highly supervised clinical settings with psychological support staff, and restrictions on distribution, access, and storage in the clinical setting. Importantly, all current medical models for delivering psilocybin-assisted treatment involves patients taking the substance exclusively under the direct supervision of a professional without taking the substance home, a controlled clinical framework which greatly minimizes the potential for patients to be able to divert the substance.

Safety Concerns in Unsupervised Settings

Although evidence points to low risk of abuse, overdose, mortality, and misuse-related diversion associated with psilocybin, there are some safety questions that remain unanswered pertaining to the substance's risk for negative psychological reactions. Acute or enduring negative psychological reactions may be associated with psilocybin use for some individuals, particularly in unsupervised settings. Though the rate of experiencing adverse effects from unsupervised psilocybin use is unknown, there are lessons researchers have drawn from reports of people who have experienced negative experiences, i.e., "bad trips". A survey conducted by Johns Hopkins University deliberately recruited individuals who had experienced bad trips. Almost 2,000 individuals responded to the survey. Survey respondents reported a median of 6-10 prior psilocybin experiences. Of those that responded approximately 39 percent rated the "bad trip" to be one of the top five most challenging experiences of their lifetimes (Carbonaro et al., 2016). Eleven percent of respondents experiencing these psychological effects reported putting themselves or others at risk of physical harm, and nearly 8 percent of respondents with bad trips sought treatment for persisting psychological symptoms. Three out of 1,993 survey respondents appeared to report enduring psychotic symptoms and an additional three cases attempted suicide. However, 85 percent of all respondents indicated that they had simultaneously benefited from the same "bad trip" psilocybin session, despite the negative experiences, and a third of respondents rated the "bad trip" session to be among the top five most personally meaningful experiences of their lives. (Carbonaro et al., 2016)

Researchers analyzing the survey results pointed to some factors that may have increased the likelihood of negative or difficult experiences that could be eliminated or mitigated in supervised conditions. For instance, they found that the risk of difficult experiences increased as the dose of psilocybin used increased and also increased with the duration of the psychedelic experience. They also noted that in unsupervised settings where users experienced "bad trips", only 2.7 percent of users reported having a trusted and sober guide present who was experienced in supported psychedelic sessions and that a majority of users used cannabis immediately before or during the session where adverse psychological effects occurred. In addition, among survey respondents, those who reported receiving treatment for psychological symptoms prior to using psilocybin were twice as likely than those with no treatment history to seek care for psychological symptoms resulting from the session, suggesting that those with histories of psychological difficulty may be more vulnerable to distressing effects from the substances. Alternatively, this population may be more proactive about seeking professional attention than those without such history.

Risks may also be amplified for individuals with pre-existing psychiatric problems when their use of psilocybin is unsupervised. Unsupervised adult use would permit individuals to access the drug without the screening and monitoring procedures employed in current research. That would only increase the possibility of self-harm or self-injurious behavior. In general, the researchers highlight that, “risky behavior or enduring psychological distress is extremely low when psilocybin is given in laboratory studies to screened, prepared, and supported participants”, and that despite these reported experiences, psilocybin is known to have very low physiological toxicity and is not associated with compulsive drug seeking behavior. This conclusion is supported by evidence which similarly concludes that the adverse effects of medical-grade psilocybin are managed when administered according to safety management approaches. For instance, Johnson et al conclude in their 2018 review of psilocybin risks in medical literature that, “history and clinical research indicate that adverse events are not random but are related to controllable factors that can be addressed in labeling and by the requirement of elements to assure safe use”, such as the requirements the FDA would most likely provide with therapeutic approval.

Maintaining Safety in Research Settings

Safety concerns in research settings have been largely mitigated by careful screening practices and adherence to a therapeutic model designed to enhance participant safety. These guidelines were developed by Johns Hopkins University because of a recognition that the administration of hallucinogens like psilocybin could have serious adverse events if safety were not properly adhered to. A 2008 article authored by three Johns Hopkins researchers identified potential safety risks inherent in the use of hallucinogens.(Johnson et al., 2008) That report identified the most likely risk associated with hallucinogen administration was what is considered a “bad trip” which is characterized by anxiety, fear/panic, dysphoria, and/or paranoia. Another risk identified in that article was possible “abuse “of the substance where safety was jeopardized by poor judgement such as driving while impaired or use that impacts work or personal relationships. Although very rare, some individuals have ended their lives while under the influence of a hallucinogen. Another potential risk identified in that seminal article was that of inducing prolonged psychosis lasting days or months. This has been rarely reported in the literature but still an issue of concern. The Hopkins report believed that this occurs in individuals with a history of mental illness or schizophrenia and could be addressed through careful screening.

These safety concerns prompted Johns Hopkins to develop a set of safety guidelines that have become the benchmark for the safe administration of psilocybin and other psychedelics. These guidelines have formed the basis for protocols used in research settings that are utilizing psychedelics. Their guidelines include careful screening of study participants, training and selection of research personnel, use of a comfortable setting, and a structured therapeutic procedure that has preparatory sessions, administration session and several integration sessions. Things as seemingly minute as bathroom management are taken into consideration under these guidelines. Finally, when the administration session has ended, the study participant may be asked to remain overnight or is released to a family member to return home. While a fuller discussion of these safety guidelines are outside the scope of this report, these procedures have been used to enhance participant safety and minimize adverse events.

It should be noted that while there is promising literature given the ability of clinical research environments to control risk of adverse events, emerging research provides potentially conflicting data regarding adverse events. Compass Pathway’s Phase 2b study results (also discussed later in this report) found that 12 patients of 233 total study subjects reported serious adverse events. These psychological events, which included suicidal behavior and self-injury, were experienced by five patients receiving the highest-dose group (25 milligrams), six patients receiving an intermediate-sized dose (10 milligrams), and one in the lowest dose group (1 milligram) (*COMPASS Pathways Announces Positive Topline Results*

from Groundbreaking Phase IIB Trial of Investigational COMP360 Psilocybin Therapy for Treatment-Resistant Depression / COMPASS Pathways Plc, n.d.). Because these psychological symptoms are common in patients experiencing depression, it is possible that they could be explained by the patients not responding to the psilocybin-assisted treatment for depression, as opposed to a reaction precipitating from the treatment itself. Further research is needed to understand these psychological risks, though current research points to low incidence in supervised settings.

National Efforts Related to Psilocybin

Nationally, efforts related to psilocybin are limited outside of the research laboratory. These efforts, though limited in nature, are occurring on the state and municipal level. Some municipalities have enacted legislation to decriminalize the use of psilocybin or to restrict police activities related to the drug. These municipalities include Denver, Ann Arbor, Santa Cruz and Oakland California and the District of Columbia. These local efforts share commonalities such as decriminalization of the possession of psilocybin or have language that restricts or de-prioritizes police enforcement activities related to psilocybin. No state or municipality is currently administering psilocybin.

Oregon is the sole state in the country that has legalized the adult use of psilocybin provided it is administered in what is being labeled a Psilocybin Services Center. Oregon passed two pieces of legislation in 2020. The first piece of legislation was called Oregon Measure 110 which decriminalized the personal, non-commercial possession of a controlled substance, imposing a maximum fine of \$100 and also established a drug addiction treatment and recovery program funded partly with marijuana tax revenue and prison savings. The second initiative legalized adult use (over 21) of psilocybin if it was provided in a state-approved Psilocybin Services Center. One interesting aspect of the Oregon legislation is that it is not tied to specific medical conditions and adults are free to use the drug for non-medical purposes. Their program is scheduled to become operational in January 2023 and **psilocybin will not be administered until later in 2023**. Because Oregon moved forward without FDA approval, the state is currently undergoing a two-year development period to address crucial implementation areas including training, products, licensing, research, and equity.

Another development on the national front occurred in Texas during their most recent legislative session. The final bill directed the Health and Human Services Commission to collaborate with Baylor College of Medicine which would conduct a clinical trial on the therapeutic efficacy of using psilocybin in the treatment of treatment resistant post-traumatic stress disorder (PTSD). Researchers at Baylor are currently initiating the planning process for this study. The state of Texas committed approximately \$1.3 million for this research over a three-year period. The funds were taken from the state's general fund so funding for the project was not taken from existing state agency funds. The legislation further directed the State Department of Health Services to submit a report with their findings no later than December 1, 2024.

A group of bipartisan legislators in Pennsylvania's House of Representatives introduced a bill in October 2021 called the "Public Health Benefits of Psilocybin Act" that would give the state's Department of Health greater authority to support psilocybin research. The bill authorizes the Department of Health to license two or more growers of "natural psilocybin mushrooms" to cultivate the mushrooms for research into therapeutic purposes. The bill outlines that the manufacturers must certify that they can meet consistent quality and dosages of psilocybin compounds specified by clinical studies. It also directs the Department of Health to prioritize funding for clinical studies regarding psilocybin-assisted treatment of veterans, retired first responders, and their family members.

Across New England, several legislative initiatives have been recently introduced in New Hampshire and Maine. New Hampshire recently introduced a bill that would decriminalize the possession of small amounts of natural mushrooms. Legislation was also introduced in the current legislative session in Maine that would have created a psilocybin program similar to Oregon. That bill was recently defeated in the Health Committee and will not be advanced at this time.

Summary of Psilocybin Research

Overview of Research

During the 1950's and 1960's a significant amount of research into psychedelics was occurring. However, psychedelics became increasingly linked to the counterculture movement of the 1960's. Concerns across Europe and the U.S. began to grow and the Controlled Substances Act of the Comprehensive Drug Abuse Prevention and Control Act of 1970 served to halt research into the use of psychedelics. The enactment of this legislation severely restricted research for decades related to psychedelics.

While research slowed significantly after the Controlled Substances Act was enacted in 1970, some institutions like Johns Hopkins began conducting psilocybin research on healthy subjects in the early 2000s. Their research laid the groundwork for modern psilocybin research and seemed to trigger increased interest in this area. More recently, there has been an increase in research due to various factors. As reported earlier, the FDA granted breakthrough therapy designation for the use of psilocybin for treatment resistant depression and for major depression. This was originally done in 2018 for treatment resistant depression and again in 2019 for major depression. Two companies, Compass Pathways and the Usona Institute are now undertaking larger clinical studies as a result of that designation. The National Institute of Health (NIH) also demonstrated federal support for this research this past summer when they awarded Johns Hopkins a grant to study psilocybin's benefits with tobacco cessation. This was the first psilocybin grant award made by the NIH in over 50 years. Yale University also recently received NIH funding for a psilocybin study involving Obsessive Compulsive Disorder.

The breakthrough therapy designation had the effect of giving psilocybin priority status for regulatory purposes and has increased interest in its uses among researchers, health care entrepreneurs and investors (Anderson et al., 2020) Currently a number of institutions have either developed specialized psychedelic research centers or are conducting research related to psilocybin. This includes the Johns Hopkins Center for Psychedelic and Consciousness Research, Yale University, UCLA, NYU, University of Wisconsin Madison, Mt. Sinai Hospital in New York, University of California Berkley, Multidisciplinary Association for Psychedelic Studies (MAPS), and the Veteran's Administration among others. Within our own state, there are currently research trials being conducted at Yale University. Yale has at least three studies underway including one focused on depression, one focusing on obsessive compulsive disorder, and another focusing on cluster headaches.

Research being conducted at these institutions generally focus on 4 or 5 main areas that include depression, palliative care related to terminal cancer, substance use, and anxiety disorders. Other studies are examining the therapeutic effects of psilocybin for post-traumatic stress disorder, migraine cluster headaches and depression specifically related to Alzheimer's but are at an earlier stage of study. It is important to note that the lab research is often focused on a specific psychiatric diagnosis or medical condition and some psilocybin research is further developed than others at this time.

While outcomes are study specific and differ based on the condition that is being studied, certain outcomes are being consistently observed. For example, studies focused on depression have found rapid

and enduring changes in depression scores after a single administration of psilocybin. Various reports show these changes lasting for more than six months. Similar results have been observed in patients dealing with end-of-life anxiety and depression. Research focused on substance use including tobacco use or alcoholism show reduced use which is often greater than what is seen in current treatments. While some of these studies have a small number of participants, their results have been shown to be statistically significant.

Connecticut Research Related to Psilocybin

Yale University has been at the forefront of research related to psilocybin. Yale's studies involving human subjects have been concentrated in the areas of major depression, obsessive-compulsive disorder, and headache disorders. Another completed study related to the effects of psilocybin on the brains of mice. One other study is focused on the use of MDMA with PTSD. The current studies and a brief description of their area of focus is listed below:

Efficacy of Psilocybin in OCD - This study is investigating the effects of psilocybin on obsessive-compulsive disorder symptomatology, and corresponding neural changes.

Psilocybin-Induced Neuroplasticity in the Treatment of Major Depressive Disorder - This study aims to understand how psilocybin alters neural plasticity and behavior in those with major depressive disorder (MDD).

Effects of Psilocybin in Cluster Headache -The purpose of this study is to investigate the effects of an oral psilocybin regimen in those who suffer from cluster headache.

Effects of Psilocybin on Post-Traumatic Headache - The purpose of this study is to investigate the effects of psilocybin in post-traumatic headache, also known as post-concussion headache.

The Effects of MDMA on Prefrontal and Amygdala Activation in PTSD - MDMA (Ecstasy) is in phase 3 trials for the treatment of post-traumatic stress disorder (PTSD). Here, we are studying the effects of MDMA on brain activation – specifically in the prefrontal cortex and amygdala – in PTSD, to explore the relationship between MDMA-induced neural plasticity and the behavioral effects

Imaging the effects of Psilocybin on 5HT_{2A}, synaptic density and network function -

Additional information about these studies can be found at the following link:

https://medicine.yale.edu/psychiatry/research/programs/clinical_people/psychedelic/research/

Oregon Rapid Review

A recent report compiled by the Oregon Psilocybin Health Advisory Board identified high quality clinical trials currently underway related to psilocybin (The Oregon Psilocybin Evidence Review Writing Group, 2021). This report, which was published in July 2021, provides a comprehensive review of research that has been or is being conducted in the United States. Key conclusions from the research in the review include the efficacy of psilocybin in reducing depression and anxiety, including in life-threatening conditions, within the context of counseling support. The reviewers also found the research to suggest that psilocybin is efficacious in reducing alcohol and tobacco use.

The report also identified limitations of studies included in the review. Most importantly, they note the lack of diversity of trial participants, writing:

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 (The Oregon Psilocybin Evidence Review Writing Group, 2021)

Stemming from the lack of diverse profiles of trial participants, the authors note the lack of psilocybin-focused tools available to identify patients who may be either most likely to benefit from, or to be harmed by, psilocybin treatment in the long term. The lack of these types of tools underscore the current inability to generalize from the specific cohorts studied in psilocybin trials to the general population at large or to particular medical, racial/ethnic, or gender subgroups.

That report also offers recommendations related to Oregon's developing Psilocybin Services Program. In addition to recommending a process to review updates to the field of psilocybin research as well as to evaluate the impact of psilocybin services in Oregon, the authors recommend that Oregon develop guidance regarding dosing of psilocybin. They note that since the benefits and risks of the substance depend on dosing, parameters for providers regarding optimal dosing would be helpful to minimize risk. Relatedly, they also recommend developing a regulatory framework for measuring the psilocybin concentration of psilocybin-containing mushrooms and for cultivating mushroom species. They write that this framework should prioritize strains that minimize concerns of toxicity and include screening requirements for potential contaminants.

Compass Pathways and Usona Institute Research Trials

Research related to psilocybin continues to rapidly unfold. Since this paper was initiated, Compass Pathways completed a Phase 2b study into the effectiveness of psilocybin in the treatment of depression. Compass Pathways is a for profit company that was testing its psilocybin drug. The results of the study were released in early November 2021 (*COMPASS Pathways Announces Positive Topline Results from Groundbreaking Phase IIb Trial of Investigational COMP360 Psilocybin Therapy for Treatment-Resistant Depression* | *COMPASS Pathways Plc*, n.d.) . The study had 233 participants which was the highest number of participants included in such a research study involving psilocybin to date. Study participants were randomized and received one of three doses: a high dose of psilocybin (25 mg), a lower dose (10 mg), or a 1 mg dose.

The results were promising with participants in the high dose group showing rapid and significant improvements in their depression. The 10 mg group did not show a statistically significant treatment response. These positive results will likely culminate in a Phase 3 clinical trial that may commence as early as 2022. It is interesting to note that the study did report 12 adverse events which included suicidal behavior, injury, and suicidal ideation, mostly occurring in the 25 mg and 10 mg groups. While Compass Pathways stressed that these are behaviors often seen in patients with treatment-resistant depression, they underscore the need for close supervision and monitoring of persons receiving this therapy.

Usona Institute is also involved in a large, multi-site study using psilocybin with major depression. The study began in the fall of 2019 and was expected to conclude sometime in the fall of 2021. This study was expected to include over 70 participants. Participants were expected to be randomized and would receive a single dose of psilocybin or a placebo. Discussions held with staff at Usona Institute have indicated that they are now positioning to begin Phase 3 clinical trials, likely in the next year. These upcoming Phase 3 trials will potentially serve as the springboard to FDA approval.

Psilocybin Assisted Therapy

Therapeutic Process Used in Research Settings

Currently the therapeutic process being utilized by research labs almost exclusively involves the use of psilocybin in highly supervised settings by medical or behavioral health professionals. This is because researchers have identified serious adverse effects with unsupervised psilocybin use which include acute psychological distress, dangerousness behavior, and enduring psychological problems (Carbonaro et al., 2016)). Unlike something such as medical marijuana, most proponents do not view psilocybin as a take-home medication that an eligible client/participant would use in an unsupervised setting.

Participation in research related to psilocybin involves careful screening of participants who are not considered to be appropriate for psilocybin-assisted therapy for medical or psychological reasons. 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 (The Oregon Psilocybin Evidence Review Writing Group, 2021). Researchers generally screen for psychiatric or physical conditions which are considered contraindications for the use of psilocybin. It is believed that persons with schizophrenia or a family history of schizophrenia should not receive psilocybin. From a medical perspective, persons with uncontrolled hypertension and cardiac problems are also considered unsuitable for this treatment.

The therapeutic process typically involves a three phase process using specially trained facilitators or guides who manage the therapeutic process. There are typically two facilitators, ideally a male and female who remain involved throughout the process. The three phases include a Preparatory Phase, Administration Phase, and an Integration Phase. The preparatory visits build rapport, explore patient history, and discuss how psilocybin may impact the participants. The actual Administration Phase may last between 6-8 hours where the psilocybin is provided in a comfortable room. The participants may wear eyeshades and listen to music they have selected. It is important to note that facilitators are not directive during the session and will provide support if needed. A number of research studies involve two administration sessions, usually separated by some period of time. The Integration Phase may include several visits where the patients and facilitators discuss meaningful aspects of their psychedelic experience and how this can be applied to their life. (Johnson et al., 2008)

Training for Psilocybin-Assisted Therapy

The section above highlights the importance of adhering to the therapeutic process for psilocybin-assisted therapy. The facilitators are specially trained and certified in order to ensure they understand the therapeutic process and safety considerations necessary for these therapeutic sessions. Various organizations are conducting these training sessions which all have similar designs. The California Institute for Integrative Studies (CIIS), Usona Institute, Compass Pathways, and MAPS all provide this training. Usona, Compass, and MAPS are typically providing training to medical and behavioral health professionals that are associated with their specific research studies. CIIS' training and certification program is open to clinicians and clergy interested in this developing field.

The training process occurs over a number of months. The program at CIIS is typically a 9-month training program spanning a range of topics associated with psychedelic services. The length of the program is important because it impacts how much lead time is needed before a program can go live, especially as states try to build capacity where little or none exists. States cannot expect to quickly begin to deliver these services upon FDA approval and must begin to develop trained personnel in advance of that

approval. While it is likely that the FDA will ultimately specify who can receive the training and what it must include once the drug is approved, their approval of the structure of training programs necessary for clinical research trials is some indication of what they believe what must be part of these training programs.

Another aspect of training relates to the recruitment of facilitators. A facilitator's race or ethnicity will have some impact on who seeks this new treatment. MAPS, the organization conducting Phase 3 clinical trials for MDMA and PTSD, has found that they were having difficulty recruiting minority study participants. They undertook a large initiative to try to recruit facilitators that represented diverse communities. Their belief was that this was one of the most important ways to ensure equity in access.

Research and the Role of the Food and Drug Administration (FDA)

Experimental drugs like psilocybin are brought into common usage through the FDA approval process. The FDA uses a tiered system of research that has four phases of lab research or clinical trials. Each level typically increases the number of participants and the scientific research rigor. The FDA typically requires that Phase III clinical trials be completed prior to granting approval to a drug treatment. Phase III studies may involve up to 3,000 participants, compares the experimental treatment to existing treatments, and are double-blinded meaning that study participants and researchers do not know who has received the treatment. The purpose of Phase III clinical trials is to ensure that the experimental drug or treatment can be used safely.

It was previously discussed that there are currently two large scale clinical trials underway or recently completed related to depression. One study recently completed by Compass Pathways is a Phase IIb study involving 233 participants, while a second study through the Usona Institute involves 80 patients with Major Depressive Disorder (*Responding to an Urgent Mental Health Crisis, Compass Pathways White Paper, 2021*). Based on the information in that report, it appears that only Phase 1 and 2 Clinical Trials have been completed with psilocybin to date. Both organizations report that they are positioning themselves to potentially initiate Phase 3 clinical trials within the next year.

The Compass Pathways White Paper highlights the importance of FDA approval, containing cautions related to the subject of legalization of psilocybin without FDA approval. The authors write that the available evidence for psilocybin, “does not exist at a level that would be acceptable for the FDA or any other medicine regulator to grant a license for the medical use of psilocybin therapy.” Due to the limitations of current research, the authors write that the medical and regulatory communities are not yet certain whether psilocybin delivers consistent quality, safety, and medical outcomes for every patient. The FDA approval process, which psilocybin therapy has not completed, seeks to ensure that medicines meet rigorous standards and undergo continuous inspection while on the market. Because psilocybin has not been granted FDA approval, there is risk that the substance will not reliably deliver consistent, safe, and beneficial results to every patient population receiving treatment.

The regulated production of synthetic psilocybin is central to these efforts, as it prevents psilocybin administered in medical settings from containing any other active substances in unknown quantities. The Compass Pathways White Paper emphasizes that, while FDA approval continues to serve as the gold standard for ensuring drug safety, psilocybin used in current clinical trials is manufactured and developed according to stringent Good Manufacturing Practices (GMP) and Good Clinical Practice (GCP) guidelines. The FDA ensures that psilocybin supply meets purity, quality, safety, and efficacy standards via these production guidelines, even though it has not extended formal approval of psilocybin treatment.

FDA approval is critical from a cost perspective as well. Medicaid and Medicare will only cover medications that have been approved by the FDA. It is believed that insurance companies follow the same policy. This means that access may only be available to those with funds to privately pay for these medications if FDA approval is skirted. It is also believed that reimbursement for the costs of psilocybin-assisted therapy will only be authorized if FDA approval exists. The payment structure for the use of psychedelic services will need to be resolved in order to ensure equitable access to these services.

While FDA approval is sought after and likely increases buy-in for the treatment, states have at times ignored this approval process and moved forward with legalization or decriminalization efforts. This has been done across the country, including in Connecticut, for medical and recreational marijuana. To date, Oregon, Ann Arbor, Denver, Oakland, Santa Cruz, and Washington, DC have decriminalized psilocybin without FDA change in scheduling of the substance. Oregon's 2020 legalization of the use of psilocybin products, including magic mushrooms, to treat mental health conditions is another example of a state changing legal uses for a substance without alignment with FDA guidance.

FDA and Expanded Access

It is important to discuss that Connecticut could provide access to psilocybin to greater numbers of patients who may benefit from it prior to FDA approval through the "FDA expanded access" programs, sometimes called "compassionate use" programs. Expanded access programs are avenues for patients to access experimental treatments, termed "investigational drugs", as research is ongoing into its clinical uses but prior to formal FDA approval for market availability. Since ongoing trials cannot include all patients who may benefit from psilocybin, expanded access programs offer patients an alternative route to receiving supervised, regulated clinical treatment using the investigational substance. When participating in expanded access, patients receive treatment with an investigational medical product, such as psilocybin, under conditions of a treatment plan that is approved by the FDA, reviewed for ethical soundness by an Institutional Review Board (IRB) committee, and agreed upon by physicians or researchers of the substance. The FDA permits patients to participate in expanded access programs if they face extenuating circumstances such as life-threatening illness with mental distress and inability to enroll in clinical trials of the investigational medical product.

In addition to the benefit of increased access to patients who could greatly benefit from psilocybin, expanded access may be an attractive option to pursue because it does not require states to legalize or decriminalize the substance for patients in the state to participate. Rather, providing access to psilocybin use within controlled settings may help prevent patients from opting to "self-medicate" by purchasing psychedelics illegally. Expanded use programs also provide an opportunity for clinicians in Connecticut to become trained and to gain experience in providing psilocybin-assisted treatment prior to approval of psilocybin for widespread use. Since the treatment protocol for psilocybin is similar to those for other psychedelic substances that may be approved in the near future like MDMA, expanded access programs would prepare Connecticut clinicians to use novel psychedelic therapies broadly and would increase the medical system's capacity to implement psychedelic programs once the substances are available on the market. An expanded access program could serve as a "pilot program" positioning the state for eventual FDA approval. While such a program is not employing strict research protocols, this program could also provide additional data regarding psilocybin's effectiveness.

There are three categories of FDA expanded access programs: individual, intermediate-size, and widespread use. Each offers treatment to an increasingly large number of patients. The category most

relevant to psilocybin given its stage of current research is intermediate-size, which approves access to a patient population greater than one but less than the number that would participate in an investigational trial for FDA approval. For context regarding trial sizes, the trial from which Compass Pathways published results in November 2021 included 233 participants. However, instances of smaller expanded access programs exist, including that of Multidisciplinary Association for Psychedelic Access (MAPS) which provides access to MDMA to 50 individuals. Representatives from MAPS shared with the authors of this report that the FDA limited the expanded access program to 50 participants, subject to review, in order to ensure that MAPS was able to dedicate adequate organizational and pharmaceutical resources to completing its Phase III trials.

Requests for intermediate-size expanded access can be made to the FDA by individual licensed physicians, either in private practice or associated with a medical institution, or by industry organizations running ongoing trials. Requestors may propose to implement expanded access across multiple sites/locations. The requesting party would be responsible for all aspects of implementing psilocybin treatment according to the FDA's approved treatment protocol without federal assistance regarding drug supply, staffing, training, or recruitment. The expanded access requestor would also have to demonstrate that the proposed program would not interfere with or jeopardize supply or staffing needs for ongoing trials, and the size of expanded access programs would be limited by the requestor's capacity to devote additional organizational resources away from trials. Therefore, expanded access programs require planning and investment in resources and support.

While expanded access programs can and do operate independent of the state, funding is needed to support per participant costs and the fixed administrative costs involved in establishing and operating expanded access programs, including the expert labor needed to train and deploy providers of psilocybin-assisted treatment, clinical and organizational staff to manage the expanded access protocol, and data management skills and resources. The expanded access program cost per individual would likely include the expense of purchasing synthetic trial-grade psilocybin from the industry, although there may be opportunities for expanded access programs to secure a donation of required supply from industry or philanthropic partners. The method of sourcing psilocybin for potential expanded access programs is currently an open question and would require investigation by the state into viable options. Further exploration of this topic is needed due to the complexity involved in establishing an intermediate-sized program.

FDA Risk Evaluation Management Strategies (REMS)

Persons closely involved with the FDA approval process have indicated that it is highly likely that the FDA will require what is called "Risk Evaluation and Mitigation Strategies (REMS)" when FDA approval is granted to psilocybin or other psychedelics. A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS are designed to reinforce medication use behaviors and actions that support the safe use of that medication. While all medications have labeling that informs health care stakeholders about medication risks, only a few medications require a REMS (Research, 2021).

The REMS would specify actions or clinical interventions that would be required to address safety concerns associated with a drug. For example, it has been previously discussed that psilocybin is not envisioned to be a take-home drug. The FDA could formally place this restriction on the drug and limit

how it is dispensed by pharmacies. Similarly, psilocybin assisted therapy conducted in research settings typically requires the presence of several facilitators when the psilocybin is being administered and specific protocols for the therapeutic process. These clinical interventions can be required for psilocybin as part of the FDA approval process as well as requirements regarding which professionals may be eligible to facilitate the treatment. A REMS might also specify the training required for providers delivering psychedelic services.

When the FDA approves a new drug with REMS, the state role is very limited. The state may be required to legalize or reschedule a drug that was previously illegal but they are not responsible for developing requirements for the dispensing and distribution of the new drug. The responsibility for this rests with the drug manufacturer. Prior to approving a new medication, the FDA determines what is to be included in the REMS. The drug manufacturer must then develop a program that conforms to the specifications of the FDA and they must obtain FDA approval for their REMS program. This occurs before the medication is approved by the FDA. The drug manufacturer is responsible for monitoring that pharmacists and clinical providers are adhering to the program requirements. They are also responsible for ensuring that providers meet any training requirements. Some elements of the REMS such as training or auditing may be contracted out to specialized vendors but the responsibility for these functions reside with the drug manufacturer.

One example of a drug recently approved by the FDA with REMS is esketamine, or Spravato. The drug was approved by the FDA in March 2019. Spravato is an intranasal spray manufactured by Janssen Pharmaceuticals for treatment resistant depression. The Spravato REMS imposed requirements on pharmacies and healthcare providers that wanted to be certified to dispense and administer Spravato. The FDA required that the drug could only be administered in healthcare settings where a prescriber and medical staff were onsite at the time of administration. The REMS imposed additional requirements on pharmacies and the healthcare facilities that decided to become certified to administer Spravato. Janssen was responsible for implementing all of the requirements contained within the REMS, The complete REMS and supporting materials for Spravato can be found at:

https://www.accessdata.fda.gov/drugsatfda_docs/remes/Spravato_2020_07_31_REMS_Full.pdf

There are important differences in roles when states legalize drugs that have not been FDA approved. Recent examples of this include the legalization of medical and recreational cannabis. Since cannabis is not FDA approved, states have been responsible for developing “programs” for the licensing and distribution of cannabis. An entire set of regulations are developed to control growing and sale of cannabis. More recently, Oregon’s ballot initiative which legalized the adult use of psilocybin in approved psilocybin service centers. Because Oregon moved on this without FDA approval, the state is currently developing the entire program infrastructure which governs the production and distribution of psilocybin. They bear full responsibility for implementing what is basically a REMS-like program. Oregon is fully responsible for developing the program, regulations, licensing requirements, and an oversight system to ensure that vendors conform to the requirements of the program.

To summarize, the state’s role is very limited when a new drug is approved by the FDA and is required to have a REMS. The state roles may include legalizing and rescheduling the drug in state law or regulations, if necessary, approving the drug to be included in the state’s Medicaid formulary, and the state may support training efforts to increase clinicians certified to provide the drug. Implementing all other requirements of the REMS are the responsibility of the drug manufacturer. This includes

certification of pharmacies and providers, patient enrollment, training, and monitoring and auditing providers.

Psilocybin Study Membership List

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Co-Chair Medical Director DMHAS
2. James Siemianowski
Co-Chair DMHAS Staff
3. Mary Kate Mason
Legislative Liaison DMHAS
4. Christine Goldrick
Office of the Governor Fellow
5. Roderick Marriott
Drug Control Director Department of Consumer Protection
6. Dr. Richard Kamin
Medical Director Office of Emergency Medical Services Department of Public Health (DPH)
7. Jill Kennedy
Legislative Liaison (DPH)
8. Dr. Christopher Pittenger
Mears & Jameson Professor of Psychiatry, and Professor in the Yale Child Study Center
Deputy Chair for Translational Research, Department of Psychiatry and Director of the Clinical Neuroscience Research Unit, Yale OCD Research Clinic, and Yale Program for Psychedelic Science
9. Dr. Lynnette Averill Associate Professor, Department of Psychiatry and Behavioral Sciences, Neuropsychiatry Division, Baylor College of Medicine, Houston, TX; Clinical Research Psychologist, Michael DeBakey VA Medical Center, Houston, TX; Adjunct Assistant Professor of Psychiatry Yale School of Medicine and National Center for PTSD – Clinical Neurosciences Division, CT Dr. Lynnette Averill
10. Dr. J. Craig Allen
Medical Director Rushford and Chief of Psychiatry Midstate Medical Center
11. Senator Heather Somers
Connecticut State Senator representing the 18th District
12. Senator Tony Hwang
Connecticut State Senator representing the 28th District
13. Senator Gary Winfield
Connecticut State Senator representing the 10th District
14. Representative Michelle Cook
Connecticut State Representative representing the 65th District
15. Representative Kathy Kennedy
Connecticut State Representative representing the 119th District
16. Representative Phil Young
Connecticut State Representative representing the 120th District
17. Representative Kevin Ryan
Connecticut State Representative representing the 139th District
18. Jesse MacLachlan
Former Legislator and Connecticut Stakeholder

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Appendix 1

Section 9 of Public Act No. 21-26

AN ACT CONCERNING VARIOUS REVISIONS TO THE PUBLIC HEALTH STATUTES.

Sec. 9. (Effective from passage) (a) The Department of Mental Health and Addiction Services shall convene, within available appropriations, a working group, which shall include members of the joint standing committee of the General Assembly having cognizance of matters relating to public health, to study the health benefits of psilocybin. Such study shall include, but need not be limited to, an examination of whether the use of psilocybin by a person under the direction of a health care provider may be beneficial to the person's physical or mental wellbeing. As used in this subsection, "psilocybin" means the chemical compound obtained from certain types of hallucinogenic mushrooms that grow naturally in regions of Europe, South America, Mexico and the United States.

(b) Not later than January 1, 2022, the working group shall submit a report on its findings and recommendations to the joint standing committee of the General Assembly having cognizance of matters relating to public health, in accordance with the provisions of section 11- 4a of the general statutes. The working group shall terminate on the date that it submits such report or January 1, 2022, whichever is later.

Appendix 2

Psilocybin Workgroup Presenters and Topic Areas

October 6, 2021

Dr. Athier Abbas *Review of Oregon Rapid Review Report*

<https://ctvideo.ct.gov/dmhas/Psilocybin%20Study%20Workgroup%20-%202010-06-2021.mp4>

October 20, 2021

Dr. Christopher Pittenger Yale University *Psilocybin and Anxiety and Obsessive Compulsive Disorder*

Dr. Jordan Slowshower Yale University *Psilocybin and Major Depression*

Jon Kostakopoulos President and CEO, Apollo Pact Inc. *Experience as participant in Psilocybin and Alcohol Dependence Clinical Trial at New York University*

<https://ctvideo.ct.gov/dmhas/Psilocybin%20Study%20Workgroup%2010-20-2021.mp4>

November 3, 2021

Dr. Anthony Bossis New York University *Psilocybin and Palliative Care*

Dr. Emmanuelle Schindler Yale University *Psilocybin and Headache Disorders*

Ken Maxwell *Experience as participant in Headache Disorders Clinical Trial*

<https://ctvideo.ct.gov/dmhas/Psilocybin%20Study%20Workgroup%20-%202011-03-2021.mp4>

November 17, 2021

Dr. Lynnette Averill Baylor University and Adjunct Professor at Yale University *Psilocybin/Psychedelics and PTSD*

Jonathon Wilson, Special Operations Forces Veteran, *Therapeutic experience outside of the US in a legal clinical setting*

Allison Wilson, Military Spouse, Founder, The Hope Project, *Therapeutic experience outside of the US in a legal clinical setting*

Ethan Abend, Retired NYPD Detective, *Therapeutic experience outside of the US in a legal clinical setting*