PSYCHEDELICS IN MENTAL HEALTH SERIES: PSILOCYBIN

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FOREWORD AND ACKNOWLEDGEMENTS

First and foremost, I write this book for all those who are currently suffering from depression and addiction. I was addicted to drugs for seventeen years of my life and eventually ended up homeless approximately five years ago. Through my addiction I lost a lot of things and almost lost my life. To say I am grateful to be alive and sober today is an understatement and obviously God has much bigger plans for me. Unfortunately, many do not survive a crippling opiate addiction.

Despite my addictions, I was able to make my way through law school and obtained licensure to practice law in 2011. In 2010, during final exams my second year of law school, I found out one fateful day my mother had passed away unexpectedly from a heart attack at the age of 52. It was the toughest thing I have ever had to confront, and it simply added fuel to the fire that was my addiction.

In the spring of 2011, just prior to graduating to law school, my anecdotal research uncovered that psilocybin had potential to treat mental illnesses. Unfortunately, my growing addiction to opiates prevented me from furthering my research at that time.

Fortunately, while my addiction worsened and my life steadily spiraled out of control, brave researchers from highly reputable and respected institutions across the United States and the world continued to pursue psilocybin research.

In late 2015, I was incarcerated due to my addiction and was given the option to go to long-term inpatient treatment in a therapeutic community. Due to my bleak circumstances at that time, I obliged. I entered long-term drug and alcohol treatment in a therapeutic community in February 2016. There I remained until I graduated the program in September of 2018. In all, I did 31 months of intense inpatient drug and alcohol treatment.

During my time in the treatment facility, I encountered individuals with the worst addictive tendencies known to man and most residents were "dual diagnosis," which meant they were also diagnosed with some other mental disorder, usually depression, in addition to their substance abuse disorder. To say I have seen severe cases of depression and addiction is an understatement. The treatment facility where I resided was basically the end of the line before long stints in prison or the grave.

I have seen hundreds of people suffer with addiction and depression. I have seen more people die from their addiction, during my lifetime, than I can even remember, as the number is easily into the hundreds. One thing is for sure, current treatment regimes for depression and addiction do not work for many of those who suffer. Therefore, when I was finally allowed to have access to a cell phone and the outside world, late in 2018, I resumed my research into the mental health benefits of psilocybin.

At that time, I realized the research had progressed considerably since my last foray into the subject in early 2011. I started reading multiple articles about various studies which had been

conducted with psilocybin and was completely amazed at the results being reported. I could not help but wonder at that time whether those I saw in the treatment center could have benefited from some form of psychedelic therapy. As the body count kept rising, my interest increased exponentially.

Fortunately, I was able to maintain my law licensure and, by the grace of god, landed an extremely good job back in the legal profession shortly before my graduation from treatment in 2018. Once I graduated, I was able to move out on my own and finally resume my life normally at the age of 32. However, due to the demands of my new legal position ,I was unable to continue my psilocybin research to any significant degree for quite some time.

In the interim between graduating from the treatment facility and the time I started to research and write this book, I was given the opportunity to sharpen my research and writing skills by drafting federal and state appellate court briefs for my firm. I was even given the task of drafting a brief which was filed with the U.S. Supreme Court. Therefore, while my psilocybin research had been put on hold, my research and writing skills were increasing by the week.

Fast forward to March 2020, the Coronavirus took hold in the U.S. and across the world and many businesses were shut down for over a month. While working from home, I started to resume my psilocybin research project in my spare time. I was not quite sure at that time whether I necessarily wanted to write a book. However, I became somewhat agitated by the fact that I could not find any single resource where all the relevant scientific data was compiled and easy to review. Eventually, I decided that I would put together the single resource I so desperately sought.

In furtherance of my research, I joined hundreds of psychedelic-based groups on Facebook. I quickly realized the scientific data was indeed scattered all over the internet in various articles and

publications, but not in one single resource. I felt at that time, those who indeed wanted to advocate for medicinal use of psilocybin would be best served by having all pertinent scientific data bundled in one place for quick and easy reference to the facts. Furthermore, those who were either on the fence about psychedelics or perhaps opposed thereto, could be best served by having access to same.

During my downtime, I researched and wrote this book over about a 45-day period. Writing this book has been a journey and one that I will cherish for as long as I live. In order to write the book, I had to overcome residual fear and self-doubt that lingered inside of me from before I got sober in 2016. Therefore, what you read in these pages was just as much a personal development project for me as it was building a single scientific resource for my audience. For those of you who purchase and read this book, I am forever grateful.

While I truly believe the worldwide community of psychedelic advocates are gaining momentum and popular beliefs and opinions are swaying in a pro-psychedelic direction, I also warn they are fighting against over 50 years of terrible social conditioning built upon outright lies and misinformation. Unfortunately, we live in a day and age where scientific facts and data do not matter to and cannot sway the opinion of many individuals, especially in the U.S. This mindset obviously transcends the issue of psychedelics and has become rather pervasive over the last four years.

While writing this book, I was personally confronted with the ramifications of said 50-year social conditioning. Long story short, an immediate family member of mine became so offended and upset about this book, which the individual had not read, they cut off all communications with me. Therefore, be aware that while momentum has been gained, not all minds can be won

over by citation to science and/or history. Many people still do, unfortunately, judge books by their cover.

I chose to compile and publish the data herein in hopes that I could help further the conversation regarding a sensible solution to a perceived omnipresent and demoralizing set of individual and societal ills. I made the choice to use my skills to educate people about an issue far bigger than myself and I hope that this book finds its way into the right hands.

There has been considerable progress made in terms of the legal status of psilocybin, and other natural plant "entheogenic" plant medicines in some of the more liberal jurisdictions in the United States over the last couple years. Furthermore, there are currently two statewide decriminalization measures which should go up for popular vote over the next two years. The science discussed herein obviously paved the way for these measures.

Leading psilocybin researchers are gearing up to argue that psilocybin should be placed in Schedule IV of the Controlled Substances Act when the time comes, as there are currently two "breakthrough" Phase II clinical trials examining the efficacy of psilocybin as a treatment for major depressive disorder and treatment resistant depression. It is my humble opinion, after examining the science and history of psilocybin, that within the next five years, possibly sooner, psilocybin treatments for depression will be available in the United States. It is my sincere hope the same treatments for addiction will follow suit, as millions of lives could be saved on both fronts.

First off, I want to thank all of those who supported me throughout this project. The amount of support that I received in my personal life and online throughout the Facebook

communities was overwhelming. At times when I thought this book was a stupid idea and no one would want anything to do with it, these people lifted my spirits and gave me the drive to keep moving forward to completion. The two gentleman I work for at the law firm really deserve a pat on the back. When I had absolutely nothing to my name and was merely an ex addict coming out of rehab, they gave me chance to prove myself and make something of myself, when I couldn't even get a call back from anyone else in the legal community. Without them, I venture to say, none of this would have been possible. Not to mention, the opportunity I was given to sharpen my research and writing skills over the last two years, which are still far from perfect, absolutely contributed to the creation of this work.

I also want to thank Terence McKenna, Michael Pollan, Don Lattin, and Paul Devereux as their works provided the groundwork for me to start this book, and provided relevant factual material needed for the introductory chapter. I highly encourage all my readers to check out their books, which are cited herein, especially if they seek a more robust picture of psychedelic history. I would also like to thank all the psilocybin researchers cited herein, who so bravely proceeded forward with psilocybin research in the face of adversity. Their dedication to finding solutions to mental illnesses in natural psychedelic substances, such as psilocybin, will in my opinion, change the way we treat mental illnesses in the future.

I also would like to thank the following Facebook profiles, some for their consistent support of this project and others for inspiration I received along the way: Dr. Sola Loy, Christine Miranda, Jiggs Dee, Randall Simpson, Violet Roig, Aaron Hadel, Sarah Futrell, Incrosnatu Danut, Brandon Batstone (Bohemian Brandon), Willy Myco, Carla Crochet, Cara Stringari, Barry Cooper and countless others that gave me the motivation to push forward when I thought my idea was stupid. I

would also like to make note of the following Facebook groups which are full of people who support responsible medicinal psychedelic research: Psychedelic Seas, Psychedelic Society, Awakened Heartists, Canadians for Improved Mental Health, Durango Entheogenic Society, Depression and Microdosing, and Psychedelics and Philosophy. This list is not exhaustive, there are many more not mentioned. Thank y'all very much!

Lastly, I want to thank my father Butch. He has remained open minded throughout this whole process and truly wants what is best for me. His support throughout my entire life, including through my addiction, embodies the definition of unconditional love. I would also like to thank my sister for her support for most of my endeavors and the support she has provided me while resuming my normal life post-treatment. Lastly, I also want to thank my Aunt Jamie for the love and support she has always provided, especially since the passing of my mother. I love all of you unconditionally. I dedicate this book to my nieces AP and RC!

MUCH LOVE!

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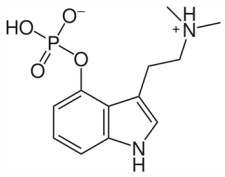
HISTORY OF PSILOCYBIN USE AND RESEARCH



Psilocybin is the main active ingredient in psilocybin or "magic" mushrooms.[1] However, it is not the only active or psychedelic compound within the mushroom. The other active compounds are psilocin and baeocystin. When ingested, psilocybin is converted, via a process called dephosphorylation, into psilocin in the body after consumption.[2] Psilocin is the most potent psychedelic compound in psilocybin mushrooms and is mainly responsible for producing the altered states of consciousness that are the hallmark of the psilocybin experience.[3] While baeocystin is known to be an active compound in psychedelic mushrooms, its effects on the brain are still largely unknown to the scientific community.[4]

Psychedelic mushrooms grow all around the world. The main genera of psychedelic mushrooms are Psilocybe, Panaeolus, and Straphoria.[5] Psilocybe is the most common genus and contains about 230 species of mushrooms.[6] Psilocybe Cubensis is the most common species found in circulation. While Psilocybe Cubensis is the most popular mushroom, it is not the most potent

of the psilocybe genus. Psilocybe Azurescens are considered to be the most potent species of psilocybin containing mushrooms.[7]

As we will see throughout this book, there has been a major resurgence in psilocybin research. Psilocybin's reputation remained partially intact after the infamous assault on psychedelics of the late sixties and early seventies. Although it was classified as a Schedule I drug pursuant to the Controlled Substances Act in 1970, [8] it did not receive as much negative publicity as LSD did during that time. When it came time for scientist to re-engage in psychedelic research, the path of least resistance led to psilocybin. Hence, there have been quite a few modern studies done examining therapeutic benefits of psilocybin.

The effects of psilocybin vary depending on the dose consumed[9] and the amount of psilocybin contained in any given mushroom varies wildly from one specimen to the next.[10] In order to combat these inconsistencies, researchers administer synthetic psilocybin. However, psilocybin enthusiasts have invented a dosage scheme which aims to describe the subjective effects of psilocybin at various dosages. Psilocybin mushrooms are comprised of ninety percent water.[11] Therefore, when a specimen is dried, its weight is approximately one-tenth of the initial weight. Most anecdotally based dosage schemes operate on the assumption that dry mushroom specimens will be consumed.

According to researchers, effects of psilocybin are standard in some ways but also vary amongst individuals. However, a typical "non-scientific" dose to effect chart looks like the following:

> **0.5 Grams:** Considered a microdose. Produces a light body high, feelings of euphoria, senses become heightened (slightly), colors and light will become

brighter and slightly more vivid, sounds become slightly sharper. No visual anomalies will be experienced at this dose. People tend to use this dose to increase their creativity and enter "flow" states.

1.75 Grams: Is said to be a standard dose. There will be slight visual anomalies. Things will probably begin to move and/or breathe. Senses become more heightened than a microdose. Color becomes very vivid and light is brighter, one's sense of smell increases, things one touches feel better than normal, and one can hear things much better. Perception of music becomes heightened. One will be able to hear more of the distinct sounds within a given musical composition. Pupils become dilated at this dose.

3.5 Grams: For most, this dose can occasion a mystical or religious type experience which would get stronger as the dose increases. The body high is very strong, and visuals become very apparent. Lines of different colors may appear and wave around. Walls and other objects begin to breathe strongly. Confusion of the senses may occur, such as you might smell a sound or taste a color. One may be overcome with a strong sense of peace, tranquility, and/or euphoria.

4.5 Grams: This is the strongest standard dose. At this dose, the body high is very strong and visuals even more intense than the 3.5-gram dose. One will likely see visuals in different ancient motifs such as mandalas and other ancient and intricate patterns. Confusing or reminiscent thoughts can occur. One may think two contradictory things at the same time.

5 Grams: This is considered the Heroic Dose. This term was coined by Terrence Makenna in his lectures about taking a heroic dose alone in a dark and completely silent room.[12] Strong visual hallucinations occur, extremely strong body highs, and extreme contradictory or reminiscent thoughts occur. Ones emotions are amplified immensely. One may experience ego death at this dose. Time will become meaningless, and some things may seem unreal. Auditory hallucinations may occur. This is the approximate dose researchers administer to occasion "complete" mystical experiences in study participants. According to scientific studies, this is the approximate dose that can mediate long-term positive effects.[13]

I would like to note a few things about the above chart specifically and its inclusion in this book. First, the chart is not a scientific chart. I gathered the content for the chart from various sources online and to the best of my knowledge it is strictly based on anecdotal evidence. ***Under no circumstances do I suggest and/or recommend anyone consume psilocybin where such activity is either prohibited by local law, state law, federal law, international law and/or not under the care of medical professionals.*** This chart is strictly for illustrative purposes and is meant to provide a frame of reference for the types of feelings/experiences of study/trial participants discussed herein. The standard dose of synthetic psilocybin in research studies is said to be equivalent to approximately five dried grams of psilocybin mushrooms.[14]

ANCIENT HISTORY

There is archeological evidence suggesting that psilocybin mushrooms have been used in order to alter states of consciousness for at least ten thousand years.[15] Out of the limited psychedelic research I have conducted to date, which has mostly focused on psilocybin, I must say that psilocybin's ancient history is very intriguing.

Perhaps the oldest evidence discovered which indicates ancient use of psychedelic mushrooms, was found on Tassili n'ajjer Plateau in the Sahara Desert of southern Algeria.[16] There, archeologists uncovered ancient rock art contained within eroded rock escarpments which have been formed into a labyrinth of rocky passageways.[17] At that location, archeologists uncovered two different motifs depicting use of psychedelic mushrooms.[18] One seemingly depicts a shaman in antler headgear with the face of a bee holding and sprouting mushrooms out of his body.[19] The other motif depicts two figures with mushroom-shaped heads running while holding a mushroom in their hands.[20] Dotted lines are drawn from the mushroom in the figures' hand to their mushroom-shaped heads, which obviously suggests a brain-mushroom connection.[21] These ancient rock art motifs have been dated to approximately 5,000-7,000 B.C.[22]

Experts believe the ancient civilization which created these motifs was possibly a mushroom cult.[23] Since most works of ancient rock art were related to religious practice, it comes as no surprise that rock art depicts the reverence for and use of psychedelic mushrooms. In Fact, the ability of psilocybin mushrooms to occasion religious and/or mystical experiences is well documented by modern science.

At this juncture, I would like to make quick mention of the "Stoned Ape Theory" originally advanced by Terence Mckenna

in his book *Food of the Gods*.[24] In a nutshell, the theory posits that around 100,000 B.C. early human ancestors Homo Erectus were transformed into Homo Sapiens through the ingestion of psilocybe cubensis mushrooms. The basis of this theory comes from the idea that the effects of psilocybin mushrooms at varying doses would have enhanced prehistoric man's ability to hunt, procreate, and build communities. The theory is very intriguing, and I encourage anyone interested to read Makenna's books. Furthermore, Terrence Makenna was a very influential ethnobotanist, mystic, psilocybin enthusiast, lecturer, and author. Anyone wanting to know more about psilocybin mushrooms and/or psychedelic experiences generally, should read and/or listen to anything by Terence Mckenna. While the oldest confirmed evidence of psilocybin mushroom consumption was between 5,000-7,000 B.C., perhaps it could be much older and played a much more profound role in human development than recognized by modern science and archeology.

There is also evidence of ancient use of psychedelic mushrooms in Mexico and Central America.[25] At least 53 different species of mushrooms from the psilocybe genus are found in Mexico, the most common of which are P. Semilanceata, P. Mexicana, P. Aztecorum, P. Cubenses, and P. Caerulescens.[26] The consumption of psilocybin mushrooms in religious ceremonies was widespread among Mesoamerican cultures.[27] Native American mushroom stones have been discovered in Mexico, Honduras, Guatemala, and El Salvador dating back to approximately the firs millennium B.C.[28] It is believed that the ingestion of psilocybin mushrooms assisted them in communicating with their gods. In fact, the Aztecs referred to psilocybin mushrooms as teonacatl or "flesh of the gods."[29] Other tribes in Central America such as the Zapatec, Mazatec, and Nahua were also ingesting psychedelic mushrooms for religious purposes.

When the Spanish arrived in the 16th century, they attempted to eradicate the ritualistic use of psilocybin mushrooms, but were not entirely successful.[30] Instead, the practice was driven underground and would not be rediscovered by the west until natives of Oxaca, Mexico showed samples of psilocybin mushrooms to Richard Evan Schultes in 1938.[31] It is worth noting that by the time these rituals were rediscovered, the natives in the region had integrated Christian thoughts and ideas into their ceremonies.[32]

PSYCHEDELICS IN MODERN TIMES

Though use of psychedelic plant medicines had been occurring for thousands of years all around the globe, western medicine and society did not really catch on to psychedelics until the early twentieth century. During that time, a few events took place that had the effect of bringing to light, in the western world, the existence of psychedelics. At this juncture I would like to note that while this book is about psilocybin, the early history and research of psilocybin is so intertwined with that of LSD I address the research history of both.

In 1938, Lysergic Acid Diethylamide (LSD) was discovered by swiss chemist Albert Hoffman.[33] While working for the pharmaceutical company Sandoz in Basel, Switzerland, Hoffman had been searching for a compound that would increase circulation.[34] His research centered around alkaloids of ergot, a fungus parasite that grows on rye and other species of grain.[35] Earlier research had already uncovered the common nucleus to all ergot alkaloids, lysergic acid.[36] Hoffman set about trying to prepare the ergot alkaloid synthetically.[37] During his research, Hoffman synthesized LSD-25 (Lysergic acid diethylamide), which was the twenty-fifth substance in the series.[38] Testing on animals did not yield much promise for the newly discovered

substance.[39] Nevertheless, Hoffman seemed to have a hunch that this compound in particular had certain qualities and uses not discovered in the earlier tests.[40]

It was not until a fateful day in April 1943 that Hoffman ultimately discovered the true nature and capabilities of LSD. On that day, Hoffman set about to resynthesize LSD-25.[41] However, during this second round of synthesis, Hoffman's skin somehow managed to come in contact with the substance.[42] According to Hoffman, his work "was interrupted" by "unusual sensations."[43] Due to his condition, Hoffman had to leave the lab and go home that day.[44] When he got home, Hoffman laid down and began to experience the first LSD trip known to man. Hoffman recalled a dreamlike state with strange shapes and kaleidoscopic colors.[45] It occurred to Hoffman at the time that he must have only absorbed a minuscule amount of the substance.[46]

Several days after this first experience, Hoffman engaged in the first intentional LSD trip known to man. On that day, Hoffman ingested a quarter of a milligram of LSD.[47] Approximately forty minutes after ingesting his monster dose, Hoffman was taken on one hell of a ride. According to Hoffman, he was experiencing, "dizziness, feelings of anxiety, visual distortions, symptoms of paralysis, and desire to laugh."[48] His condition was such that he asked his lab assistant to escort him to his house.[49] At that time, due to the ongoing war, Hoffman and his assistant were forced to ride bicycles back to Hoffman's abode.[50] Needless to say, it turned out to be one of the most famous bike rides ever. In fact, the psychedelic community worldwide celebrates "Bike Day" on April 19th every year in honor of Hoffman's famous ride home.

Once home, Hoffman was forced to lay down on his sofa and instructed his assistant to call his doctor.[51] While lying on the couch, Hoffman experienced many of the common effects of an LSD trip. For instance, he experienced both out of body

sensations as well as ego dissolution, amongst other effects.[52] By the time Hoffman's doctor arrived on scene, he could find nothing physiologically wrong with Hoffman and recommended that he be monitored while in bed.[53]

The next day, Hoffman described the afterglow that often follows a psychedelic experience. Everything for Hoffman seemed fresh and new and his senses were highly sensitive.[54] To put the dose that Hoffman ingested into perspective, later tests conducted amongst other Sandoz personnel determined that three hundred thousand doses of LSD could be obtained from one ounce.

Due to the nature of Hoffman's and other Sandoz personnel's experiences on LSD, Sandoz believed that they had a drug that would be beneficial to psychology and psychiatry.[55] The University of Zurich conducted experiments with the drug and subsequently published the first paper on LSD's effects on the mind in 1947.[56] Afterwards, Sandoz began to send quantities of the drug to psychiatrists in the United States for further testing.[57] In 1950, American psychiatrists A.K. Busch and W.C. Johnson recommended that LSD be further explored for its potential in psychotherapy.[58]

Although LSD was initially thought to be a "psychotomimetic" drug, which means the effects mimic that of psychosis, it was later determined that this was not the case and that the effects of LSD were distinguishable.[59] Originally, doctors believed that by taking LSD they would peer into the minds of the schizophrenic patients, which would make them better able to treat them.[60] In fact, many of the therapists who used LSD at the time were quick to test the drug on themselves prior to administering it to their patients.[61]

Papers on the medicinal benefits of LSD were produced throughout the early 1950's.[62] The world's first public LSD

clinic opened in England in 1953, which was then followed by numerous other clinics throughout Europe.[63]

During this time, Humphrey Osmond, a British psychiatrist based in Canada, was successfully treating alcoholics with LSD.[64] Originally, Osmond, a central figure in early psychedelic research, was based out of St. George's hospital in London.[65] While there, he developed an interest in mescaline and its effects.[66] Unfortunately, the powers that be at St. George hospital were not as enthusiastic about his psychedelic interests.[67] However, that did not deter Osmond from furthering his interest in psychedelic research. To chase his dream, Osmond decided to take a job at a hospital in the western Canadian province of Saskatchewan, where he found both funding and support for his psychedelic research, especially as it related to treating alcoholics.[68]

With his partner Albert Hoffer, Osmond began to treat alcoholics with LSD, the thought at the time being that the LSD experience resembled the delirium tremors of alcohol withdrawal.[69] As such, the theory was a heavy dose of LSD would shock alcoholics into staying sober. During this time, Osmond and Hoffer dispensed LSD to over seven hundred alcoholics.

According to their results, in approximately half of the cases, alcoholics were able to obtain sobriety and maintain same for at least several months.[70] However, they were eventually confronted with the fact that the LSD experience did not resemble delirium tremors. Instead, the LSD trip looked more like a spiritual and blissful experience.[71] This thought was further validated by Aldous Huxley's mescaline experience, which was embodied in his book, *The Doors of Perception*.[72] However, their research did reveal the importance of set and setting as it relates to the LSD trip.[73] They found the conditions under which the subjects ingested LSD had a bearing on the

kinds of experiences they had. Other psychologists at the time were conducting experiments in standard hospital settings, many times involving restraints and/or blindfolds, which set off anxiety and other adverse effects in many of the patients.[74] Consequently, the results differed from those obtained by Osmond and Hoffer. As discussed later in this book, set and setting still play a major role in psychedelic therapy today. Eventually, Osmond and Hoffer's treatment of alcoholics with LSD was so successful the Saskatchewan provincial government made it a standard treatment option for alcoholics.[75]

Throughout the 1950's, LSD treatment centers were set up throughout North America and Europe. The psychologists and psychiatrists administering LSD and other psychedelics kept in close contact and shared secrets and techniques in administering psychedelics, as to elicit the best results. These methods and practices persist today and have formed part of the methodology employed by researchers in modern times. Unfortunately, LSD and other psychedelics slowly leaked from therapists' offices and into the streets.[76] At the time, psychologists and psychiatrists were hosting parties, under the guise of guided sessions, outside of the office and in homes and other non-professional settings.[77] As discussed below, this would eventually start the movement to make psychedelics illegal and hinder their use for legitimate medical research for quite some time.

Another landmark event in the 1950's was the introduction of psilocybin. In 1936, R.J. Weitlaner, an ethnobotanist, became aware that there were psychedelic mushroom cults in Oxaca, Mexico.[78] While in Oaxaca in 1936, Weitlaner was able to collect some psychedelic mushroom samples from Mazatec Indians, which he then sent to the Botanical Museum of Harvard University.[79] Unfortunately, by the time they arrived, they were deteriorated to the point of being unidentifiable.[80] In 1938, Weitlaner and his colleagues were able to witness a Mazatec

Indian curing ritual at the village of Hualta de Jiminez which involved the ingestion of psychedelic mushrooms by a Mazatec shaman.[81] A month after Weitlaner and company witnessed the curing session, another team of researchers were able to secure samples of psychedelic mushrooms from Hualta de Jiminez.[82] A year later, the leader of that team, Richard Evan Schultz, published a paper on the psychedelic mushrooms found at Oxaca.[83]

In the fall of 1952, retired J.P. Morgan banker and amateur mycologist, Gordon Wasson was reading about 16th century Spanish conquistador accounts of psychedelic mushrooms fulfilling a divine role in the religion of Mexican native Indians.[84] Wasson also learned that pre-columbian mushroom-shaped artifacts were turning up in Mexico and central America, particularly in Guatemala. Intrigued by what he was reading and seeing, Wasson determined he was going to conduct an expedition to find out exactly what mushrooms held such a sacred position in the native Indian religions.[85] In preparation for his journey, Wasson read the papers of Schultz and other explorers who had been to Oxaca approximately two decades earlier.[86]

In 1953, Wasson and his wife Valentina traveled to Oxaca.[87] However, it took Wasson approximately two years to gain enough of the Indians' trust before he was invited to partake in their healing ceremony. In particular, he had to gain the trust of an individual who is now a psychedelic icon, Curandera Maria Sabina.[88] Maria Sabina is a mythical figure in today's psilocybin mushroom and psychedelic scene. She was the curandera who introduced Wasson, and consequently western civilization, to psychedelic mushrooms. Pictures of this first ceremony and the specimens consumed during the course thereof, ended up in a Life magazine article published by Wasson after his return to the United States.[89] This was the west's first introduction to ancient

plant medicine, and as we will see, even today science struggles to figure out the enigma that is psilocybin mushrooms. A few days after the historic session with Maria Sabina, Wasson, along with his wife daughter, again consumed psilocybin mushrooms, but this time outside of the ritual context, possibly becoming the first people to consume psilocybin recreationally.[90]

After his spiritual session with Maria Sabina, Wasson continued to visit Mexico to collect samples of psilocybin mushrooms. Eventually, some of the samples are sent for laboratory analysis by none other than Albert Hoffman.[91] A gentleman by the name of Roger Heim, a Parisian who accompanied Wasson on his subsequent trips to Mexico, cultivated samples of Psilocybe Mexicana which he sent to Hoffman.[92] In addition to chemically analyzing the samples, Hoffman self-experimented with the mushrooms and reportedly found their effects to be quite powerful.[93]

Hoffman published his analysis of the psilocybin mushrooms in 1958.[94] In his paper Hoffman identified two indole compounds in the mushrooms, psilocybin and psilocin. He found the compounds very similar to LSD in both chemical structure and effects. Hoffman also found these chemicals to be structurally similar to serotonin, the natural brain chemical that regulates mood. Lastly, Hoffman determined psilocybin and psilocin could be created synthetically in the laboratory.

As mentioned above, Wasson reported his findings and experiences in Oxaca to Life magazine in 1957. Naturally, the article created a wave of enthusiasts seeking to travel to Oxaca and partake in the sacred and ancient ceremonies offered by Maria Sabina.[95] Celebrities such as John Lennon, Peter Townsend, Mick Jagger, and Bob Dylan were rumored to be among the patrons that flocked to Maria Sabina's ceremonies after publishing of the Life article by Wasson.[96] Unfortunately,

due to the lack of respect shown by subsequent tourists for native traditions and sacred mushrooms, Maria Sabina believed the mushrooms, her "saint children," lost their power and purity. Until the day she passed Maria Sabina is said to have regretted ever allowing Wasson and company into her sacred ceremony.[97] Despite Maria Sabina's reported feelings on the issue, many in the psychedelic community revere her as the patron saint of psychedelic mushrooms.

By 1960, three psychedelic substances, LSD, psilocybin, and mescaline had been discovered and research was conducted as to their efficacy in treating illnesses and improving lives. Regarding psilocybin, there were some studies which occurred in the 1960's worth note. As we will see, at least one of these studies was re-examined during the psychedelic renaissance of the 1990's and 2000's and served as a catalyst for scientists to reengage in psychedelic research.

One of the most notable psychedelic figures of all time was Harvard psychology professor Timothy Leary. Many psychedelic scientists and researchers of that era place much of the blame for the downfall of psychedelic research on Leary, although his actions alone were not necessarily the proverbial straw that broke the camel's back. Leary was hired by Harvard in 1959 and was first introduced to psychedelics in 1960 when he ingested psilocybin mushrooms while in a swimming pool in Cuernavarca, Mexico.[98] This experience reportedly expanded both Leary's personal consciousness as well as his view of consciousness and the innerworkings of the human mind.[99] This experience would change the course of psychedelic research and medicine for many decades to come.

Once back in Cambridge, Massachusetts, Leary enlisted the help of his assistant professor, Richard Alpert and together the two, with approval from the powers that be at Harvard University,

created the Harvard Psilocybin Project.[100] The only restriction Harvard placed upon the Project was the drugs could only be given to graduate students, not undergraduates.[101] Initially, Leary and Alpert experimented with subjects from all different walks of life. After administering the drugs, the two would have the subjects fill out a questionnaire about their experience. While not every reported experience was life changing, most of the subjects at least reported that the psilocybin generated a very positive experience for them. These sessions were not conducted in the most professional of settings and were said to have been more like parties than university sanctioned research. [102] Moreover, Leary and Alpert regularly ingested psilocybin with their subjects.[103] Many professionals who later reviewed the papers authored by Leary and Alpert, were skeptical of the results.[104] However, Leary and Alpert were able to expand more on the concept of set and setting and how it affected the psychedelic experience, a concept that was originally explored by Hubbard.[105]

Next, Leary and another graduate student, Ralph Metzner dreamed up what they called the Concord Prison Experiment.[106] This new study sought to examine whether the use of psilocybin could change the personality of prison inmates in such a way that would reduce recidivism.[107] The study was conducted inside the prison and involved 32 inmates. One group would receive the psilocybin and the other group would not. During the sessions, two people from Leary's team would be present. One would ingest psilocybin with the prisoners[108] and the other would take notes. The inmates would then be followed for months subsequent to their release in order to track rates of recidivism amongst the participants.[109] At the conclusion of the experiment, Leary published results that showed only twenty-five percent of the prisoners who ingested psilocybin ended back up in prison while eighty percent of those who didn't ingest the substance did

end back in prison. While the results appeared to be amazing, other researchers in the field had serious questions regarding their validity and many concluded there were no differences between the two groups.[110]

The last study involving Leary was the Good Friday Experiment.[111] This was a double-blind experiment where 20 divinity students at Harvard were chosen to partake. All participants were given a capsule full of white powder, ten of which contained psilocybin and the other ten a placebo, Niacin. Eight of the ten participants who consumed psilocybin reported they had a powerful spiritual experience, while only one of the participants in the control group reported same. In the mid 1980's, another researcher, Rick Doblin, followed up with all but one of the Good Friday participants.[112] Most of the participants reported that the experience had changed their lives and their work in profound ways.

Not long after the Good Friday Experiment, Timothy Leary resigned from Harvard. From that point on, he began a quest to turn the entire world on to LSD and other psychedelics. Also, during the 1950's and 1960's, the CIA was engaged in an effort to research LSD and other psychedelics for use as various instruments of war and espionage. This effort was termed MK ULTRA.[113] By 1962, the authorized distribution of LSD became tightly controlled by the U.S. government. At that time, it was coined an "experimental drug" which restricted its use solely for research purposes. This in effect prohibited therapeutic studies conducted by psychiatrists in general practice. In 1965, the U.S. governments control of LSD became even tighter, restricting access only to those with an FDA-approved exemption. With this, the illicit manufacture of LSD became a misdemeanor. It is said Senator Robert Kennedy voiced objection to the increasing regulations upon LSD because his wife had been cured from alcoholism by an LSD session.[114] However, this was not enough

to prevent the downhill slide psychedelic research then found itself on. In 1968, the sale of LSD became a felony and its possession was a misdemeanor. Lastly, in 1970, LSD and psilocybin were placed in Schedule I of the Controlled Substances Act[115] as the government had determined them drugs of abuse and no medical value.

Placement of LSD and psilocybin in the Controlled Substances Act[116] brought psychedelic research to a halt. Except for one or two research establishments which were able to continue limited research, psychedelics were forced into the black market where they reside today. The dark ages of psychedelic research lasted for over twenty years. Since the 1990's, psychedelic research has been slowly gaining steam. While much of the negative thoughts and ideas about psychedelics perpetuated by the government, the media, and society still loom today, the veil is slowly being lifted and researchers are starting to prove the benefits of these substances are greatly outweighed by any real or perceived harms.

2

PSILOCYBIN'S EFFECTS IN HEALTHY SUBJECTS

Modern day (post 1960's) psilocybin research can be traced to approximately 1999. At that time, Johns Hopkins University professor Dr. Roland Griffiths applied to both the DEA and FDA to research the effects of psilocybin on psychologically and physically healthy volunteers. The objective was to examine whether psilocybin could occasion spiritually significant and personally meaningful experiences in healthy volunteers. The interest in this research came from the Good Friday Experiment conducted by Walter Pahnke at Harvard in the 1960's and the follow up study conducted 25 years later.[1] Surprisingly, FDA and DEA approval proved not particularly difficult for Griffiths to obtain. The biggest obstacle faced by Griffiths came from Johns Hopkins University's own Internal Review Board. Due to misunderstandings and backlash from non-medical use of psychedelics in the 1960's, the Internal Review Board had some misgivings about granting Griffiths carte blanche approval to proceed with the proposed psilocybin study. In making its determination, the Internal Review Board sought counsel from outside attorneys and consultants. Eventually, Dr. Griffiths was given the green light to proceed.

PSILOCYBIN CAN OCCASION MYSTICAL-TYPE EXPERIENCES HAVING SUBSTANTIAL AND SUSTAINED PERSONAL MEANING AND SPIRITUAL SIGNIFICANCE.

As stated above, this first study involved 36 psychologically and physically healthy individuals.[2] These participants received eight clinical contact hours with Griffiths and his team prior to undergoing the psilocybin session. During the session, participants were placed on a couch in a room specifically set up to facilitate a positive psychedelic experience. The team understood the concept of and accommodated for proper set and setting. Additionally, the participants were given a blindfold, headphones with music, and were invited to look inward. The participants were given a dose equal to 30mg/70kg (of body weight) of synthetic psilocybin in a capsule. Such a dose would be equal to approximately five dried grams of Psilocybe Cubensis mushrooms.

The study was conducted under double blind conditions and involved an active placebo. As we will see, the blinding procedures have continued to evolve and become more and more sophisticated as psilocybin research has progressed. A double-blind study is one in which both participants and the professional guiding the participants psilocybin experience are unaware whether the substance being consumed is the tested substance or a placebo.

An active placebo is a placebo that gives participants a feeling of some kind. In this study, the participants were given methylphenidate as an active placebo. Methylphenidate, commonly known as Ritalin, is a medicine normally prescribed for ADHD and narcolepsy and is similar in effect to amphetamines. Administering an active placebo in psychedelic studies is very important. Due to the nature and notoriety of psilocybin, most study participants will have a preconceived

notion that psilocybin will have powerful and profound effects. If the participants do not feel anything after a certain amount of time, they will know they have not received psilocybin. Researchers have found these expectations can negatively impact the way that participants respond to the study. Therefore, researchers try and protect against this "expectation bias" by administering an active placebo; the theory being participants will not necessarily know whether or not they received psilocybin.

Another aspect of this study that was unique is that all participants were deemed psychedelically naïve, which means participants stated at intake they never had a psychedelic experience prior to their participation in the study; which in turn reinforces the idea the participants would not necessarily know whether they received psilocybin or the active placebo. At the time, this was the first study to use psychedelically naïve participants is approximately thirty years.

The average age of participants was 46 years old and all were well educated. Ninety-seven percent were college graduates and fifty-six percent had post-graduate degrees. Eighty-three percent of the participants were employed full time, the remaining volunteers were employed part-time. Fifty-three percent reported affiliation with a religious or spiritual community. All 36 participants reported at least intermittent participation in religious or spiritual activities. Participants were randomly assigned to either two (n=30) or three sessions (n=6) conducted at two-month intervals.

At the 1-2 month post psilocybin session follow up and one year post psilocybin session follow up, participants reported the psilocybin experience had positively changed their attitudes about themselves, their lives, and other people. They reported finding themselves more prosocial, generous and loving.

Moreover, many had begun taking better care of themselves by engaging in meditation, healthy eating, and exercise. In general, the psilocybin experience changed the participants' core sense of who they are and what they are doing in this world. Researchers even went a step further and verified much of what was being reported to them by participants through speaking with participants' family, friends, and colleagues. Moreover, the psilocybin experience was found to have changed the participants' personality. Post-experience testing revealed the participants were showing higher levels of openness, which in this context, is defined as being linked with intelligence, problem solving, being sensitive to yours and others' feelings, open to new ideas, more flexible in approaching new situations.

By engaging in psilocybin sessions, the psychologically and physically healthy participants were able to have a mystical type experience which in turn had profound and positive effects on their life in general. Moreover, as stated above, these results were independently verified by other uninterested parties. Since this first study began, Griffiths and his team at Johns Hopkins University have administered psilocybin to over 250 participants in more than 500 sessions.

MYSTICAL-TYPE EXPERIENCES OCCASIONED BY PSILOCYBIN MEDIATE THE ATTRIBUTION OF PERSONAL MEANING AND SPIRITUAL SIGNIFICANCE 14 MONTHS LATER.

Subsequent to this initial study, the team at Johns Hopkins followed up with participants 14 months after their last psilocybin session to measure long-term effects.[3] To assess these effects, researchers conducted this follow-up study by asking volunteers to complete questionnaires which assessed personality, affect, quality of life, spiritual experience, and

persisting changes in attitude and behavior attributed to their psilocybin experiences.

The researchers re-measured participants' responses to mystical experience questionnaires.[4] What they found was 22 of the 36 participants had a "complete" mystical experience based upon their immediate post-psilocybin questionnaire responses. At the 14-month follow up, 21 of 36 participants continued to be rated as having had a "complete" mystical experience.

Compared to the placebo, psilocybin sessions produced significant increases in participants' ratings of positive attitudes, mood, social effects, and behavior rated retrospectively at both the 2-month and 14-month follow up. Therefore, psilocybin experiences produced profound and stable changes in these measures which held steady for the 12-month period in between the follow up periods.

No participants rated the psilocybin experience as having decreased their sense of well-being or life satisfaction at either the two month or fourteen-month follow-up. At the fourteen-month follow-up, 58% of the volunteers rated their psilocybin experience as among the five most personally meaningful experiences of their lives; Sixty-seven percent of participants rated the psilocybin experience as among the top five most spiritually significant experiences of their lives; 11% of participants rated the psilocybin experience as the single most meaningful experience of their lives and 17% rated it as the single most spiritually meaningful experience of their lives.

Sixty-four percent of the 36 volunteers indicated the psilocybin session increased their overall sense of well-being or life satisfaction either moderately or very much at the fourteen-month follow up, while Sixty-one percent responded that the experience was associated with moderate to extreme positive behavior change. Additionally, researchers asked participants

open-ended questions regarding their description of the experience. All responses had common themes such as sense of unity of all things, a separate "self" ceasing to exist, and merging and/or an encounter with god were woven throughout the open-ended responses.

It is worth note that there were no reports of persisting perceptual phenomena which are sometimes attributable to use of hallucinogens. Moreover, the study's authors observed that all study participants seemed to be well-adjusted, high-functioning, and productive members of society at the fourteen-month follow up.

In the comments section of the article, the study's authors note, "…it is remarkable that an 8-hour laboratory-based intervention could have such large and sustained personally and spiritually significant effects in such a large proportion of volunteers." Also they observe these results are consistent with the findings of the twenty-five year follow-up study conducted on participants in the Good Friday experiment.[5] Lastly, they noted all participants in this study reported at least some periodic participation in religious or spiritual activities prior to the study. Consequently, they theorized this fact might increase the likelihood that the psilocybin experience would have substantial personal and spiritual meaning to participants in the study.

PSILOCYBIN OCCASIONED MYSTICAL-TYPE EXPERIENCES: IMMEDIATE AND PERSISTING DOSE-RELATED EFFECTS.

In 2011, researchers at Johns Hopkins published yet another study involving healthy individuals.[6] The study enlisted 18 adult participants, 17 of which were hallucinogen naïve. The psilocybin was administered in five 8-hour sessions approximately one month apart. What is interesting about this study is they randomly assigned participants to two separate

groups, wherein one group would receive psilocybin doses in ascending order and the other group in descending order.

The participants were on average 46 years old, well educated, 56% were employed full time, 33% were employed part-time, and 11% were retired. Fifty percent of the participants indicated affiliation with a religious or spiritual community, such as a church, synagogue, or meditation group and all 18 participants indicated they participated, at least intermittently, in religious or spiritual activates such as religious services, prayer, or mediation; 39% reported daily activities and another 39% reported at least weekly activities.

As stated above, psilocybin was administered in either ascending or descending doses at 0, 5, 10, 20, or 30 mg/kg. Researchers employed the 0mg psilocybin dose as an active placebo which was randomly assigned to be administered to each of the 18 participants. The study measured the psilocybin experience seven hours after each administration, and longitudinal personality measures were taken at screening, one month after each psilocybin session, and 14 months after the last psilocybin session. Community observations of the longitudinal personality measures were recorded one week after study initiation, 3-4 weeks after the last psilocybin session, and at the fourteen-month follow up.

Participants met with monitors for eight total hours prior to the first psilocybin session, once for approximately an hour the day after each psilocybin session, and one more time three weeks after each psilocybin session. The monitors were trained by other study personnel who had extensive experience administering and monitoring prior psilocybin sessions, and the sessions were conducted in a setting similar with prior Johns Hopkins studies.

The subjective effects measures showed effects significantly increased in tandem with the dose administered, with significant

effects noted even on the lowest dose of 5mg/70kg. The effects measured included perceptual changes, feelings of transcendence, grief, joy, anxiety, sense of meaning, insight, and/or ideas of reference.

As stated above, seven hours after psilocybin administration, researchers measured participants' mystical experience ratings. These ratings were also significant, and the effects increased in tandem with the dose administered. The proportion of participants who qualified as having a "complete" mystical experience also increased in tandem with the dose (0%, 5.6%, 11.1%, 44.4% and 55.6% having "complete" mystical experiences were reported at the following doses respectively: 0mg, 5mg, 10mg, 20mg, 30mg/70kg). In total, 72% of volunteers had "complete" mystical experiences at either or both of the 20mg and 30mg/70kg sessions.

Many participants reported adverse effects, especially at the larger doses, but were not affected by the ascending or descending dose sequencing. Overall, 39% of participants had extreme ratings of fear, fear of insanity, or feeling trapped at some time during the session. Most adverse effects were experienced after the 30mg/70kg dose and one case reportedly occurred during the 20mg/70kg dose. These adverse effects did not affect the overall ratings of participants having "complete" mystical experiences. Seventy-one percent of those reporting adverse effects also reported effects consistent with having a "complete" mystical experience. However, the study's authors note the two participants who sustained the most anxiety during the 30mg/70kg session did not have "complete" mystical experiences. Lastly, there was no consistent relationship between adverse effects and subsequent ratings of the session having personal meaning or spiritual significance. In fact, no participant rated the overall psilocybin experience as decreasing their sense of well-being or life satisfaction.[7]

As stated above, measures were taken of participants one month after each psilocybin session and these measures showed the psilocybin sessions caused significant and generally increasing ratings, in tandem with dose, in positive attitudes about life, attitudes about self, mood, social effects, and behavior. Negative ratings of these measures were extremely low and did not differ across the various dosages except negative attitudes about self, which showed small increases at the two lowest doses.

Personal meaningfulness, spiritual significance of the experience, ratings of well-being, and ratings of life satisfaction were all significant and increased in tandem with dose at the one-month post-psilocybin mark. Persisting effects measures (attitudes about life, attitudes about self, mood, altruism, behavior, spirituality, and sense of well-being or life satisfaction) showed dose increases or decreases based upon the dosing scheme. In the ascending dose sequence, these measures were more significant at the 20mg and 30mg/70kg doses and were less significant at the lower doses compared to the descending dose sequence.

Endorsements on the persisting effects questionnaire increased in tandem with dose. Sixty-one percent of participants rated either or both the 20mg and/or 30mg/kg psilocybin sessions as the single most spiritually significant of their lives; Eighty-three percent of participants rated these experiences in the top five most spiritually significant in their life; Ninety-four percent and 89% of participants, respectively indicated the experiences in the same psilocybin sessions increased their well-being or life satisfaction and noted positive behavior changes. *Not one psilocybin session was indicated to have decreased well-being or life satisfaction*.

At the fourteen-month follow up, no participant indicated the two highest dose psilocybin sessions affected them negatively or

experienced a decrease in well-being or life satisfaction. It was found the ascending dose sequence accounted for more significant results on internal unity, mood, and total of the States of Consciousness Questionnaire.

When asked at the fourteen-month follow up which sessions were strongest, 83% of participants indicated the 30mg/70kg dose was the strongest and 17% indicated the 20mg/70kg dose was strongest. When asked which session was the most personally meaningful, 44% of participants answered the 30 mg/70kg, 44% answered the 20 mg/70kg, and 11% answered the 10mg/70kg dose. Interestingly, 67% of participants in the ascending dose sequence rated the 30mg/70kg dose as most personally meaningful and 78% rated it most spiritually significant. This is contrasted with the descending dose sequence where 22% of participants rated the highest dose as most personally meaningful and another 22% rated the highest dose as most spiritually significant.

Also at the fourteen-month follow up, participants were asked to provide written descriptions based on memories of the two highest dose sessions and how it affected their behavior. Only two of eighteen participants reported no positive change in behavior. The remaining participants reported better social relationships with family and others, increased physical and psychological self-care, and increased spiritual practice.

Longitudinal measures of mystical experience, death transcendence, and community observer ratings of changes in participants' behaviors and attitudes increased similarly to the above-described persisting effects. Positive community observer ratings of behavior and attitudes taken one-week post-enrollment through fourteen-month follow up were also significant. This was also mirrored in the ratings of behavior and attitude reported by participants' study monitors. No reports of persisting negative

effects such as persisting perception phenomena were reported at the fourteen-month follow up.

According to the study's authors, this study extended previous observations indicating psilocybin's ability to cause persisting and positive changes in attitudes, moods, life satisfaction, behavior, and altruism/social effects.[8] They also believe this study's findings suggests an ascending dosing sequence is more likely than descending dosing sequences to mediate long-lasing positive changes in attitude, behavior, and memorable mystical-type experiences. Therefore, it is likely higher doses will have more positive and prfound effects if preceded by smaller doses.

MYSTICAL EXPERIENCES OCCASIONED BY THE HALLUCINOGEN PSILOCYBIN LEAD TO INCREASES IN THE PERSONALITY DOMAIN OF OPENNESS.

Johns Hopkins University published yet another study in 2011 which analyzed the effects of mystical experiences on the personality trait of openness.[9] This study utilized results from the first two studies and analyzed the data therefrom to reach their conclusions. The study's authors note longitudinal studies have shown individual personality traits are predominantly stable across the lifespan. While some personality changes naturally occur after age 30, these shifts are generally slow and subtle.[10] Therefore, this study combined the data from the previous Johns Hopkins[11] psilocybin studies to determine if mystical experiences caused changes in participants' personalities.

Personality change was assessed at 1-2 months post high-dose psilocybin sessions and again one year later to ascertain the persistence of personality change. This study excluded from its purview two participants in the prior studies, as one participant was not hallucinogen naïve and the other reported incomplete personality data. Therefore, a total of 52 participant reports were examined.

Here, researchers were most interested in examining changes in openness, which in this context includes a wide range of personality traits. These personality traits include, but are not limited, to the following: aesthetic appreciation and sensitivity, fantasy and imagination, awareness of feelings in self and others, and intellectual engagement. Typically, individuals who have high levels of openness are "permeable to new ideas and experiences" and "motivated to enlarge their experience into novel territory."[12] Openness is associated with creativity[13] and some of its facets (ideas, values) are associated with general fluid intelligence and cognitive ability.[14]

The researchers found the personality trait openness increased from the time participants were screened for the study until one to two months post psilocybin session. However, other personality traits measured (neuroticism, extroversion, agreeableness, and conscientiousness) showed no significant changes from screening through the 1-2 months post psilocybin session mark. Moreover, mystical experience scores were found to correlate significantly with openness but did not correlate with levels of openness at screening. Therefore, the study's authors propose mystical experiences were likely the catalyst for post psilocybin session increases in openness.

Participants who had "complete" mystical experiences showed higher levels of openness at 1-2 months post high dose psilocybin session. Other participants who did not have "complete" mystical experiences failed to show significant increases in openness from screening through 1-2 month post high dose psilocybin session. At the fourteen-month follow-up, participants who had "complete" mystical experiences showed slightly decreased levels of openness from the 1-2 month post high dose psilocybin session levels. However, those who failed to have "complete" mystical experiences had nearly identical

levels of openness at the fourteen-month follow up as the 1-2 month post high dose psilocybin session mark.

The results of this study showed significant increases in openness after high dose psilocybin sessions which were larger in magnitude that those changes typically observed in healthy adults over decades of life experience.[15] Importantly, according to the study's authors, it was the "complete" mystical experience which mediated enduring changes in openness. In comparison, these increases in openness are larger than increases seen in individuals who are treated with anti-depression medication[16] and those who have undergone intensive outpatient counseling services for substance abuse.[17]

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.

In 2018, Johns Hopkins University researchers published another study which examined the effects of psilocybin on healthy individuals.[18] This goal of this study was to determine whether a psilocybin-occasioned mystical-type experience in conjunction with meditation and other spiritual practices caused positive changes in psychological functioning and/or in trait measures of prosocial behaviors and attitudes.

This study involved two psilocybin sessions for all participants and randomly assigned third to thirty-nine participants. The study enlisted seventy-five (75) healthy individuals who undertook a program of mediation/spiritual practices as part of the study. Participants were randomly divided into three separate groups of twenty-five (25) participants each. The first group was given a very low dose of psilocybin (1mg/70kg on sessions 1 and 2) combined

with moderate-level ("standard") support for spiritual practices. The second group was given a high dose of psilocybin (20 and 30mg/70kg on sessions 1 and 2, respectively) with standard support for spiritual practices. Finally, the third group was also given a high dose of psilocybin (20 and 30mg/70kg on sessions 1 and 2, respectively) with high support for spiritual practices.

The study was double blinded and both participants and guides administering the psilocybin were unaware of the dose administered. A sub-perceptual dose of psilocybin (1mg/70kg) was used as a placebo. The randomly assigned third session was implemented in order to decrease expectancy effects through 6-month follow up. Both participants and guides were instructed participants would receive psilocybin each session and the dose levels could range between very low to very high. Both groups were told each participant would receive two or more different dosage levels during two or three sessions and each participant would have at least one session consisting of a moderately high or high dose of psilocybin.

All 25 low dose psilocybin participants were assigned to a third session where they received a high dose of psilocybin. The total length of time the participants were involved in the study ranged from six to eight months. Guides and participants met numerous times throughout the study. These meetings served to establish rapport and provide instructions and support for spiritual practices and began and ended with a brief period of meditation.

The standard spiritual practice support groups (n=50 participants total) had 3 one-hour meetings and 1 two-hour meeting with their guides prior to the first psilocybin session. After each psilocybin session, the standard support group met with guides for one hour within a day or two after the session as well as a ten-minute teleconference with their therapist approximately two weeks later. In all, the standard support group received

approximately 7 hours and 20 minutes of contact with their guides through the 6-month follow up.

Prior to the first psilocybin session, participants in the high spiritual support group had 5 two-hour meetings with their guides. After the first psilocybin session and before the second session, which was approximately one month, the participants had 3 one-hour meetings with their guides. The first post-psilocybin meetings occurred approximately 1-2 days after the first psilocybin session. During the approximately four-month period following the second psilocybin session, these participants met with their guides once for an hour a day or two after the second psilocybin session and then one more session the very next week. After this period, meetings occurred twice per month for the remainder of the four-month period. Additionally, during the four-month period following the second psilocybin session, the guides and high support participants met twice monthly for 90-minute dialogue group sessions.

Each participant was given a copy of the book, *Meditation: A simple 8-Point Program for Translating Spiritual Ideas Into Daily Life*[19]; a blank journal; and a one page outline of spiritual practice suggestions. Participants were required to read the book which provided three specific spiritual suggestions: 10-30 minutes of daily meditation, daily awareness practice, and daily self-reflective journaling of insights, beliefs, and challenges of spiritual practice of daily life. Furthermore, participants were encouraged to engage in activities they believed would facilitate spiritual growth. At each therapeutic session, guides discussed and encouraged spiritual practices.

Researchers gave a questionnaire to the guides after each psilocybin session to test the integrity of the blinding procedures. The questionnaire asked them about their impression of the study and dose conditions. Most guides made incorrect inferences

regarding the study drug and dose conditions. No guide correctly understood the study design, implying the blinding procedures were highly effective. Some believed drugs other than psilocybin had been administered and others believed high dose psilocybin had been administered when in fact a low dose had been administered.

Participants were asked to complete two questionnaires seven hours after psilocybin administration to measure mystical experiences. Overall, 4% of the low dose standard spiritual support group had "complete" mystical experiences across both psilocybin sessions. The high dose standard spiritual support group saw 61% having "complete" mystical experiences across both psilocybin sessions. The high dose high spiritual support group saw 64% of participants in that group having "complete" mystical experiences. This suggests that dose, and not spiritual practices, was the catalyst for "complete" mystical experiences.

The study results did not show psilocybin dose affected the participants engagement in spiritual practices at the six-month follow up. The high spiritual support group showed greater engagement in spiritual practices compared with the other two groups. However, both the standard spiritual support groups (low dose and high dose) showed no significant difference in spiritual practices. Therefore, this suggests psilocybin dose did not affect the amount of engagement in spiritual practices.

Consistent with a previous Johns Hopkins study,[20] high dose groups showed greater increases in persisting positive effects attributable to psilocybin sessions at the six-month follow up. The measures of positive change were as follows: attitudes about self, mood, altruism/positive social effects, behavior, and increased spirituality. Compared to the low dose group, the high dose groups attributed significantly more personal meaning, spiritual significance, and change in well-being or life

satisfaction to psilocybin sessions. The percentage of participants in the high dose group endorsing personal meaning, spiritual significance, and change in well-being or life satisfaction was greater than the low dose group.

The most intriguing measures in this study, according to the study's authors, were the longitudinal trait measures such as psychological well-being, prosocial disposition, and spiritual worldview. They found generally large and significant effects of psilocybin dose across these measures. These results differ from a prior Johns Hopkins study.[21] According to them, popular belief had been that psychedelic experiences lead to rejection of traditional worldviews.[22] Here, the results showed that life value of tradition increased significantly from baseline to six months in the high dose high spiritual support group. That subscale is comprised of items assessing respect for tradition, moderation of feelings and action, humility, accepting one's life circumstances, and holding religious belief and faith. The study's authors propose that administering psilocybin in the context of spiritual practices accounts for this strengthening effect. Moreover, they observe that *such a finding is consistent with traditional use of psilocybin mushrooms and other classic psychedelic substances in the indigenous-sacramental setting. Put another way, they propose that consuming psychedelics in the context of spiritual practices reinforces one's beliefs in spiritual/religious traditions and values*.

Another measure seemingly affected by the injection of spiritual practices was personality domain of openness. Here researchers found openness increased from baseline to six months in the high dose high spiritual support group but not the other two groups. However, they did not find a correlation between mystical experience and openness, which is in contradiction with another study which found such a correlation.[23]

The acute effects of high dose psilocybin on the high spiritual support group were greater than that of the high dose standard spiritual support group. The guides' ratings of tears/crying and the participants' scores on the mysticism scale were greater for the high dose high spiritual support group than the other two groups. The study's authors suggest this difference likely reflects the fact the high spiritual support group spent about twice the amount of time with their guides prior to the psilocybin sessions, and this extra time was mostly spent focusing on spiritual practices and support for same.

Other measures which showed significant differences between the two groups at the six-month follow up were altruism/positive social effects, positive behavior change, increased spirituality, and the ratings and percentage of strong endorsements of spiritual significance. Approximately 56% of participants in the high dose high spiritual support group rated their experiences in one or both psilocybin sessions as the single most significant spiritual experience of their whole life, with 96% rating it among the top five most spiritually significant experiences. The study's authors note these results suggest administering psilocybin in the context of high support for spiritual practices increases both reported spiritual significance of the psilocybin experience and the attribution of the psilocybin experience to increased spirituality. Ancient Mesoamerican cultures have been administering psilocybin in the ceremonial and spiritual context for over a thousand years and the results of this study seem to validate their psilocybin administration methodology.

Longitudinal measures at the six-month follow up also showed differences between the high dose standard support and high dose high spiritual support groups. These measures included positive changes in interpersonal closeness, gratitude, life meaning/purpose, forgiveness, death transcendence, daily spiritual experiences, religious faith and coping, sanctifications

of life strivings, and ratings of participants by community observers. As well on the longitudinal measures, high dose high spiritual support group scores were significantly different from baseline on 20 of the 23 measures.

According to the study's authors, the results here suggest both mystical experiences and spiritual practices contribute to positive outcomes in psilocybin therapy. However, they also note mystical experiences likely made a more substantial contribution. This, they say, was evidenced by the fact measures of mystical experiences occurred approximately 4-5 months before the outcome measures. Consequently, they argue mystical experiences and/or their neurophysiological or other correlates likely determine the enduring positive benefits of psilocybin.

The take-away from this study is high dose psilocybin administration in conjunction with significant spiritual support can strengthen the positive effects of mystical experiences. In turn, this can lead to significant, enduring, and positive changes in personality in healthy individuals. Moreover, these findings appear to be consistent with ancient practices of consuming psilocybin in a spiritual or ceremonial context.

EMOTIONS AND BRAIN FUNCTION ARE ALTERED UP TO ONE MONTH AFTER A SINGLE HIGH DOSE OF PSILOCYBIN.

A more recent study, published in February 2020, found that a single high dose of psilocybin in healthy individuals increased positive affect and possibly increased emotional and brain plasticity.[24] This open label pilot study involved twenty healthy volunteers who were administered one high dose (25mg/70kg bodyweight) of psilocybin. The participants were subjected to fMRI brain imaging the day before, one week after, and one month following the psilocybin session. While in the fMRI scanner, participants were subjected to a battery of emotional

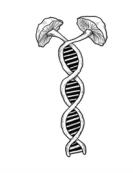
stimuli tests to allow researchers to assess changes in the brain occasioned by high dose psilocybin versus baseline.

Generally, study results showed that a week after the psilocybin session, negative affect and brain response to facial affect stimuli were reduced while positive affect and associated brain function were increased. One-month post psilocybin session, negative affect and associated brain functions had returned only to baseline while positive affect remained elevated and anxiety was reduced. Interestingly, researchers found the number of resting state connections across the brain had increased from baseline (one day prior to psilocybin session) to one-week post psilocybin session, and even at the one-month mark. Overall, the study's authors concluded psilocybin in health individuals can increase emotional and brain plasticity.

The research covered in this chapter reveals some extraordinary effects of psilocybin on healthy individuals. *First, at certain dose levels, psilocybin can occasion a "complete" mystical experience*. *Second, that these mystical experiences can occasion positive changes in behavior and personality*. *Third, that heightened spiritual practices in combination with mystical experiences can increase the positive results attained from psilocybin. Lastly, that psilocybin can increase emotional and brain plasticity*.

3

PSILOCYBIN'S EFFECTS IN CANCER PATIENTS



This next area of psilocybin research focuses on the benefits of psilocybin derived by those with terminal illnesses. As one could imagine, people facing probable death in a determinate amount of time tend to suffer from crippling anxiety and depression. As we will see, mystical experiences occasioned by psilocybin have been shown to greatly reduce or eliminate end of life anxiety and depression. Essentially what psilocybin does, is allow people with terminal illnesses to live out the remainder of their days relatively free from anxiety, depression, and despair. It is saddening to think about the countless number of individuals who have suffered and continue to needlessly suffer from anxiety and depression associated with facing end of life.

Research into psychedelic therapy for those suffering from end of life depression and anxiety began in the 1960's. From the 1960's to 1970's psychedelic assisted psychotherapy was researched as a treatment for cancer-related psychological and existential distress.[1] This research involved several hundred participants and showed psychedelic therapy for cancer

patients was an effective treatment.[2] The most compelling early study was published in 1973 by Czech psychiatrist Stanislav Grof.[3] That study explored whether a psychotherapeutic program utilizing psychedelic compounds could help alleviate the emotional and physical suffering of cancer patients. The study involved sixty participants, all of which were cancer patients. Forty-four of the participants were administered LSD along with psychotherapy. Nineteen of the participants were administered another psychedelic drug called dipropyltryptamine (DPT). Three of the participants received both LSD and DPT in separate sessions. The participants were rated before and after their psychedelic sessions on the degree of depression, psychological isolation, anxiety, difficulty in management, fear of death, and pain. The majority of participants in the study showed significant improvement in all measures. Specifically, the study's results were as follows: 29% of participants showed dramatic improvement, 41.9% showed moderate improvement, 22.6% were unchanged, and 4.6% scored lower on the measures after the psychedelic session(s). The most significant impact of this and other early studies is they paved the way for future studies regarding end of life depression and anxiety in terminally ill patients.

PILOT STUDY OF PSILOCYBIN TREATMENT FOR ANXIETY IN PATIENTS WITH ADVANCED-STAGE CANCER

The first modern study to examine psilocybin's effectiveness at reducing or eliminating end of life anxiety and depression, conducted by Dr. Charles Grob, began at UCLA medical center in approximately 2004.[4] This was the first study in more than thirty five years to explore the potential of a psilocybin treatment model for patients with reactive anxiety associated with advanced-stage cancer.[5] The aim of this study was to establish

the feasibility and safety for a hallucinogen treatment model in patients with advanced-stage cancer and anxiety.

Dr. Grob's study involved 12 terminally ill individuals in a double-blind[6] placebo-controlled study. Participants were involved in two sessions, one with psilocybin, given a moderate dose of .2 milligrams per kilogram of body weight, and the other with an active placebo (nicacin). Which session participants received either the psilocybin or placebo was randomized and only known to the research pharmacist.

The study found that participants' anxiety and mood improved as well as their overall quality of life. While past research reported more pronounced therapeutic benefits with a higher-dose model, the lower dose of psilocybin used here did provide some therapeutic benefit as measured by quantitative psychological evaluations. More specifically, researchers found participants' anxiety scores showed a sustained reduction that reached significance at the 1 and 3-month marks post psilocybin treatment. In regards to mood, participants' scores improved for 2 weeks following psilocybin treatment with sustained improvement reaching significance at the 6 month post treatment follow-up. Interestingly, while prior psychedelic studies in terminally ill patients found the psychedelic experience lessened participants' pain and need for narcotic pain medication, no such finding was made here. The study's authors seem to attribute this to the moderate dose administered,[7] and recommend this measure be addressed with higher doses in the future.

It is worth note that some common themes were discovered between participants' psilocybin experiences. More specifically, participants reported examining how their illness had impacted their lives, relationships with family and close friends, and sense of security in their existence. Furthermore, participants reported a powerful empathic focus of mental energy to close friends and

family members and examined how they wished to address their limited life expectancy. In their monthly follow up discussion with researchers, participants reflected on these new insights and perspectives gained during their psilocybin experiences.

This study lasted from 2004 through 2008 and was eventually published in the January 2011 issue of the Archives of General Psychiatry, which is generally considered to be the number one impact journal in the whole field of psychology. More importantly, this study laid the groundwork for the next two studies we will examine.

PSILOCYBIN PRODUCES SUBSTANTIAL AND SUSTAINED DECREASES IN DEPRESSION AND ANXIETY IN PATIENTS WITH LIFE-THREATENING CANCER: A RANDOMIZED DOUBLE-BLIND TRIAL

In December 2016, two more studies were published regarding psilocybin's propensity to relieve end of life anxiety and depression in terminally ill patients. The first study was conducted by Dr. Roland Griffiths and his team at Johns Hopkins University.[8] This study involved 51 cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety. The study was a randomized double-blind trial and sought to examine the effects of a low dose (1 or 3mg/70 Kg of bodyweight) versus high dose (22 or 30mg/70Kg of body weight) administered in counterbalanced sequence with five weeks between sessions and a six month follow up after the last session.

After enrollment in the trial, participants baseline measurements were taken and before their first psilocybin session they met at least twice with their two session monitors who would be present for their psilocybin sessions. The day following each psilocybin session and twice during the five weeks between the two psilocybin sessions, participants again met with their assigned

monitors. After the second and final psilocybin session, participants met with their monitors two more times prior to the six-month follow-up.

This study demonstrated the efficacy of a high dose of psilocybin administered under supportive conditions to decrease symptoms of depressed mood and anxiety and increase participants' quality of life. Eleven of the 17 relevant anxiety and depression measures satisfied conservative criteria for demonstrating efficacy of the high dose of psilocybin. These effects were sustained at the six-month follow-up. More specifically, clinical response to clinician-rated measures of depression and anxiety, respectively, were 78% and 83% and the overall rate of symptom remission was 65% and 57% at the six-month follow up. Participants stated the high dose psilocybin experience caused positive changes in attitudes about life, self, mood, relationships and spirituality, with 80% of participants endorsing moderately or higher increases in well-being and life satisfaction. These positive changes in participants' attitudes and behavior were independently verified by friends, family, and work colleagues.

The results of this study also showed mystical type experiences were associated with most of the enduring changes in therapeutic outcome measures five weeks post high dose psilocybin session. The study's authors note this finding is consistent with findings of previous studies which also found mystical experiences to predict long-term positive changes in attitudes, mood, behavior, and spirituality.[9]

RAPID AND SUSTAINED SYMPTOM REDUCTION FOLLOWING PSILOCYBIN TREATMENT FOR ANXIETY AND DEPRESSION IN PATIENTS WITH LIFE-THREATENING CANCER: A RANDOMIZED CONTROLLED TRIAL.

The second study was conducted by Dr. Stephen Ross and his team and New York University.[10] This study involved a double-

blind placebo-controlled crossover trial and involved twenty-nine patients with cancer-related anxiety and depression. The purpose of this study was to investigate the efficacy of a single psilocybin dosing session versus one dosing session of an active control (niacin) administered in conjunction with psychotherapy to treat clinically significant anxiety or depression in patients with life-threatening cancer. Participants were randomly assigned and received treatment with a single dose psilocybin (.3mg/Kg of bodyweight) or niacin, both in conjunction with psychotherapy.

As stated, this trial employed a crossover design which means participants were randomly assigned to two oral dosing session sequences: psilocybin during the first session then niacin during the second session, or the inverse. The first session occurred on average 18 days after intake into the trial after baseline measures were taken, and the crossover occurred at approximately 52 days (7 weeks) after the first session, at which time the participants underwent the second dosing session. Outcome measures were taken at baseline (2–4 weeks prior to dose 1), 1 day prior to dose 1, day of dose 1 (7 hours post-dose/mystical experience measures), 1 day after dose 1, 2 weeks after dose 1, 6 weeks after dose 1, 7 weeks after dose 1 (1 day prior to dose 2), day of dose 2 (7 hours post-dose), 1 day after dose 2, 6 weeks after dose 2, and 26 weeks after dose 2; and total duration of participation in the study was approximately 9 months. The primary measures were anxiety and depression assessed prior to the crossover and the secondary measures (assessed prior to and after the crossover) were existential distress, quality of life, and spirituality, as well as immediate and sustained effects of psilocybin administration on subjective experience (mystical experience), cognition, affect, spirituality, and behavior.

For each of the six primary anxiety and depression outcome measures, there were significant differences between participants

who received psilocybin and those who received the placebo prior to the crossover. More specifically, the psilocybin group showed immediate, substantial, and sustained clinical benefits in terms of reduction of anxiety and depression symptoms. Moreover, according to the study's authors, these differences were large. Regarding the psilocybin first group (prior to the crossover), those participants demonstrated significant reductions in anxiety and depression immediately after receiving psilocybin and those reductions remained significant at each time point though 26 weeks. Prior to the crossover, the niacin first group demonstrated either no significant reductions or a transient reduction that become non-significant prior to the second dose. However, the niacin first group demonstrated significant reductions in anxiety and depression immediately after receiving the psilocybin dose and those reductions were maintained until the end of the study. Generally, the study's authors observe, psilocybin produced immediate and enduring anxiolytic and anti-depressant response rates, as well as significant anti-depressant remission rates.

Secondary measures also showed significant improvements following psilocybin administration. In the short-term (2 weeks after dose 1), psilocybin, as opposed to the control, produced decreases in cancer-related demoralization and hopelessness, while improving spiritual well-being and quality of life, which were maintained at the final 6.5 month follow-up. Interestingly, while there were no significant improvements in end of life anxiety, there was a significant improvement in attitudes and adaptions towards death in the psilocybin first group compared to the niacin first group. When asked overall what they thought about their psilocybin experiences, 52% and 70% rated the psilocybin experience as the most or top 5 most spiritually significant or the top 5 most personally meaningful experience of their entire lives, respectively. Overall, 87% reported increased

life satisfaction or well-being attributed to their psilocybin experience.

Lastly, this study found the quality of the acute psilocybin experience (mystical experience) mediated a significant portion of the effect of psilocybin versus the control treatment on four of the six primary outcome (anxiety and depression) measures. Moreover, the study's authors note the psilocybin sessions produced mystical experiences commensurate with that of other prior studies with normal volunteers[11] and patients with terminal cancer.[12]

A few salient points made by the study's authors are worth mention. They note that enduring and clinically significant anxiety and depressive symptoms have been found to be present in 30-40% of cancer patients in hospital settings.[13] These symptoms were associated with a host of negative outcomes, including medication non-adherence, increased health care utilization, adverse medical outcomes, decreased quality of life, decreased social function, increased disability, hopelessness, increased pain, increased desire for hastened death, increased rates of suicide, and decreased survival rates.[14] Moreover, they observe there are no FDA approved pharmacotherapies for cancer-related psychological distress and the onset of clinical improvement with anti-depressant therapy is delayed, relapse rates are high, and the side effects of the anti-depressant therapy compromise treatment adherence.[15]

LONG-TERM FOLLOW-UP OF PSILOCYBIN-ASSISTED PSYCHOTHERAPY FOR PSYCHIATRIC AND EXISTENTIAL DISTRESS IN PATIENTS WITH LIFE-THREATENING CANCER.

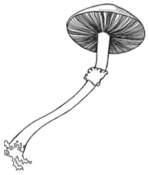
In February of 2020, another study was published that conducted a long-term follow up of 15 participants involved in the NYU study (parent study)[16] who were still alive and agreed to be

participate.[17] The study was an analysis of self-reported symptomology of those participants. Two follow-ups were conducted at an average of 3.2 and 4.5 years following the parent study. The results of this study showed there were sustained reductions in anxiety, depression, hopelessness, demoralization, and death at the first and second follow ups.

At the second follow up (approximately 4.5 years after the parent study), roughly 60-80% of the participants met the criteria for clinically significant antidepressant or anxiolytic responses. The majority (71-100%) of the participants attributed positive life changes to their psilocybin sessions and rated their psilocybin experience among the most personally meaningful and spiritually significant experiences of their lives. The study's authors concluded these findings suggested psilocybin therapy has potential to promote long-term relief from psychiatric distress caused by cancer!

4

PSILOCYBIN'S EFFECTS IN PATIENTS WITH DEPRESSION



This chapter examines psilocybin's ability to treat depressive disorders. Depression affects hundreds of millions of people worldwide and is the leading contributor to the global burden of disease.[1] Depression alone, costs the United States approximately $200 billion annually.[2] Antidepressants and cognitive behavior therapy, while effective for some, does not elicit a response in approximately 20% of patients, and many of those who do not respond eventually relapse.[3] As we will see, the vast majority of psilocybin-depression studies have centered around patients with treatment resistant depression. While there is no consensus, the most common definition for treatment resistant depression for major depressive disorder requires a minimum of two prior treatment failures and confirmation of adequate dose and duration.[4] There are currently two "breakthrough" Phase II clinical trials underway which are testing psilocybin's effectiveness at treating major depressive disorder and treatment resistant depression. Considering the results from the studies examined herein and the "breakthrough" designation received by two of the current Phase II trials, it is my humble opinion that

psilocybin treatment for depression will be a reality within the next five years.

PSILOCYBIN WITH PSYCHOLOGICAL SUPPORT FOR TREATMENT-RESISTANT DEPRESSION: AN OPEN LABEL FEASIBILITY STUDY.

The leading researchers in the area of psilocybin and depression are Robin L. Carhart-Harris and his team at Imperial College London. The psilocybin research team at Imperial College has focused on psilocybin's effects on depression and the brain. Carhart-Harris's first study regarding psilocybin and treatment resistant depression was published in 2016.[5]

The main objective of the underlying clinical trial was to optimize the protocol for the administration of oral psilocybin in patients with treatment resistant depression, while gaining an initial impression of treatment efficacy. At the outset, the study's authors note that modern trials have shown psychedelics reduce anxious,[6] depressive,[7] and obsessive-compulsive symptoms,[8] as well as substance abuse or addictive behaviors,[9] for months at a time with as little as one or two dosing sessions. Moreover, they point out that historical and modern evidence supports the view, that when psychedelics are administered in a controlled environment with appropriate support, they have a favorable safety profile.[10]

The underlying clinical trial was an open label[11] feasibility trial involving 12 participants.[12] Each participant received two sperate doses of psilocybin, one 10-milligram dose and one 25-milligram dose, seven days apart. The 10-milligram dose was considered a "safety" dose which was administered prior to the 25-milligram treatment dose. Once participants were properly screened and admitted into the trial, they were given the opportunity to meet with two clinical psychiatrists who would support them throughout. Eligible participants then attended a

subsequent visit involving an fMRI session which lasted approximately an hour. This was then followed by an extensive preparatory session with their assigned clinical psychiatrists.

After the preparatory sessions, participants attended two separate psilocybin dosing sessions seven days apart. After the high dose session (25 mg), participants returned the next day for another fMRI scanning session and afterwards completed interim questionnaires regarding their depressive symptoms. Next, they were invited to speak with their assigned clinical psychiatrists about their high dose psilocybin experiences.

One week after high dose psilocybin sessions, participants were again administered depressive symptom questionnaires and were provided another opportunity for debriefing with their clinical psychiatrists. Subsequent assessments of participants' clinical progress were conducted via email at weeks 2, 3, and 5. The final assessment was conducted on month 3 after the final high dose psilocybin session. The primary outcome measure for depressive symptoms was the average change in depressive symptoms from baseline to one week post high dose psilocybin session. The study's authors explain the one-week mark was chosen to gauge the primary outcome measures because prior studies of ketamine infusion for treatment resistant depression also measured at that interval.[13]

The participants reported experiencing some adverse reactions during their high dose psilocybin sessions. The most commonly reported reactions were transient anxiety during onset, transient confusion and thought disorder, mild and transient nausea, and transient headaches which tended to subside one to two days after onset. The study's authors note no prolonged psychotic episodes were observed in any of the participants.

The depressive symptom questionnaires completed on the day following the high dose psilocybin sessions showed some

reduction in depressive symptoms. The Quick Inventory of Depressive Symptoms[14] questionnaire showed depression scores were drastically reduced from baseline to both one week and three months post high dose psilocybin session, with reductions peaking at the 2-week mark. These results were confirmed by ratings of the clinical psychiatrists assigned to each participant.

All participants showed a reduction in depression severity at one week post high dose psilocybin session which lasted in the majority of participants through the third month. Eight of 12 patients (67%) achieved complete remission of depressive symptoms at one week and seven of those patients showed 50% reduction in depressive symptoms through the 3-month mark, with 5 of them showing complete remission at three months. Furthermore, both anxiety and anhedonia scores were significantly reduced at both one week and three months post high dose psilocybin session.

The study's authors note that while the results from this study are not conclusive and no strong inferences regarding psilocybin's efficacy treating depression can be drawn, further research is warranted. In regards to safety, they admit psilocybin has a low toxicity profile and is not associated with drug seeking behavior in humans or animals. Lastly, they state that spontaneous recovery from refractory depression, as seen in some of the trial participants, is rare and many participants reported having depression for most of their adult lives. This initial trial, as we will see, provided the underlying data for the series of studies that followed.

PSILOCYBIN WITH PSYCHOLOGICAL SUPPORT FOR TREATMENT-RESISTANT DEPRESSION: SIX-MONTH FOLLOW UP.

Six months following the trial participants' high-dose psilocybin sessions, the researchers at Imperial College London conducted a

follow-up on the entire 20 participant population. [15] Only 19 of the original 20 participants recruited for the trial completed all measures. The objective of this study was to report on the safety and efficacy outcomes six-months following the high dose psilocybin sessions administered as part of the original trial. At the outset, the study's authors note four separate trials have reported improvements in depressive symptoms after psilocybin-assisted psychotherapy.[16]

This study measured outcomes at 1 week, 2 weeks, 3 weeks, 5 weeks, 3 months, and 6 months post high dose psilocybin session. Depressive symptoms were significantly reduced at all six post-treatment time points relative to baseline, with the maximum effect size at 5 weeks. Of the 19 participants who completed all study measures, all showed some reduction in depression severity at the 1-week mark, which was sustained in the majority of participants for 3-5 weeks. The psychiatrist observed ratings of depressive symptoms also showed a reasonable correspondence with the self-reported QIDS questionnaire responses across the same time period.

The Beck Depressive Inventory (BDI)[17] also showed a reasonable correspondence with the QIDS self-reports of depressive symptoms, and the relationship between the two was very strong at week one. BDI scores were significantly reduced at 1 week, 3 months, and 6 months post high dose psilocybin session. Anxiety scores (STAI-T) were significantly reduced at 1 week, 3 months, and 6 months. Anhedonia scores (SHAPS) as well were significantly reduced at the same three time periods as anxiety. Both psychiatrist-observed depressive symptoms ratings (HAM-D and global functioning) were significantly reduced at 1 week post high dose psilocybin session.

Scores on the QIDS and psychiatrist-observed (HAM-D) measuring suicidality were significantly reduced at both 1 and 2

weeks post high dose psilocybin session. Sixteen of 19 patients scored 0 on the psychiatrist observed (HAM-D) suicidality ratings one week post high dose psilocybin session. Scores on genital/sexual dysfunction were significantly reduced at one week and no participants showed an increase in sexual dysfunction from baseline.

As we have seen previously with healthy individuals, mystical states during high dose psilocybin sessions tend to be the catalyst for positive changes post session. The results of this study reinforce those observations. Here, researchers examined scores on experience of unity, spiritual experience, and blissful state. When they combined these factors and analyzed the scores, they found higher scores predicted better clinical outcomes. More specifically, they found higher scores on these factors correlated with lower QIDS depressive symptoms scores at 5 weeks post high dose psilocybin session.

The researchers also collected information from participants regrading other depression treatments they received post high dose psilocybin session through month six. With the exception of one participant, no additional treatments were received within 5 weeks after the high dose psilocybin session. After the third month, six participants began courses of antidepressant medication, five received psychotherapy either shortly before or after the 3-month mark, and five participants sought and obtained psilocybin on their own accord between months 3 and 6. However, the study's authors observe that removing the five participants who acquired illicit psilocybin from the 3 and 6 month measures did not substantially alter the results.

At the six month mark, out of nine participants who showed a response to treatment at five weeks, only three had relapsed.[18] As such, the study's authors suggest these results imply psilocybin possibly protects against relapse to an equivalent

degree as daily use of antidepressant medications, as seen in prior discontinuation trials where responders either continue on an antidepressant medication or switch to a placebo.[19] In closing, they note the results of this study can be "cautiously described as 'promising,'" but if the results can be bolstered by larger and better controlled trials, that psilocybin's low toxicity, favorable side effect profile, and putative rapid and sustained antidepressant qualities could make it competitive with currently available treatments for major depression whose therapeutic actions are either delayed (SSRI's) or short-lived (ketamine).

PSILOCYBIN FOR TREATMENT-RESISTANT DEPRESSION: FMRI-MEASURED BRAIN MECHANISMS.

Carhart-Harris and his team at Imperial College London also published a study which examined fMRI imaging taken of 16 participants in the original trial.[20] In this study, researchers measured with functional magnetic resonance imaging (fMRI) cerebral blood flow (CBF) and blood oxygen-level dependent (BOLD) resting-state functional connectivity (RSFC) both before and after the participants high dose psilocybin session (25mg). The fMRI images were taken upon trial intake (baseline) and one day after the high dose psilocybin session. As the study's authors explain, the reasoning for obtaining fMRI images one day following high dose psilocybin sessions was to capture brain changes related to the so called "after glow" effect that might correspond to current mood improvements and/or longer-term prognoses. The researchers originally theorized resting state cerebral blood flow and functional connectivity would be altered post high dose psilocybin treatment and would thereby correlate with both immediate and longer-term clinical improvements.

In assessing long-term outcomes for the purposes of this study, the researchers decided to use the 5-week post high dose

psilocybin session as the endpoint because in the original study, there was a 50/50 split between those who responded and those who did not respond to the treatment yet none had gone on to receive other treatments by that time. As the study's authors explain, they chose certain select regions of the brain for examination because those particular brain regions have been previously implicated, by other studies, to be involved with depression and its treatment.[21]

The researchers calculated whole-brain cerebral blood flow both pre and post treatment and found decreases in cerebral blood flow occurred post treatment and that these decreases reached statistical significance in the left Heschl's gyrus, left precentral gyrus, left planum temporale, left superior temporal gyrus, left amygdala, right supramarginal gyrus and right parietal operculum.[22] A significant relationship was found between reductions in cerebral blood flow to the amygdala and reductions in depressive symptoms which is consistent with prior studies showing increased amygdala blood flow and metabolism in depression.[23] Once the researchers split the participant sample into responders and non-responders at five weeks, then compared cerebral blood flow, no significant differences were found.

Next, the researchers performed a seed-based resting state functional connectivity (RFC) analyses using blood oxygen-level dependent (BOLD) data. The researchers then targeted the following four areas of the brain for analysis: the subgenual anterior cingulate cortex (agACC), the ventromedial prefrontal cortex (vmPFC), the bilateral amygdala, and the bilateral parahippocampus (PH). Again, these regions were chosen for their prior implication in the pathophysiology of depression and response to treatment.[24]

Increased agACC resting state functional connectivity was found

with the posterior cingulate cortex/precuneous (PCC) post treatment but this was not correlated with reductions in depressive symptoms between the baseline fMRI scan and the scan taken one day post high dose psilocybin session, nor did it correlate with responses to treatment at week 5. Increased vmPFC resting state functional connectivity was observed with the bilateral inferior parietal cortex (ilPC) post-treatment. While this effect did not correspond to reductions in depressive symptoms between the first and second scans, it was predictive of treatment responses at week 5, with treatment responders showing significantly greater vmPFC-ilPC resting state functional connectivity increases than those who did not respond to treatment.

Decreased PH resting state functional connectivity was observed with a pre-frontal cortex cluster incorporating the lateral and medial prefrontal cortex. This effect did not correlate with a reduction in depressive symptoms between the first and second scans, but did correspond with treatment responses at 5 weeks with responders showing significantly greater PH-PFC resting state functional connectivity decreases than those who did not respond to treatment. Importantly, amygdala resting state functional connectivity was not significantly altered post treatment.

The fMRI results revealed increased default mode network (DMN), dorsal attention network (DAN), and posterior optical network (POP) resting state functional connectivity post-treatment. However, they did not correlate with depression outcomes. More specifically, the relationship between changes in default mode network resting state functional connectivity and reduced QIDS scores between the first and second fMRI scan were insignificant and were not predictive of treatment outcomes at week 5.

Due to indications from prior studies,[25] the researchers examined the possibility that the quality of acute psilocybin experience may cause post-acute changes in the brain. The researchers examined the resting state functional connectivity in the parahippocampus in relation to mystical experience scores. The parahippocampus was chosen because prior studies implicated it to be involved in mystical states.[26] What they found here was participants scoring highest on 'peak' or 'mystical' experience showed the greatest decreases in parahippocampus resting state functional connectivity in limbic (bilateral amygdala) and default mode network-related cortical regions.

The results of this study were surprising for several reasons. The changes in brain activity observed one day after high dose psilocybin sessions were very different than those that had been previously observed during the acute psychedelic state. More specifically, the acute psychedelic state observed in healthy volunteers is characterized by modular disintegration[27] and global integration[28] whereas here the researchers observed trends towards modular reintegration and minute effects on global integration/segregation post psilocybin for depression.

Prior research has focused on the involvement of the default mode network in depression.[29] Other studies found decreased default mode network functional integrity during acute psilocybin experiences. Here, researchers observed increased default mode network functional integrity one-day post high dose psilocybin session. Because prior studies have suggested that increased default mode network integrity may be a marker of depressed mood and rumination, observing decreases in depressive symptoms post psilocybin session while also observing an increase in default mode network integrity was very surprising.

The study's authors note these results indicate the effects of

psilocybin are similar to electroconvulsive therapy (ECT) in that they both have an antidepressant action in which the default mode network integrity is decreased acutely and increased or normalized post-acutely, accompanied by improvements in mood. What they propose is that psilocybin acts as a sort of 'reset' mechanism in which acute modular disintegration in the default mode network allows a subsequent re-integration and resumption of normal functioning.

INCREASED AMYGDALA RESPONSES TO EMOTIONAL FACES AFTER PSILOCYBIN FOR TREATMENT-RESISTANT DEPRESSION.

This next study used fMRI images from 19 of the 20 participants in the initial trial[30] to examine whether amygdala responses to emotional faces would be altered subsequent to high dose psilocybin sessions.[31] The study's authors note prior studies found patients with depression have heightened amygdala responses to fearful faces and there is also evidence that treatment with SSRI's reduces amygdala responses.[32] They further note the amygdala has been implicated in the pathophysiology of depression[33] as well as the action of some SSRI's[34] and psychedelics.[35]

The amygdala is a complex structure of the brain that is particularly sensitive to emotional stimuli.[36] Prior fMRI studies of clinically depressed patients has revealed amygdala hyper-sensitivity to emotional stimuli.[37] SSRI treatments have been shown to reduce the amygdala's hyper-sensitivity, both with chronic use of SSRI's and prior to the appearance of clinical improvements therewith.[38] As such, this study aimed to examine the antidepressant action of psilocybin on amygdala responses to emotional faces by measuring amygdala activity with an fMRI machine.

For this study, participants underwent balanced versions of

emotional face paradigms before and one day following their high dose psilocybin sessions. Because psilocybin has been previously associated with improved mood in the sub-acute period days after ingestion,[39] the researchers predicted that amygdala responses to emotional faces would be altered post high dose psilocybin session and furthermore, that this alteration would be related to a decrease in the severity of participants' depression. The researchers also hypothesized the nature of the acute psilocybin experience would relate to post-treatment changes in amygdala responses. Lastly, the researchers were interested in participants' reactions to fearful faces, as prior research found SSRI's reduce the amygdala's response to negative emotional stimuli.[40]

As part of this study, participants were shown faces with either fearful, happy, or neutral expressions which were selected from the Karolinska Emotional Faces set.[41] An equal number of male and female faces were selected for the study and each face was presented for 3 seconds and 5 faces of the same expression were shown in each 15 second block. The participants passively viewed the faces but were also instructed to press a button with their thumb at the presentation of each new face to confirm the participants were paying attention.

The researchers found increased amygdala responses to emotional faces one day after high dose psilocybin sessions. Post high dose psilocybin session increases in amygdala responses to fearful versus neutral faces were related to successful clinical outcomes for the participants. The study's authors note these findings are in contrast to prior studies with SSRI's and other conventional antidepressants which showed decreased amygdala response to negative emotional stimuli. They also observe that while decreased amygdala responsiveness to negative emotional stimuli under SSRI's has been proposed to be a key component of their therapeutic action, [42] this study's findings suggest that

this model does not extend to the therapeutic action of psilocybin.[43]

It has been suggested that reduced amygdala responses to negative emotional stimuli[44] and reduced behavioral response biases to negative stimuli while individuals are under the influence of conventional antidepressants[45] is evidence of a functional remediation, linked to correcting negative cognitive biases in depression. It has also been suggested that antidepressants have a more generalized effect on emotional processing, affecting not only a patient's response to emotional stimuli, but also to emotional stimuli generally.[46] Therefore, the study's authors suggest the proposition that SSRI's only effect amygdala responses to negative stimuli could be mistaken.

It is important to note that in this study, in contrast to SSRI's, there was increased amygdala responses one day post high dose psilocybin session. This suggests that participants were able to actually feel and confront their emotions as opposed to a blunting of emotional response that occurs under the influence of SSRI's. The study's authors note that most participants, post high dose psilocybin session, described a greater willingness to accept all emotions. This response was contrasted with participants' statements that previous depression treatments worked to reinforce emotional avoidance and disconnection.[47] Opposite to SSRI therapy, participants stated that psilocybin made emotional 'confrontation' more likely, and the accompanying psychological support from their assigned psychiatrists helped them achieve an emotional breakthrough and resolution.[48] Lastly, the study's authors note recent studies have suggested that overcoming challenging emotional phenomena under the influence of a psychedelic is predictive of better long-term mental health outcomes.[49]

Here, findings of increased amygdala responsiveness post high

dose psilocybin session is consistent with participants' descriptions of feeling emotionally re-connected and accepting of their emotions.[50] It is suggested that psilocybin could mediate long term positive changes and decreases in depressive symptoms by allowing patients with depression to confront their emotions and process through them, as opposed to treatment with SSRI's, where there is a blunting or muting of responses to emotional stimuli generally. As we will see later in this chapter, there is currently a Phase II clinical trial assessing the effectiveness of SSRI versus psilocybin treatment.[51] Those results should be published in the very near future.[52]

PSILOCYBIN WITH PSYCHOLOGICAL SUPPORT IMPROVES EMOTIONAL FACE RECOGNITION IN TREATMENT-RESISTANT DEPRESSION.

Using 17 of the 20 participants from the original trial,[53] this next study investigated whether psilocybin altered participants' emotional processing biases.[54] Depressed patients exhibit negative affective biases in processing static emotional face stimuli, which has been attributed to their low mood.[55] SSRI's and SNRI's (selective noradrenaline reuptake inhibitors) have been shown to correct these biases in depressed patients.[56] In healthy volunteers, these drugs produce a bias towards happy faces both acutely and after seven days of administration.[57] It is thought these neuropsychological changes underlie the clinical effects of SSRI's and SNRI's[58] and therefore determine clinical outcomes.[59]

In the real world we process emotional facial expressions dynamically,[60] as facial expressions are constantly changing and rarely static for significant amounts of time. Therefore, researchers have created a set of dynamically changing facial recognition tasks which serves to validate emotional face recognition biases in those with depression.[61] It has been

observed that depressed patients also show a negative affect bias when identifying dynamic faces;[62] and these abnormalities in dynamic facial recognition are not evident in those on antidepressants.[63] Under the acute effects of psilocybin, healthy volunteers showed an impaired ability to recognize negative but not positive or neutral faces in the 'Mind in the Eyes Task.'[64] The study's authors suggest that revising negative cognitive and emotional biases in depression could be one way in which psilocybin acts to reduce depressive symptoms.[65]

In this study, researchers used a dynamically changing facial expression task (DEER-T)[66] to investigate the impact of the psilocybin treatment on emotional processing biases in participants by having them complete the facial recognition task at baseline and then one week post high dose psilocybin session[67]. These results were then compared to those of 16 healthy control group subjects. The researchers hypothesized depressed patients would have impaired facial processing at baseline compared with healthy controls and psilocybin treatment would remediate this difference. Also, they hypothesized these changes would correlate with changes in depressive symptoms.

The DEER-T task utilizes static color photographs of six male and six female Caucasian actors taken from the NimStim Face Simulus Set.[68] These facial expressions are then morphed to create the six following dynamic emotional stimuli: happiness, neutrality, anger, sadness, fear, or disgust. The stimuli are morphed in full display over 3000 ms. Here, participants had a response button for each separate emotion being displayed and were asked to respond to the emotions as quickly and accurately as possible. Additionally, at baseline and one week post high dose psilocybin session, participants completed the QIDS-16[69] to index depression and the SHAPS[70] to index lack of enjoyment of usually pleasurable activities (anhedonia).

Prior to psilocybin treatment, participants were shown to have a global deficit in processing emotional faces as compared to healthy control subjects. This deficit was reflected in participants' longer reaction times to identify all emotional face types. However, post psilocybin treatment, participants performed just as well as healthy control subjects in reaction time to all emotional faces. Therefore, the initial deficit was remediated post high dose psilocybin session. The healthy control subjects showed no differences between the first and second tests. Therefore, the study's authors posit that improvements experienced by participants were due to the psilocybin treatment and not merely a learning effect.

Regarding depressive symptoms, researchers discovered a positive correlation between faster reaction times to all emotion and improvements in anhedonia scores. As we have seen, anhedonia is a key component of depression and is largely unresponsive to traditional antidepressant treatments.[71] Since there were no observed correlations between facial processing performance and depressive symptoms (QIDS-16), the study's authors suggest the post-treatment changes in emotional processing are selective to anhedonia. Furthermore, they note the "emotional reconnection" reported by the participants should account for the inter-related improvements in anhedonia and emotional processing post high dose psilocybin session.

QUALITY OF ACUTE PSYCHEDELIC EXPERIENCE PREDICTS THERAPEUTIC EFFICACY OF PSILOCYBIN FOR TREATMENT-RESISTANT DEPRESSION.

This next study examined whether the quality of the acute high dose psychedelic experience was indicative of long-term improvements in participants' mental health.[72] Here, researchers used data collected from all 20 participants in the original trial.[73] They hypothesized the occurrence and magnitude of Oceanic

Boundlessness and Dread Ego Dissolution would predict long term positive clinical outcomes in the trial participants. Moreover, they also hypothesized that sensory perceptual effects of the psychedelic experience would have little or no effect on positive clinical outcomes.

It is a well-established principle in psychedelic psychotherapy that the occurrence of profound and meaningful psychological experiences while under the influence of psychedelics is important to the efficacy of psychedelic treatment. Prior studies have shown that these psychedelic experiences can even be the most meaningful in a person's life.[74] Overwhelmingly, psychedelic researchers over the last fifty years have come to the inescapable conclusion that profound, psychedelic-induced psychological experiences can be predictive of subsequent psychological health.[75] These conclusions have been mirrored in recent studies with Ketamine, which found a link between the quality of the acute psychedelic experience[76], including the occurrence of mystical type experiences,[77] and subsequent positive clinical outcomes. Furthermore, past researchers have been able to study these experiences in depth and invent ratings scales used to measure the quality of the psychedelic experience.[78]

The study's authors readily admit the "mystical experience" has been a problem for mainstream psychology and mainstream science more generally. Moreover, they suggest the term "mystical" in and of itself is problematic because of its associations with the supernatural. They believe the terms' associations with the supernatural may be "obstructive or antithetical to science method and progress."[79] Therefore, the authors make sure the reader understands that when they use the term "mystical" to describe the psychedelic experience, they are only referring to the phenomenology of the experience and in no way are endorsing any associations between supernatural or

metaphysical ideas. As we will see later in this chapter, researchers have made little progress towards explaining the biological mechanisms underlying the "mystical" experience and continue to deny any existential or supernatural underpinnings.

"Mystical-type" experience measures came to fruition around 1960 and were originally developed by William Richards and Walter Pahnke, who both happened to be former pupils of Timothy Leary. Richards and Pahnke were able to develop what is known as the Mystical Experience Questionnaire, which measures six components of the psychedelic experience: sense of unity or oneness, transcendence of time and space, deeply felt positive mood, sense of awesomeness, reverence, and wonder, meaningfulness of psychological or philosophical insight, and ineffability and paradoxicality.[80] This scale has been found to be predictive of long term therapeutic outcomes in trials of psilocybin for cancer-related distress,[81] tobacco smoking,[82] and alcohol dependence.[83]

A more widely used measure is the Altered States of Consciousness Questionnaire (ASC).[84] The researchers here chose to use the ASC over the MEQ due to its broader scope and ability to capture a wide array of subjective phenomena not measured in the MEQ. According to the study's authors, this allowed them to test the specificity of the relationship between mystical-type experiences and subsequent therapeutic outcomes. They note that one of the principal measures of the ASC is "oceanic boundlessness," and many of its sub-items are embodied within the MEQ. Additionally, the researchers measured "dread of ego dissolution," which is related to acute anxiety experienced during the psychedelic experience. The goal in this study was to examine whether psilocybin-induced oceanic boundlessness and dread of ego dissolution were predictive of decreases in depression at a key endpoint; and whether the relationship between oceanic boundlessness and decreased depression were

more significant than the relationship between psilocybin's generic sensory perceptual effects and depression changes.

The ASC questionnaire was used to measure the acute subjective aspects of the psychedelic experience and was administered to participants as the high dose psilocybin session was ending, approximately 5-6 hours post ingestion. Again, the researchers hypothesized that oceanic boundlessness and dread of ego dissolution would predict clinical outcomes in participants at the five-week post high dose psilocybin session follow up.

The study results showed psilocybin-induced high oceanic boundlessness and low dread of ego dissolution predicted positive long-term clinical outcomes. Moreover, oceanic boundlessness was significantly more predictive of positive clinical outcomes than altered visual and auditory perception. The study's authors state these results suggest psilocybin's therapeutic effects are not simply pharmacological and are obviously experience dependent. Further bolstering this observation, the researchers found that dread of ego dissolution (anxiety during psychedelic experience) was predictive of less positive clinical outcomes.[85]

Despite acknowledging the role of mystical experience in mediating positive clinical outcomes, as the results of this study show, the study's authors suggest the research community should work towards a "secular and biologically-informed account" of the mystical-type experience that doesn't resort to "explaining away" or "reducing down" the core phenomenology and depth psychology involved in the psychedelic experience. To that end, they suggest the end goal for better understanding the biological mechanisms underlying the mystical experience is to "demystify" it and thereby facilitate an easier conversation about it with mainstream psychology.

EFFECTS OF PSILOCYBIN THERAPY ON PERSONALITY STRUCTURE.

This next study examined whether psilocybin with psychological support affected personality traits in patients with treatment resistant depression.[86] The study included all twenty participants in the original trial[87] and measured their personality traits at baseline and three month post high dose psilocybin session. Specifically, it aimed to explore whether psilocybin with psychological support affected participants' personality traits, whether those changes, if any, were related to the quality of the psychedelic experience, and whether the personality effects could help researchers better understand the long-lasting nature of psychedelic-assisted therapy.

The personality traits measured here were neuroticism (anxious, insecure, emotional), extraversion (sociable, optimistic, talkative), openness to experience ("openness") (curious, imaginative, creative), conscientiousness (hard-working, ambitious, persistent), and agreeableness (good-natured, cooperative, helpful); all of which are part of the NEO-PI-R instrument.[88] Regarding neuroticism and extraversion, the study's authors note that post-treatment changes in these traits have been previously linked with SSRI/SNRI-induced decrease in depression severity.[89]

From baseline to the three-month follow up, neuroticism scores significantly decreased while extraversion, openness, and conscientiousness significantly increased. For those who responded to psilocybin treatment, neuroticism scores decreased more from baseline to three-month follow up than those participants that did not respond. Conscientiousness followed the same trend, in that those participants who responded to psilocybin treatment saw larger increases in their score as opposed to those participants that did not respond. Responders

and non-responders did not differ significantly in scores of openness, agreeableness, and extraversion.

The degree of insightfulness experienced during the peak of the high dose psilocybin session significantly correlated with a reduction in neuroticism scores as well as an increase in extraversion scores. There was also a positive correlation between spiritual experience and increased extraversion scores, compared to baseline, at the three-month follow up. The study's authors note there were no correlations between any of the altered states of consciousness measures and changes in openness or conscientiousness.

Interestingly, the researchers also examined the relationship between baseline personality scores and the quality of the peak psilocybin experience of the high dose session. What they found was a borderline positive association between baseline openness and blissful state during the high dose psilocybin session. More specifically, they found openness to aesthetics and openness to fantasy were positively correlated with blissful state experienced during the high dose psilocybin session. Also, they found associations between openness to fantasy and experience of unity and spiritual experience.

Lastly, the researchers examined the correlation between baseline personality scores and participants' response to psilocybin treatment. They found participants with higher neuroticism scores at baseline showed reduced clinical improvement after the high dose psilocybin session.

In closing, the study's authors note that, to their knowledge, this was the first time that personality traits had been reported to have changed after undergoing psychedelic therapy for depression. They also pointed out the results from this study were for the most part in accord with previous trials of depressed patients undergoing SSRI/SNRI treatment for major

depression.[90] However, they also suggest the changes in openness experienced by participants in this study were not mirrored in prior SSRI/SNRI studies and therefore are likely a sperate and additional personality change that has not yet been seen with antidepressant treatment.[91]

MORE REALISTIC FORECASTING OF FUTURE LIFE EVENTS AFTER PSILOCYBIN FOR TREATMENT-RESISTANT DEPRESSION.

This next study was conducted with 15 of the 20 participants in the original trial.[92] The aim of this study was to investigate the effects of psilocybin therapy on pessimism biases in patients with treatment-resistant depression. According to the study's authors, cognitive therapy is the most widely studied and practiced psychotherapeutic intervention for major depressive disorder.[93] Moreover, the cognitive-bias model of depression posits that those with depression have an unrealistically negative perspective of themselves and the world more generally.[94] Early research indicated that people with major depressive disorder have more dysfunctional attitudes, feelings of hopelessness, negative thoughts and pessimism than healthy people.[95] More recent research has buttressed this idea by finding people with major depressive disorder exhibit pessimistic biases when predicting future life events.[96] In contrast, the study's authors also note, as we have seen, that psilocybin has been shown to increase optimism, psychological well-being, trait openness, and life satisfaction in healthy individuals.[97] Moreover, psilocybin acts upon regions of the brain that are associated with major depressive disorder.[98] Therefore, the researchers hypothesized the participants would show a significant pessimism bias that could be effectively treated with psilocybin therapy.

Again, this study involved 15 of the 20 participants in the original trial.[99] The researchers also recruited an equal number of

healthy and matched control subjects. At screening, the participants were asked to complete the Prediction of Future Life Events (POFLE)[100] task, which involved predicting 40 different life events over the following 30 days; 20 of the events desirable and 20 undesirable. The control subjects completed the same task over an equivalent time period. Thirty days after each POFLE task was completed, the researches followed up with participants to determine the accuracy of the predictions. In this study, trial participants completed the POFLE tasks at screening and one week after their second-high dose (25mg) psilocybin sessions.

Prior to the high dose psilocybin session, at baseline, trial participants gave similar probability estimates to both desirable and undesirable events. However, the study's authors note at the thirty day follow up, more desirable than undesirable events came to fruition for trial participants. Conversely, healthy control subjects gave higher probability estimates for desirable events versus undesirable events at baseline. Their probability estimates proved to be substantially accurate predictors of future life events which transpired over the ensuing thirty days. Between the two groups, trial participants predicted significantly less desirable events at baseline than healthy control subjects. However, there was no significant difference between predictions of undesirable events at baseline. The study's authors observe that trial participants incorrectly expected an equal number of desirable and undesirable life events and predicted significantly less desirable life events that health control subjects.

These results, according to the study's authors, are consistent with an unrealistic pessimism bias in patients with treatment resistant depression. Lastly, they state the results of the first thirty day follow up showed that there was no difference between the rate at which desirable and undesirable events

happened between trial participants and healthy control subjects; which again suggests a pessimism bias on behalf of trial participants, as they remained pessimistic about future life events despite encountering similar life circumstances as healthy control subjects.

Post-high dose psilocybin session, trial participants gave significantly higher probability estimates for desirable life events than undesirable life events. Moreover, trial participants reported a higher percentage of desirable life events occurring during the 30-day period following the second round of POFLE tasks. Therefore, the results show trial participants became more accurate at predicting future life events after their high dose psilocybin session.

Healthy control subjects, as they did at baseline, gave higher probability estimates for desirable life events at the second round of POFLE tasks. Their predictions did not differ between baseline POFLE tasks and the second round of POFLE tasks. Furthermore, there was no difference in the accuracy at which healthy control subjects predicted actual future life events between the two POFLE tasks. Post high dose psilocybin session, trial participants were equally as accurate as predicting future life events as the healthy control subjects.

The results of this study demonstrated trial participants were indeed unjustifiably or erroneously pessimistic at baseline and that this bias was corrected post high dose psilocybin session. Additionally, trial participants' depressive symptom scores correlated with their bias scores at baseline. No correlation was found between depressive symptoms and bias scores for healthy control subjects. The results from the second follow up showed trial participants' depressive symptoms scores were significantly related to decreases in bias scores. There was no such relationship in healthy control subjects' scores.

These findings, taken together, suggests psychologically supportive administration of psilocybin can alleviate negative cognitive biases which are characteristic of severe depression. This enables individuals with severe depression to forecast their futures more accurately, unobstructed by unrealistic pessimism.

INCREASED NATURE RELATEDNESS AND DECREASED AUTHORITARIAN POLITICAL VIEWS AFTER PSILOCYBIN FOR TREATMENT-RESISTANT DEPRESSION.

The last study in this chapter examined the effects of psilocybin therapy on nature relatedness and libertarian-authoritarian political perspective on seven participants from the original trial.[101] The trial participants' results were matched with those of seven healthy control subjects who did not undergo psilocybin therapy. The main outcome measures were collected at baseline, one-week, and 7-12 months post high dose psilocybin session.[102]

The authors of the study note psychedelic drug users have been shown to exhibit greater optimism than non-users,[103] as well as increased concern for nature, others, and the environment when compared to users of cannabis, amphetamine, or heroin.[104] Furthermore, psychedelic use has been found to positively affect an individual's sense of feeling a part of nature as opposed to feeling separated from it, which in turn leads to pro-environmental behavioral changes.[105]

In the context of this study, nature relatedness means one's subjective sense of connection with the natural environment, which is associated with lower anxiety[106] and has been shown to promote psychological wellbeing.[107] It has also been shown that interacting with the natural environment can improve mood and cognitive functioning in those with major depressive disorder.[108] Additionally, visits to greenspaces of 30 minutes or more have

been shown to reduce population prevalence of depression by approximately seven percent.[109] The study's authors suggest, that taken together, the foregoing indicates psychedelics can promote enduring changes in personality traits, attitudes, and beliefs. This assumption, they suggest, is bolstered by a recent correlation study which found that lifetime psychedelic use in the general population predicted increased nature relatedness and negatively predicted authoritarian political views, in a manner that appeared to be caused by acute and temporary "ego dissolution."[110]

The study found at one-week post high dose psilocybin session, nature relatedness significantly increased, and authoritarianism significantly decreased from baseline. At the seven to twelve-month mark, nature relatedness remained significantly increased and authoritarianism also remained significantly decreased from baseline. There was no difference in any of the measures in control subjects throughout all points in time. Also, they found that trial participants' depressive symptoms were drastically reduced at both the one week and seven to twelve-month marks. Taken together, the authors conclude the study's findings indicate that the psychological support in the context of psilocybin administration could induce sustained changes in attitudes and beliefs, which includes feeling closer to nature and less allied to authoritarian political views.

As far as authoritarian political views, the study's authors note psychedelic drug use in the sixties and seventies was associated with anti-establishment and egalitarian counter movements,[111] yet very little controlled research had been conducted regarding the correlation between the two, if any. There has been some support for a link between authoritarianism and better mental health.[112] However, they claim this study is the first controlled study to link lasting changes to political views and exposure to psychedelics.

Lastly, the study's authors end by suggesting the idea that legal drugs such as alcohol[113] and caffeine,[114] and medications such as stimulants[115] and SSRI's[116] can modify belief systems, including political perspective is a relatively new one, but they believe it is one with potentially serious implications. They wonder, considering the possibility that alcohol promotes detachment from nature[117] and that chronic stimulant use may promote an aggressive industriousness and hubris—and potential for paranoia[118] while psychedelic drugs promote a generalized sense of connectedness,[119] including greater altruism,[120] what kinds of implications that might have for our society and the policies that we have towards these various substances? They further suggest this subject might require the creation of a brand-new branch of political science which specifically focuses on the psychology and neurobiology of political perspectives![121]

CURRENT PHASE II TRIAL: PSILOCYBIN V. ESCITALOPRAM.

Currently there is an ongoing Phase II clinical trial comparing the efficacy and mechanisms of action of psilocybin with Escitalopram, an SSRI, for major depressive disorder.[122] The study is being conducted by Imperial College London where, as we have seen, the majority of research involving psilocybin and depression is being conducted. The trial began in January of 2019 and is expected to be completed in May of 2020.

This Phase II trial will be implementing fMRI imaging to study the effects of multiple psilocybin sessions versus Escitalopram every day for six weeks. The fMRI images will be compared at baseline and six weeks post psilocybin session. The trial will be randomized, double-blind, and will implement a group who will undergo multiple psilocybin sessions and compare those results against a group taking a placebo every day for six weeks and a group taking Escitalopram for six weeks. Hopefully, this study

will provide an even clearer picture on the effectiveness of psilocybin versus standard SSRI treatments.

CURRENT PHASE II TRIALS: "BREAKTHROUGH" THERAPY DESIGNATION

Currently there are two separate Phase II clinical trials examining the efficacy of psilocybin to treat major depressive disorder and treatment resistant depression. Both trials have received a "Breakthrough" designation from the FDA. "Breakthrough" therapy designation was introduced in 2012 as a way of presenting a faster route to approval for drugs that display treatment-related advantages over current options for serious or life-threatening conditions.[123] When a therapy is designated "breakthrough" the FDA offers developmental assistance to whatever organization is sponsoring the research. The designation is further considered a positive endorsement towards the veracity and social impact of a prospective treatment. Generally, the "breakthrough" designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. In order to attain this designation, it requires preliminary clinical evidence that demonstrates the drug may have at least one clinically significant endpoint over available therapy.

In October 2018, Compass Pathways, a life sciences company, received a "breakthrough" designation for its Phase II clinical trial which is examining the safety and efficacy of psilocybin in patients with treatment resistant depression.[124] This trial will involve 216 participants, will be randomized, quadruple blind, but will not utilize a placebo.[125] The trial will be experimenting with three different dosages of psilocybin, a low, medium, and high dose.[126] The effects of the three dosages on the participants depression scores will be tracked over a 12 week period.[127] The trial will be carried out at facilities across the United States,

Canada, and Europe and is set to be completed by August 2020.[128]

The other Phase II clinical trial that received a "breakthrough" designation, sponsored by the USONA Institute, is examining psilocybin's effects on major depressive disorder.[129] This trial will involve 80 participants and will be conducted at various facilities across the United States.[130] Each participant will have met the Diagnostic and Statistical Manual of Mental Disorders criteria for Major Depressive Disorder and will be randomly selected, under double blind conditions, to receive either a single 25 mg dose of psilocybin or a 100 mg dose of Niacin, which will serve as the active placebo.[131] The stated purpose of the trial is to evaluate the efficacy of a single 25mg dose of psilocybin for major depressive disorder compared to an active placebo in otherwise medically-healthy participants, assessed as the difference between groups in changes in depressive symptoms from baseline to 8 days post dosing session.[132]

As justification for the trial, the "Detailed Description" section of the trial registration document states that major depressive disorder has become a health crisis of epidemic proportions in the modern world, one in six individuals in the United States will experience an episode of major depression in his or her lifetime, and most patients with depression do not experience a complete resolution of symptoms with antidepressant treatment.[133] It goes on to say, as we have seen, there is evidence that psilocybin may have behavioral effects relevant to the treatment of depression and that recent studies also suggest that psilocybin may possess antidepressant properties.[134] This trial is expected to be completed by February 2021.[135]

PSYCHEDELIC PSYCHIATRY'S BRAVE NEW WORLD.

To end this Chapter, I would like to mention an article published in February of this year by the team at Imperial College London, which summarized the findings from all previous depression studies.[136] The authors make the observation that in most studies, psilocybin is given once, twice, or three times over the period of weeks as part of an ongoing course of psychotherapy, whereas traditional SSRI medications are given at least every day and often with little therapeutic support. They suggest the fundamental difference between psilocybin and the standard treatment is the standard treatment is like insulin to a diabetic, it suppresses symptoms much like insulin suppresses hyperglycemia. The fundamental difference between the two, they suggest, is anti-depressants protect against stressors that cause and perpetuate depression but provide little in the way of actually targeting and healing the underlying biopsychological issues; whereas *psilocybin therapy harnesses a therapeutic window whereby the effects open up the brain and allow the patient to experience insight and emotional release. If this insight and release is followed up with proper psychotherapeutic support, the patient can obtain a "healthy revision and outlook on life*."

5

PSILOCYBIN AND SUBSTANCE ABUSE DISORDERS

As we have seen in the preceding chapters, psilocybin has shown promise in treating both treatment resistant depression and end of life depression and anxiety. However, from the 1950's through the 1970's, the use of psychedelics in the treatment of alcohol and opiate dependence showed great promise.[1] Unfortunately, these early studies were not conducted with rigor and controls commensurate with standards for modern clinical research.[2] However, as we will see, researchers have begun to reexamine the effectiveness of psychedelics, specifically psilocybin, in treating various substance abuse disorders.

Substance abuse disorders are very common, however, current treatment regimes are not very effective.[3] Substance abuse disorders are defined as chronic disorders of brain reward, motivation, and memory processes that have gone awry.[4] Current treatments for substance abuse disorders include, but are not limited to: cognitive behavioral therapy, family therapy, certain medications, and twelve step and/or faith based programs.[5] Unfortunately, even while the effectiveness of current treatment

regimes continue to increase, about 50-60% of people with substance abuse disorders end up relapsing within 6-12 months after treatment.[6] Consequently, new treatments that aim to reduce cravings and subsequent substance use are needed in order to effectively treat substance abuse disorders. It has been proposed that psilocybin possesses the requisite properties to curb cravings and reduce relapse.[7]

As a former addict of 17 years, I sympathize with those suffering from substance abuse disorders. Unfortunately, I've seen over six cases in the last year of people I went to treatment with, who spent more than twenty-four consecutive months in inpatient treatment, that graduated the rehabilitation program and died from heroin overdoses within three months of being released. Could some of those lives been saved if they had access to psilocybin assisted psychotherapy? The studies examined in this chapter certainly show psilocybin holds promise in treating substance disorders. Hopefully in the future this type of treatment will be an option for those suffering from substance abuse disorders because conventional treatment, short and long term, is not enough for many addicts.

PSILOCYBIN ASSISTED TREATMENT FOR ALCOHOL DEPENDENCE: A PROOF-OF-CONCEPT STUDY

The first modern study to research psilocybin's effectiveness at treating substance abuse disorder, conducted at NYU, examined psilocybin's effects on alcohol dependence.[8] According to the National Institute on Alcohol Abuse and Alcoholism, 14.4 million adults age 18 and older has alcohol use disorder.[9] Alcohol use disorder is defined a chronic relapsing brain disease characterized by an impaired ability to stop or control alcohol use despite adverse social, occupational, or health consequences.[10] The study at NYU sought to quantify the acute

effects of psilocybin in alcohol dependent participants and provide preliminary outcomes and relevant safety data.

The study involved ten volunteers who met the DSM criteria for alcohol dependence. The participants received twelve weeks of psychotherapy which included two psilocybin sessions at weeks four and eight. Each participant had two therapists, one of which provided Motivational Enhancement Therapy, which is designed to build motivation by evoking the participant's reasons for wanting to change and strengthening the participant's skills at achieving their goals related to alcohol use. The other therapist was provided to assist the participant in preparing for and successfully integrating their psilocybin experiences.

The four weeks prior to the psilocybin treatment, there were no increases in alcohol abstinence recorded by the participants. Subsequent to the psilocybin session(s), alcohol abstinence increased significantly. Moreover, the gains in abstinence realized by the participants were maintained at follow up to 36 weeks post psilocybin session. As usual, researchers found that the quality/intensity of the psilocybin experience (which occurred at week four of the study) bore a strong correlation to the change in drinking for weeks five through eight and also bore a strong correlation to decreases in cravings and increase in abstinence self-efficiency during week five. The preliminary data obtained in this study was sufficient to warrant the Phase II clinical trial which is currently underway.

PHASE II CLINICAL TRIAL: A DOUBLE-BLIND TRIAL OF PSILOCYBIN-ASSISTED TREATMENT OF ALCOHOL DEPENDENCE

Subsequent to the 2015 study, the researchers at NYU, University of New Mexico, and Heffter Research Institute immediately began a Phase-II clinical trial.[11] The clinical trial is a multi-site, double blind, active placebo-controlled trial

consisting of 180 participants. The overarching goal of this clinical trial is to contrast the acute and persisting effects of psilocybin to those of diphenhydramine (Benadryl) in the context of outpatient alcoholism treatment. More specifically, the study will seek to accomplish the following: characterize the acute effects of various dosage amounts of psilocybin (25mg/70kg; 30mg/70kg; and 40mg/70kg) in patients that are alcohol dependent; evaluate the effect of psilocybin treatment on drinking outcomes for 32 weeks after the first psilocybin session, relative to the effects of the active placebo (diphenhydramine); test whether or not characteristics of the psilocybin sessions cause psilocybin's effects on drinking behavior; evaluate the explanatory value of changes in alcohol craving, self-efficacy, motivation, and other psychological domains in accounting for the observed experimental effect of psilocybin relative to the active placebo (diphenhydramine); and to evaluate pre-post changes in drinking in participants after they receive psilocybin in the third session.

The treatment in the double-blind period will last a total of twelve weeks, and the drug administrations during the double-blind period will occur at weeks four and eight. The dose of psilocybin and/or the active placebo will be increased each session depending on the participants reaction to the previous dose. After the double-blind period is complete, the participants will be offered an additional third psilocybin session which will be administered during an eight-hour session in an outpatient setting under close medical and psychiatric monitoring. This trial is estimated to be completed December of 2020.

CLINICAL INTERPRETATIONS OF PATIENT EXPERIENCE IN A TRIAL OF PSILOCYBIN-ASSISTED PSYCHOTHERAPY FOR ALCOHOL USE DISORDER

While the Phase II clinical trial has yet to be completed, some of the NYU researchers published a study which describes the treatment trajectories of three trial participants, in order to illustrate the range of experiences and persisting effects of psilocybin treatment.[12] More specifically, the study examined the mystical experiences of three participants and analyzed how those specific experiences effected the participants' alcohol use.

The authors of the study note that three-doses of psilocybin in the context of evidence-based addiction treatment and preparation, support, and integration of the psilocybin sessions employed in the Phase II trial, is in accord with other recent studies of hallucinogen-assisted addiction treatment. Furthermore, they note the current models are similar to the original "psychedelic-peak therapy" models employed in research and clinical practice in the 1950's through 1970's.[13]

Regarding the historical view of mystical experiences, the authors note the psychedelic therapy model held that 'peak-psychedelic' experiences were crucial for therapeutic benefit. Although a clear definition of peak psychedelic experience has never been clearly delineated, the authors note that it describes something similar to what modern researchers now call a "mystical experience." A "mystical experience" is generally characterized by being high in unity/oneness internally and with one's surroundings, insightfulness, knowledge of ultimate reality, and spiritual or religious sacredness.[14] In the authors' initial experiences with psilocybin-assisted treatment of alcohol use disorder, they observed that participants reported a wide array of psychological experiences under the influence of psilocybin that they considered to be crucial to mediating positive changes with respect to their alcohol use.

The study's authors observe that many aspects of the mystical experience reported by participants in the Phase II trial, are not captured by measures that have been formulated to gauge mystical experiences. As I will discuss in greater detail below, the mystical experiences reported by participants in the Phase II trial are highly individualized, meaning the reported mystical experiences addressed items specific to the individual. These specific items are not included on the generalized measures created to gauge mystical experiences. It is worth note the participants in this study were not unblinded for the study, meaning participants were not aware whether they received psilocybin or the active placebo for their first two dosing sessions, but are aware that they received psilocybin at the third "unblinded" session.

The first participant examined was a gentleman by the name of Mark.[15] Mark was a Caucasian male in his twenties who drank an average of twenty-two drinks a day prior to his participation in the clinical trial. During his first psilocybin session, Mark reported that it was like he had found "the Holy Grail" and that he had found the "answers to all of life's questions." In the month after the first session, Mark refrained from using alcohol and found it relatively easy to abstain because he thought very little about alcohol. During his second session, Mark's dose of psilocybin was increased per trial parameters. During that session, Mark was confronted with the harmful effects of his drinking on himself and others. He felt at one point as if he could have cried tears of joy at the realization that he was being given "a new slate." After the second session, Mark noted he felt increased motivation and drive to abstain from drinking alcohol, as well as a strong motivation to contribute to the world in a meaningful way.

Mark opted into the third "unblinded" psilocybin session. Generally, Mark described his experience as a "crash course" in

dealing with a wide array of negative emotions including regret, shame, and disappointment. By the end of the session, Mark explained that he had a feeling of "calmness, comfort, and reassurance" and stated he got exactly what he needed out of the experience. Two years after his participation in the study, Mark called the research team and stated that he had remained alcohol abstinent since his participation.

The next participant examined was an African-American man in his forties named Rob.[16] At the time of the study he was averaging four alcoholic drinks per day but had eight days abstinent leading up to the first psilocybin dosing session. During that first session, mark had trouble with abdominal pains and discomfort, was unable to vomit, and ended up just spitting into a trash can. Rob's father was an alcoholic and had died prior to his participation in the study from health complications due to his alcoholism. Rob described sensing the presence of his father during the first session and that he and his father communicated mutual forgiveness during that time. While spitting up into the trash can, Rob began to understand the bubbles in his spit as beer suds, which he took to represent the toxic effects of his drinking. He then began to understand his spit to be shame, regret, resentment, and anger. Rob declined the subsequent therapy session as he found the first extremely difficult. However, as a result of his psilocybin session, Rob reported feeling an increased urgency to start moving his life in a positive direction. To that end, Rob obtained employment and enrolled himself in school. Lastly, Rob reported that he valued the contact that he had with his dead father.

The last participant examined by the study's authors was a latin-american female in her fifties by the name of Lisa.[17] Lisa began problematic drinking in her thirties which resulted in a host of negative consequences. Lisa had previously attempted AA to no avail. At the time of the study, Lisa drank an average of three

drinks per day for twenty of the eighty-four days leading up to her enrollment in the clinical trial. During her initial psilocybin session, Lisa spent time examining her mother's neglect and abuse. She also examined negative feelings she had for herself and god. An inner voice asked God why he had left her to which God exclaimed "why are you so controlling?" After the first session, Lisa acquired a brighter mood and was less self-critical. While she did not completely discontinue drinking after this session, she reported finding herself drinking a lot less.

In her second psilocybin session, according to the trial's protocol, Lisa received an even higher dose of psilocybin. While she initially experienced some chaotic thinking, she was able to surrender control over the experience and fell into a state of peacefulness, until her thoughts completely quieted. Once her mind quieted, Lisa reported a voice telling her that she is "a perfect creation of the universe." At that moment, Lisa felt everything in existence was unified and was made of love, though a part of her was reluctant to believe this wholeheartedly. She finally came to accept the above proposition, which then propelled her into a state of profound self-acceptance and well-being.

Later, Lisa stated that "All there is is love, this is all that you are, this is all that matters." Following this second psilocybin session, Lisa reported that her self-critical thoughts had completely vanished, and alcohol had lost all its appeal. According to her, the session had illuminated how bad she had been to her body through alcohol abuse. She also found that she was able to better manage stress and that she was taking more time to take care of herself and socialize. Importantly, she found improved concentration, decreased anxiety, a spacious quality of mind, peaceful feelings, and generally she reported feeling good in her own body.

Unfortunately, due to anxiety surrounding the results of the 2016 presidential election, Lisa suffered from a lot of anxiety during her third psilocybin session. However, she reported the positive aspects of her first two sessions had endured and that alcohol was no longer problematic for her. At fifty-four weeks, Lisa reported a persistent reduction in her alcohol consumption and reduced anxiety.

A common thread seen throughout all psilocybin studies, and especially in addiction studies, is the strength of the mystical experience is always correlated with positive post-psilocybin outcomes.[18] Typically, a mystical experience is a transformative spiritual experience that often leads to immediate and everlasting positive changes. In regards to treatment for alcohol addiction, a transformative spiritual experience has long been regarded as an essential component to sobriety by the traditional Alcoholics Anonymous philosophy.[19] What is interesting is that in the Big Books of Alcoholics Anonymous [20] nearly all of the specific examples of recovery provided involve discrete and sudden experiences that resemble phenomenon of quantum change.[21] This is not to say that the individuals in those examples were using psychedelics to effectuate their spiritual experiences, but to say that discrete and sudden spiritual awakenings seem to be the most effective at fostering the kinds of positive change required to overcome an addiction.

A SIDE NOTE ON AA CO-FOUNDER BILL WILSON AND PSYCHEDELICS

[22]The use of LSD in the treatment of alcoholics caught the attention of Alcoholics Anonymous co-founder Bill Wilson. When Bill Wilson finally got sober at Towns Hospital in Manhattan in 1934, he was given a drink that contained belladonna, a hallucinogenic flower. The hallucinations Bill Wilson experienced caused him to have the spiritual/mystical

experience to which he directly attributed his sobriety. Approximately twenty years later, Bill Wilson heard about LSD and became curious about its effects. Starting on August 29, 1956, Bill Wilson went through several LSD session with Syndey Cohen and his team of therapists at the Brentwood VA Hospital in Los Angeles.

Through these sessions, Bill Wilson came to believe that LSD could cause the kind of spiritual experience necessary for alcoholics to get sober. More specifically, he believed alcoholics could use LSD to find a "power greater than" themselves that "could restore them to sanity" per step two of AA. To Bill Wilson, this was likely a groundbreaking revelation as alcoholism and atheism often goes hand in hand and Bill Wilson himself was a self-professed atheist prior to getting sober. Therefore, as I am assuming Bill Wilson thought, a substance that could put someone into contact with a power greater than themselves, could do wonders for assisting alcoholics in getting sober and working the twelve steps.

At the time he had his first LSD session, Bill Wilson had been battling both depression and his addiction to tobacco. The LSD sessions were unable to cure Bill Wilson of his tobacco addiction, but did provide some relief from his depression for some time. However, Bill Wilson did feel a renewed sense of beauty in life with stuck with him after his LSD session. As well, Bill Wilson noted his emotional reactions to things in life had improved.

Unfortunately, the other members on the fellowship board of AA did not exactly see it the same as Bill Wilson. To them, advocating the use of a mind-altering substance would fly in the face of the message of AA, as AA advocates for the total abstinence from mind-altering substances. Bill Wilson defended his use of LSD by pointing out that it had been given to hundreds

of subjects with no real adverse effects or tendency towards addiction. In the end, Bill Wilson removed himself from the governing body of AA so he would be free to pursue outside interests without giving the impression they were endorsed by AA.

PILOT STUDY OF THE 5-HT2AR AGONIST PSILOCYBIN IN THE TREATMENT OF TOBACCO ADDICTION.

The next major study, conducted by researchers at Johns Hopkins University, examined psilocybin's potential to treat addiction to tobacco.[23] At the time of the study in 2014, it was estimated that there were approximately 480,000 deaths in the U.S.[24] annually and 5 million worldwide[25] smoking-related. These numbers are expected to rise globally to 8 million deaths annually by 2030.[26] Moreover, most pharmacotherapies and behavioral interventions for smoking are not very effective, typically exhibiting a less than 35% success rate.[27] Therefore, the study's authors conducted this open-label pilot study to determine the safety and feasibility of psilocybin-facilitated smoking cessation treatment.

The study consisted of 15 psychiatrically healthy individuals that were nicotine-dependent smokers with an average of six previous lifetime attempts to quit smoking, smoked an average of 19 cigarettes per day, and had been smoking on average 31 years.[28] The study consisted of three psilocybin sessions, with the third being optional. Each participant was given a target quit date that coincided with their first psilocybin session at week five of treatment. The four weeks leading up to the target quit date, participants were provided with cognitive behavioral therapy that consisted of four weekly meetings. The participants were administered a moderate dose of psilocybin at their first session (20mg/70kg). After the first session, participants

continued weekly meetings with study staff. At week seven, participants were administered another dose of psilocybin at a higher optional dose of (30mg/70kg). Again, the higher dose at the second session was optional, and as we will see, not all participants opted for the higher dose. Also optional was the third psilocybin session at week 13.

The optional second and third doses were to give those who had not maintained abstinence after the first session another chance to quit. For those who did quit and remained abstinent, the second and third session were to provide support motivation for long-term abstinence. According to the study's authors, the support motivation approach (termed "afterglow") was ascertained in previous studies of hallucinogen-facilitated substance dependence treatment where the researchers described an extended, time-limited, post-session period associated with decreases in substance use, elevated mood and energy, decreased anxiety, and increased ability to foster close interpersonal relationships.[29] They suggest, in accordance with other prior studies, that long-term abstinence might be enhanced by including multiple sessions, which may work to extend the "afterglow" period through the period of time with greatest chance of relapse, or to increase the probability of a transformative mystical experience.[30]

Only twelve participants completed three psilocybin sessions, as three participants opted out of the third session but otherwise completed the entire study. One participant chose a moderate dose at the second session, but the other participants chose to follow the recommended ascending dosage scheme. During the 42 psilocybin sessions conducted, no clinically significant adverse events requiring physician or pharmacological intervention occurred. As is the case in most psilocybin studies, some participants experienced various degrees of anxiety and fear which were readily managed by

interpersonal support of the study staff on hand to guide the session.

Twelve out of fifteen (80%) of the participants showed seven-day point prevalence abstinence at the six-month mark. Eleven of those twelve reported quitting smoking at their target quit date which was verified by biological testing throughout the ten weeks of active treatment. Unfortunately, one participant who was verified as being abstinent through the second psilocybin session unexpectedly had to leave the country on business and was unable to complete the third psilocybin session. Three of the twelve participants had self-corrected relapses consisting of 1,4 and 48 cigarettes between the end of the 16-weeks of treatment and six-month follow-up. One participant had a relapse after 13 weeks of continuous abstinence for 14 weeks, but resumed abstinence prior to the six-month follow-up, which was biologically confirmed. Three participants tested positive for smoking at the six-month follow up and reported periods of 4, 11, and 22 days of smoking abstinence post target quit date. Those individuals resumed daily smoking at a significantly reduced rate.

The participants reported they found significant personal meaning in their psilocybin experiences. Thirteen participants rated at least one of their psilocybin sessions in the top ten most meaningful experiences of their lives; Eleven rated at least one psilocybin session amongst the top five most meaningful experiences of their lives; Thirteen reported that personal well-being and/or life satisfaction had increased substantially as a result of at least one of the psilocybin sessions.

Compared to other smoking cessation treatments, psilocybin was much more effective as 80% of the participants were abstinent at the six-month mark. The study's authors note the results were not strong enough to draw any hard conclusions due to its open

label design and consisting of a rather small sample size. However, considering that other pharmacotherapies have shown abstinence rates of 24.9% to 26.3% (bupropion) and 33.5% to 35.2% (varenicline) at the six-month mark, the study does lend some credence to the conclusion that psilocybin therapy could be much more effective.[31] Moreover, they observe that a randomized study of smoking cessation cognitive behavioral therapy (Quit for Life) only produced abstinence rates of 17.2% at the six-month mark.[32] Ultimately, they call for further investigation in the form of a randomized controlled trial.

PSILOCYBIN-OCCASIONED MYSTICAL EXPERIENCES IN THE TREATMENT OF TOBACCO ADDICTION.

Next, the research team at Johns Hopkins published a study[33] which analyzed the role of mystical experiences in mediating the results of the first tobacco study.[34] The study's authors note that prior psychedelic-addiction researchers have only speculated about the potential mechanisms of psychedelics in addiction treatment. At the biological level, past explanations have centered around the molecular and neurological actions of the drugs involving serotonergic, glutamatergic, and dopaminergic signaling, as well as local brain metabolic activity and functional connectivity among brain regions including the amygdala, thalamus, and anterior and posterior cingulate cortex.[35] However, effects of psychedelic-occasioned experiences on higher-order psychological constructs have also been implicated in mediating the potential efficacy of psychedelics in the clinical treatment context.[36] These "higher" order psychological constructs include the following: reductions in craving and anxiety, increased motivation and self-efficacy, and acute alterations in autobiographical recall and cognitive bias. The ability of psychedelics to occasion mystical, transcendent, or peak experiences has been proposed as a potential psychological

mechanism in precipitating changes in behavior and insight.[37] In measuring the quality of the mystical experiences, the researchers implemented four different measures: Hallucinogen Rating Scale,[38] Mysticism Scale,[39] States of Consciousness Questionnaire,[40] and ratings of personal meaning, spiritual significance, and well-being.

The results from the study showed higher States of Consciousness Questionnaire scores among participants that remained abstinent from smoking than those who did not remain abstinent through the six-month mark. The results also showed participants who remained abstinent through the six-month mark reported higher ratings of personal meaning, spiritual significance and impact on well-being.

Out of the 42 total psilocybin sessions conducted, thirteen of them were categorized as "complete" mystical experiences according to *a priori* criteria used in previous research.[41] Ten of the thirteen "complete" mystical experiences occurred during high dose sessions (30mg/70kg) and the other three occurred during moderate dose (20mg/70kg) sessions. Using the SOCQ scoring criteria, sixty percent of participants had a "complete" mystical experience during at least one psilocybin session. Of the three participants who were not abstinent from smoking at the six-month follow-up, one did not have a "complete" mystical experience; the second had one "complete" mystical experience; and the third had two "complete" mystical experiences. Out of the twelve participants who were abstinent at the six-month follow up, five had no "complete" mystical experience, four of them had one "complete" mystical experience, and three of them had two "complete" mystical experiences.

The results of the study show that psilocybin administered to drug dependent individuals in the context of addiction treatment can occasion "complete" mystical experiences at rates

comparable to those occasioned in healthy individuals. The study's authors again note that although no definitive conclusions can be drawn from the results of the tobacco study due to its open-label design and lack of control group; the mystical-type qualities of some of the experiences reported, as well as their personal meaning, spiritual significance, and impact on well-being were all significantly correlated with smoking cessation outcomes at the six-month mark. Moreover, they state the intensity of the psilocybin sessions did not correlate with smoking cessation treatment outcomes, which suggests to them that mystical effects of psilocybin are more determinative of long-term outcomes. In turn, this implies the intensity of a psilocybin experience does not necessarily correlate with the mysticism of the experience. Ultimately, as we have seen, the mystical quality of the psilocybin experience is the ultimate driver for positive change.

Regarding psilocybin's efficacy at treating addiction generally, *the study's authors admit the exact mechanisms of how psychedelic-occasioned mystical experiences might elicit profound changes in addictive behavior is not "well understood" though research and anecdotal reports have substantiated the occurrence of significant improvements in substance abuse after psychedelically induced mystical experiences*.[42] There have been two hypotheses advanced as to the role of mystical experiences in mediating positive changes in addictive behavior. One is that the high degree of personal meaning attributed to participants psilocybin session experiences are associated with subsequent decrease in temptation to use tobacco and the other is that it causes an increase in self-efficacy to quit smoking.[43]

Finally, the study's authors make a few great points at the end of the paper. First, they point out that the idea of a single discrete experience (such as a psilocybin-induced mystical experience) can result in sustained positive effects in an

individual's attitudes and behaviors is unusual and/or unprecedented within the modern biomedical paradigm because the normal therapeutic processes are conceptualized as gradually happening over time. The authors go on to compare the psilocybin mystical experience to the type of salient event that causes post-traumatic stress disorder, except the inverse. They posit that mystical experiences are PTSD-like in the sense they are single discrete events that can cause lasting behavioral changes, but are inverse to PTSD because the changes are positive in nature whereas the effects of an event that causes PTSD are normally detrimental.

LONG-TERM FOLLOW-UP OF PSILOCYBIN-FACILITATED SMOKING CESSATION.

The next study examined the results from a long-term follow-up with participants in the original smoking cessation study.[44] All 15 participants completed a twelve-month follow-up with study staff; however only twelve of the fifteen returned for the long-term follow-up, which was on average 30 months after the target quit date. All participants in the follow-ups provided information regarding their current smoking status and past treatment experience. At 12 months post target quit date, 10 participants (67%) were biologically confirmed as abstinent from smoking with eight of them being abstinent the entire time from their target quit date to present. At the long-term follow-up, nine of the participants (60%) were biologically confirmed as abstinent with seven of those reporting continuous abstinence since their target quit date.

Participants attributed significant personal meaning and spiritual significance to their psilocybin session at the twelve-month follow-up. Thirteen, or 86.7% of the participants rated the psilocybin experience among the top five *most personally meaningful* of their lives, and thirteen (86.7%) rating the

psilocybin experience as one of the five *most spiritually significant* experiences of their lives.

PHASE II CLINICAL TRIAL: PSILOCYBIN-FACILITATED SMOKING CESSATION TREATMENT: A PILOT STUDY.

Currently, there is a Phase II clinical trial being conducted to try and replicate the results of the first study with a larger population, controls, and other standards.[45] This trial is being spearheaded by the researchers from Johns Hopkins in conjunction with the Beckley Foundation and the Heffter Research Institute. This trial, involving 95 participants, will be randomized and open label. It is estimated to be complete by December of 2021.

The Phase II trial involves participants engaging in thirteen-weeks of cognitive behavioral therapy with a psilocybin session (30mg/70kg) on the target quit date at week five. These results will be compared with another participant population undergoing nicotine replacement therapy combined with thirteen weeks of cognitive behavioral therapy. In this case, the nicotine replacement therapy will consist of a transdermal patch which the participants will be given starting at their target quit date at week five. I am assuming the dosage of the nicotine patch will be reduced as the study progresses towards week thirteen.

What is also interesting about this trial is the inclusion of brain MRI scans of a smaller population (50 participants) of study participants throughout treatment. According to the description, MRI scans will be taken at two weeks pre-target quit date, the day following their target quit date, and those who are confirmed smoking abstinent at the three month follow up will also undergo an MRI. The brain imaging acquired during this clinical trial should give researchers more insight into the exact biological functions involved with psilocybin's role in treating addiction.

PHASE II CLINICAL TRIAL: PSILOCYBIN-FACILITATED TREATMENT FOR COCAINE USE.

There is currently a Phase II clinical trial, conducted by Dr. Peter Hendricks and his team at the University of Alabama Birmingham, aiming to evaluate the feasibility and estimate the efficacy of psilocybin-facilitated treatment for cocaine use, as well as monitor the impact of psilocybin-facilitated treatment on the use of other drugs and outcomes relevant to cocaine involvement (i.e. criminal activity). [46] The trial involves 40 participants, will be quadruple blind (participant, care provider, investigator, and outcomes assessor), and will study the effects of psilocybin at 16 and 28 weeks after administration. The psilocybin will be administered at a dosage of .36mg/kg in one eight-hour session. This trial will also utilize an active placebo (Benadryl), to be administered as a control.

The trial will compare at 16 and 28 weeks the number of participants with biochemically verified (urine testing) cocaine abstinence. What makes this trial particularly interesting is the addition of MRI brain imaging. The imaging will explore further whether changes in the brain's default mode network functional connectivity is a potential biological mechanism of psilocybin's effect.[47] The first images will be acquired after intake and the second image will be acquired approximately two days after the psilocybin session. The trial will provide preparation and integration sessions to participants in addition to counseling sessions four weeks following the psilocybin session. Long-term follow ups will be conducted at three and six-month post-psilocybin session. This trial is estimated to be competed in August 2020.

PHASE I CLINICAL TRIAL: ADJUNCTIVE EFFECTS OF PSILOCYBIN AND BUPRENORPHINE.

Approximately 21% to 29% of patients prescribed opioids for chronic pain misuse them.[48] Between 8% and 12% of those individuals develop an opioid use disorder.[49] An estimated 4% to 6% who misuse prescription opioids eventually transition to heroin.[50] About 80% of people who use heroin first misused prescription opioids.[51] Opioid overdoses increased 30% from July 2016 through September 2017 in 52 areas in 45 states.[52] The midwestern region of the U.S. saw opioid overdoses increase 70 percent from July 2016 thought September 2017.[53] Opioid overdoses in large cities increased by 54 percent in 16 states.[54] Despite the above numbers being a few years old, it is no secret that the opioid epidemic has only gotten worse over the last several years.

In the United States alone, 128 people die every day due to opiate overdoses.[55] Opiate addiction and abuse is a serious national crisis that has a negative effect on both public health and economic welfare. The Centers for Disease Control and Prevention estimates that the total economic burden of prescription opioid misuse alone is approximately $78.5 billion a year, including costs of healthcare, lost productivity, addiction treatment, and criminal justice involvement.[56] Therefore, effective treatments for opiate addiction are needed now more than ever.

Outside of the medical establishment, psychedelic use is associated with decreased risk of opioid abuse and dependence.[57] More specifically, the National Survey on Drug Use and Health found, from 2008 to 2013, that among respondents with a history of illicit opioid use, psychedelic drug use is associated with a 27 percent reduced risk of past year opioid dependence and 40 percent reduced risk of past year opioid abuse.[58] These numbers

suggest, consistent with the scientific studies on the issue, that use of psychedelics correlates with positive psychological characteristics that are effective at treating substance abuse disorders.[59]

There is currently a Phase I clinical trial examining the interaction between psilocybin and buprenorphine/naloxone (Suboxone®).[60] Burprenorphine/naloxone is used to treat opiate addiction.[61] It works by both reducing urges to use opiates and the naloxone helps to reverse the effects of opioids. Naloxone is supposed to prevent the patient from feeling the effects of opiates. The buprenorphine acts on the opiate receptors in the brain which reduces the urge to use opiates.

The Phase I trial is being conducted by the University of Wisconsin, Madison and will include a total of ten participants. This trial is an open label pilot study and will involve two psilocybin dosing session approximately four weeks apart. The trial will determine the safety of psilocybin in adult patients with opioid use disorder concurrently taking buprenorphine/naloxone (Suboxone®). Also, this trial will examine the mysticomimetical aspects of the participants' psilocybin experiences and analyze how it affects their ability to refrain from using opiates. The trial is estimated to be completed in June 2021.

6

PSILOCYBIN'S CURRENT AND FUTURE LEGAL STATUS

Psilocybin research has made considerable progress over the last ten years and has provided evidence that psilocybin has potential to successfully treat a multitude of mental illnesses, as well as increase the mental health and well-being of otherwise healthy individuals. As such, psilocybin researchers are preparing for a re-scheduling of psilocybin under the Controlled Substances Act.[1] On the other end of the spectrum, psychedelic advocates have been pushing for decriminalization measures at the state and local levels with varying degrees of success. In fact, as we will see, multiple local ordinances have been passed which decriminalize psilocybin, and in some instances, all entheogenic plant medicines. Additionally, there are at least two statewide decriminalization measures to be placed on ballots in 2020 and 2021. At the core of all legalization efforts are the scientific studies discussed in this book.

THE ABUSE POTENTIAL OF MEDICAL PSILOCYBIN ACCORDING TO THE EIGHT FACTORS OF THE CONTROLLED SUBSTANCES ACT

In 2018, the researchers at Johns Hopkins University published an article which analyzes the science of psilocybin in light of the eight scheduling factors of the Controlled Substances Act.[2] Below we will follow their analysis, which eventually concludes that psilocybin should not be placed in a schedule any more restrictive than Schedule IV. Schedule I of the Controlled Substances Act (CSA), where psilocybin currently resides, is reserved for drugs or other substances that have a high potential for abuse, no currently accepted medical use in treatment in the United States, and lack of accepted safety for use of the drug or other substance under medical supervision.[3]

While it was mixed at the time, when psilocybin was placed in Schedule I of the CSA, the science had shown it had some therapeutic benefits.[4] Indocybin® had been safely used as an addition to psychotherapy for many years prior to the passing of the CSA in 1970.[5] Societal pressures around psychedelic drugs, not lack of proven medical benefits, eventually led Sandoz to discontinue its manufacturing and marketing of Indocybin® in 1966.[6]

Despite clinical studies indicating the potential safety and efficacy of psilocybin, leading researchers in the 1960's found those studies to be limited and insufficient to support safety and efficacy claims for LSD and other hallucinogens.[7] Lack of solid claims of safety and efficacy backed by clinical studies and negative and irrational media accounts of adverse events due to psychedelic use, eventually made many public and political leaders believe the benefits of psilocybin were greatly outweighed by the risks they perceived. [8] Consequently, having failed to receive approval by the FDA for therapeutic use,

psilocybin was placed in Schedule I of the CSA, where it remains today.[9]

By being placed in Schedule I of the CSA, research into psilocybin has been and continues to be limited due to restrictions in the law. These restrictions, combined with negative public attitudes about psychedelics, have led to a complete lack of prioritization by the federal government for research funding.[10] In fact, the most significant modern studies concerning psilocybin have been privately funded.[11] Despite being a Schedule I substance, psychologists, psychiatrists, pharmacologists, and neuroscientists have remained interested in researching psilocybin over the last 50 years.[12] While Schedule I status does allow some research into psilocybin, it also creates substantial barriers to research, which is why psilocybin has been so greatly under-researched.[13]

Before psilocybin can be removed from Schedule I, it must first be approved for therapeutic use by the FDA. Once that approval takes place, the FDA will have to determine whether psilocybin will be scheduled, and if so, which schedule to place it in. To be rescheduled, psilocybin would have to be analyzed pursuant to the FDA's abuse potential assessment, which includes eight factors listed in the CSA.[14] Those eight factors are: actual or relative potential for abuse, scientific evidence of pharmacological effects, current scientific knowledge regarding the drug, history and current pattern of abuse, risk to public health, physical or physiological dependence liability, and immediate precursor of controlled substance.

FIRST FACTOR: ACTUAL OR RELATIVE POTENTIAL FOR ABUSE

Psilocybin has a very low potential for abuse. In early animal studies, psilocybin and other classis psychedelics were found to have weak reinforcing and discriminative stimulus effects,[15]

which is consistent with community-level findings that most people who have used psilocybin do not develop compulsive patterns of use; instead most individuals report only using psilocybin a few times, which is consistent with a drug of overall low abuse potential.[16] While there has never been a psilocybin abuse potential study conducted in accordance with the criteria recommended by the FDA,[17] there have been many clinical laboratory studies conducted since the 1950's which examined key measures of abuse potential.[18]

The first human studies of psilocybin's abuse potential were conducted in the late 1950's by the Addiction Research Center (ARC) of the National Institute of Mental Health, and was first published in 1959.[19] Early on it was recognized that psilocybin was very different from traditional drugs of abuse (opiates, sedatives, and stimulants) in that any abuse potential-related effects were unreliable and are dependent on multiple specific conditions such as dose, set, setting, and experiential factors.[20] Moreover, it was discovered that the predominant and most reliable effects of psilocybin (fear, anxiety, dysphoria, and physical discomfort) generally serve to limit use.[21]

Several modern (post 2000) trials have included abuse potential measures as part of the research. In one study, all four varying doses of psilocybin administered (.071, .143, .286, and .429 mg/kg), produced statistically significant increases over the placebo on the amphetamine scale and the LSD scales but not the Morphine Benzine Group scale, which is the most reliable indicator of euphoria.[22] Another study in 2015 found weak elevations in the LSD and MGB scales following dosages of .3 and .4 mg/kg.[23] However, it is theorized that elevated MGB scales found in current studies are likely related to the fact studies have gone to great lengths to reduce the probability of participants experiencing the negative aspects of the psychedelic experience by paying meticulous attention to set and setting and

ensuring close interpersonal relationships between therapists administering the psilocybin and participants.[24] As expected, these factors are intended to and likely do reduce negative effects of psilocybin that were experienced in the earlier abuse studies, where less attention was given to maximizing the positive aspects of the psilocybin experience. Therefore, the MRB scores found in these modern studies can likely be attributed to the advancements in psilocybin administration.

Most modern studies have noted instances where participants experience fear and anxiety, although these instances are usually resolved quickly by the therapist present. Fear and anxiety are effects of psilocybin that cut against a finding that it has a potential for abuse. In any event, there has never been a study to show that psilocybin has a high potential for abuse according to any measure.

SECOND FACTOR: SCIENTIFIC EVIDENCE OF ITS PHARMACOLOGICAL EFFECT

There is estimated to have been over one thousand scientific and clinical studies of classic psychedelics published through the 1960's,[25] as well as several more thousand published since that time.[26] Therefore, psilocybin and other related psychedelics' pharmacological effects have been well documented.

Psilocybin's agonist activity at the 5-hydroxytryptamine (HT)2A receptor appears to account, at least partially, for its behavioral effects.[27] Psilocybin has little affinity for dopamine D2 receptors; instead it is a substituted indolealkylamine with diverse serotonergically mediated effects.[28] However, as explained throughout this book, the biological mechanisms of action behind all of psilocybin's effects have yet to be fully discovered and/or explained, at least as it relates to the "mystical experience."[29] Psilocybin's binding to and agonist effects on the 5-HT2A serotonin receptors are associated with dilation of

pupils, reduced threshold for knee reflex, commonly increased heart rate and blood pressure, and feelings of nausea.[30] Psilocybin's effects can also include visual and/or auditory hallucinations and distortions of auditory and visual stimuli and altered temporal sense.[31] It is psilocybin's tendency to contribute to introspection and increased receptivity that contributes to its use in psychotherapy.[32]

In regards to tolerance, it has been demonstrated that repeated dosing of psilocybin diminishes its effects.[33] Physical dependence and withdrawal, which refer to adverse effects upon discontinuing a drug after repeated use, have not been documented after discontinuing the use of psilocybin.[34] While the study's authors believe the FDA might require more animal studies unless it is satisfied the proposed treatment protocols would not require daily administration of psilocybin;[35] all modern studies, if they involved multiple doses of psilocybin, have been taken in sessions at least two to four weeks apart, if not longer. Therefore, it is likely the FDA would accept those treatment protocols in lieu of further animal testing regarding physical dependence and withdrawal.

As far as toxicity is concerned, psilocybin carries a low risk of overdose toxicity by respiratory depression, cardiovascular events, or other causes of death associated with drugs of abuse such as opioids and sedatives.[36] The lethal dose (LD-50) of psilocybin in humans has been determined to be approximately 1,000 times an effective dose.[37] Theoretically, it would be impossible for someone consuming actual plant material to take a lethal dose, as the average level of psilocybin per mushroom specimen is so low. Only one case has been documented where a 24 year old female, who had received a heart transplant ten years prior due to end-stage rheumatic heart disease, experienced cardiac arrest and died after consuming psilocybin mushrooms.[38] The toxicology report indicated the woman had both psilocybin

and THC in her system.[39] Therefore, the only documented overdose death due to psilocybin occurred in a medically compromised individual.

Chronic administration of psilocybin (1.5-27 mg/day for 22 days) resulted in no chronic changes in the following metrics: total leukocyte count, absolute eosinophil count, hemoglobin, curea nitrogen, creatine, glucose, serum proteins, cholinesterage activity, serum glutamic-oxaloacetic transaminease titer, cholesterol, and EEG tracing.[40] Additionally, human administration of psilocybin resulted in no change in cortisol, prolactin, or growth hormone.[41] The only adverse physical effect noted in recent studies has been transient headaches which were dose-dependent and subsided within 24 hours of administration.[42]

The pharmacodynamics of psilocybin have been well documented throughout the years. The acute psychological effects of psilocybin are varied and are highly dose dependent, as well as dependent on the interpersonal and physical environment in which it is consumed.[43] The psychological effects of psilocybin often include, but are not limited to the following: perceptual changes (visual and sometimes synesthesia across senses), emotional changes (positive and negative), cognitive changes which can include changes in time perception, and introspective focus on personal history, life relationships and circumstances, and changes in sense of self.[44] A retrospective analysis of 409 psilocybin administrations to 261 healthy participants revealed that a few certain interpersonal factors influenced an individual's response to the psilocybin.[45] More specifically, it was found being in an emotionally excitable and active state prior to psilocybin administration, and having fewer recent psychological problems predicted a more pleasant experience with more mystical-type effects whereas high trait emotionally excitability, younger age,

and a PET imaging setting, all predicted unpleasant and anxious effects.[46]

As far as the timing of the psilocybin experience, it generally begins to take effect at approximately 30 minutes post-ingestion.[47] The effects generally peak at around 60-90 minutes post-ingestion and slowly diminish over the next 60-90 minutes[48] EKG and body temperature measures do not change significantly while under the influence of psilocybin. However, it has been found that prolactin, thyroid stimulating hormone, adrenocorticotropic hormone, and cortisol began to increase starting at around the .315mg/kg dose.[49]

As stated above, psilocybin's psychological effects are largely dose dependent and can include everything from extreme fear and anxiety to outright mystical experiences. However, more times than not, these experiences are spiritually significant and often cause sustained improvements in attitudes, mood, and behavior. Moreover, throughout all studies conducted to date, no serious adverse events have been attributed to psilocybin.[50] Therefore, any negative acute effects experienced on psilocybin are often overshadowed by persisting and positive therapeutic effects.[51]

THIRD FACTOR: CURRENT SCIENTIFIC KNOWLEDGE REGARDING DRUG

Psilocybin is a phosphate derivative of N,N-dimethyltryptamine and is usually found in concentrations varying from .1-1.5% in at least ten species of mushrooms from the *Psilocybe* genus and in some species of other genera.[52] Psilocybin mushrooms are most commonly consumed, outside of the research establishment, through consuming fresh or dry mushroom material, but sometimes are boiled into a tea or consumed in capsules.[53] Due to the wild variations in psilocybin concentrations in mushrooms, it is hard for illicit users to accurately dose the

psilocybin, whereas the studies conducted with psilocybin involve presumably accurate dosing of a synthesized powder which is consistent in concentration. Approximately 50% of orally ingested psilocybin is absorbed and distributed uniformly throughout the human body.[54] Psilocybin levels peak at about 50 minutes post ingestion and slowly decline over the next five hours.[55] The total half-life for orally ingested psilocybin is estimated to be at around 163±64 minutes.[56]

As we have seen previously, modern scientific studies have made considerable progress towards understanding the therapeutic effects of psilocybin as well as the biological mechanisms driving psilocybin's therapeutic effects.[57] Researchers have examined fMRI images and determined that psilocybin acutely alters brain network activity, including decreased connectivity in the default mode network.[58] However, there has yet to be a cogent theory advanced which attempts to explain how psilocybin's acute effects lead to long-term therapeutic benefits lasting a year or more.[59] One possible explanation is psilocybin's acute destabilization of brain networks possibly provides the opportunity to alter brain network activity in a constant fashion.[60] This theory is consistent with the findings that psychotherapy in conjunction with psilocybin helps mediate psilocybin's therapeutic effects.[61] More specifically, it has been posited that acute effects of psilocybin, which alter brain network dynamics, may set the stage for said networks to re-establish themselves in new ways after the acute effects; and psychotherapy subsequent to the acute psilocybin experience possibly plays a role in the way the brain networks re-establish themselves.[62]

More recently, it has been discovered that psilocybin has anti-inflammatory effects.[63] It is now thought that psilocybin could possibly be used to treat disorders which cause inflammation of the brain, including Parkinson's and Alzheimer's.[64] It will be

interesting to see how this area of psilocybin research progresses in the future.

FOURTH FACTOR: HISTORY AND CURRENT PATTERNS OF ABUSE

As a preliminary note, I would like to point out that the use of psilocybin and psilocybin-containing mushrooms dates back at least seven millenia and ancient use of psilocybin has always been ceremoniously. In order to ascertain the current situation, the best way to assess the history and current patterns of abuse, is to examine the results published by various national monitoring agencies that track a broad range of substance abuse related behaviors, effects, and treatment seeking.[65] These monitoring systems provide insight into the current use and patterns of behavior associated with psilocybin as well as other classic psychedelics.

The Treatment Episode Datasets (TEDS), is an annual record of substance abuse treatment admissions in the United States.[66] Estimates of treatment for psilocybin use disorder are so low that it cannot be specifically assessed, therefore it is lumped into the larger category of "hallucinogens" which includes LSD, DMT, mescaline, peyote, and other hallucinogens.[67] From 2005 to 2015, "hallucinogens" were consistently reported as the primary substance of abuse in approximately 0.1% of the drug treatment admissions for those 12 years of age and older. Overall, the TEDS data shows that "hallucinogens" constitute a very minute fraction of reports and there was no evidence of increasing trends for the relevant time period.[68]

The Drug Abuse Warning Network (DAWN) monitored drug-related emergency room admission in the United States until 2011 when it was discontinued.[69] The data collected by DAWN from 2004 to 2011, saw a small increase from .2 to .4 of all emergency room admissions. It has been suggested that,

compared with the number of admissions for "pain relievers," cocaine, and alcohol, the numbers for psilocybin are very small, and therefore should be interpreted with caution.[70] On a population basis, the number of admissions for psilocybin went from 1.0 per 100,000 population to 1.9 per 100,000 population from 2004 to 2011.

The National Survey on Drug Use and Health is an annual survey which examines substance use and mental health issues in the United States.[71] From 2009 to 2015, this survey found that lifetime use of psychedelics was consistently reported each year to be about 8.5% of all respondents age 12 and older. The low figure was 8.1%, reported in both 2011 and 2012, and the high was 8.7% reported in 2013. The 2015 figure was 8.5%.

Monitoring the Future is a survey of substance use and attitudes of secondary school students, college students, and young adults in the United States.[72] This survey, like others does not have a stand-alone category for psilocybin. Instead, it splits its hallucinogen query into two different categories: "LSD" and "hallucinogens other than LSD." From 2011 to 2016, lifetime prevalence lifetime prevalence for use of "hallucinogens other than LSD" decreased from 4.9% to 3.0%. Past year use amongst high schoolers also decreased from 3.1% in 2011 to 1.8% in 2016. Lifetime prevalence for college student decreased from 10.1% in 2006 to 6.6% in 2016. Past year use in college students decreased from 5.4% in 2006 to 3.0% in 2016. Lifetime prevalence for young adults (aged 19-28) declined from 14.9% in 2006 to 10.6% in 2016. Lastly, past year use amongst young adults has declined from 3.8% in 2006 to 3.0% in 2016. Overall, use of "hallucinogens other than LSD" decreased in the decade between 2006 and 2016.

The American Association of Poison Control Centers National Poison Data System recorded that there were approximately

5,559 cases of poisoning where psilocybin was mentioned. A mention of a substance to the poison control center means the particular substance was associated with but not necessarily the cause of the suspected poisoning. Of these calls, only one death occurred for a call associated with psilocybin. Again, whether psilocybin was the cause of death is unknown, but in any event, a death related strictly to psilocybin is highly unlikely. Regardless, the AAPCC reported a decrease in cases mentioning psilocybin from 773 reports in 2007 to 473 in 2015.[73]

The data shows a consistent decrease in psilocybin related use and/or abuse. Moreover, many of these figures are inherently unreliable as they fail to account specifically for psilocybin. Consequently, by lumping psilocybin in with other "hallucinogens," many of which are significantly more toxic than psilocybin, it is impossible to come up with hard numbers on a few of the measures cited. As far as popularity of psilocybin use and/or abuse, the numbers indicate that it is declining. Regardless, the numbers do not evidence a scenario where society should be concerned about psilocybin as other substances, many over the counter, cause exponentially more negative consequences than psilocybin.

FIFTH FACTOR: SCOPE, DURATION, AND SIGNIFICANCE OF ABUSE

Unlike other psychedelics, psilocybin is a naturally occurring substance that, as we have seen, has been used ceremoniously for thousands of years across the globe.[74] Now contrast this with the histories of cocaine, alcohol, opioids, and tobacco that have histories dating back thousands of years, but which were recognized early on as addicting and harmful to the lives of their users.[75] It was observed early on with these other substances that users developed daily habits that interfered with their social and occupational lives. Moreover, it was eventually discovered that

that abstinence from these substances was difficult to obtain and often came with withdrawal symptoms.[76] Many experts and expert organizations, including the NIDA and DEA, consider psilocybin as a drug of abuse; however, they differentiate it from drugs that carry a high risk of dependence and carry a high risk of overdose and harm.[77]

As previously stated, psilocybin's status as a Schedule I drug is clearly the product of societal misunderstanding, which was driven by sensationalized media accounts along with misinformation and misunderstandings regarding the actual risk of addiction and harms associated with psilocybin.[78] Much of the negative perception regarding psilocybin and other psychedelics was a product of the ubiquitous use of psychedelic substances outside the medical establishment, often combined with other toxic substances and in unsafe environments.[79]

The authors of the present study suggest there is scientific evidence confirming that psilocybin has been abused; and this supports regulation of psilocybin as a controlled substance.[80] However, they also state, "…the actual risk of dependence and harm associated with psilocybin has been estimated to be the lowest of all major substances of abuse and dependence over the past several decades by several expert analyses, and lines of evidence evaluated in this factor and other factors of the CSA."[81] *In 1993, a study of the abuse potential of psilocybin concluded that psilocybin carried a lower risk dependence than caffeine, and also carried the lowest risks of deaths of all major substances of abuse including cannabis.*[82] Collectively, the psilocybin research community has come to a consensus regarding the relatively low harm potential of psilocybin compared to other drugs of abuse.[83]

Psilocybin does not have a significant history of abuse. Ancient peoples used psilocybin mushrooms in ceremonial settings,

likely for highly religious/spiritual purposes. In modern times, science has discovered the healing properties of psilocybin and documented many of the biological processes underpinning psilocybin's therapeutic abilities. Across the scientific studies to date, ***the safety of psilocybin and lack of severe adverse reactions to psilocybin have been noted so many times it does not warrant citation***. Moreover, as mentioned above, psilocybin has been found by at least one study to be less addictive than caffeine. *In sum, this points to the overriding conclusion that psilocybin is safe and has little to no abuse potential*.

SIXTH FACTOR: RISK TO PUBLIC HEALTH

Risks to public health are generally measured by surveys. Especially with drugs like psilocybin, where overdose is next to impossible and toxicity to the body are minimum, the only way to really get a feel for how psilocybin is affecting the public is through surveys. One online survey inquired about psilocybin users single most psychologically or challenging experience after consuming mushrooms.[84]

Eleven percent of the respondents reported putting themselves or others at risk of physical harm. The study also found that the greater the estimated dose, duration, difficulty of the experience, lack of physical comfort, and social support were all related to increased risk of harm. Roughly three percent of the respondents reported behaving in a physically aggressive or violent manner, and the three percent also reported receiving medical help. Out of the individuals that reported that their psilocybin experience occurred more than a year before the survey, approximately eight percent reported seeking treatment for persisting psychological symptoms. Three of the respondents reported that the psilocybin experience was followed by the onset of enduring psychotic symptoms.

In contrast to psilocybin, the number of alcohol related deaths continues to increase. Approximately five years ago, in 2015, 10,000 or approximately one-third of all driving-related deaths involved alcohol.[85] Also in 2015, there were more than 2,000 alcohol overdose deaths[86] and almost 80,000 liver disease deaths.[87] Increasingly, other intoxicating substances including prescription pills are becoming involved in highway fatalities.[88] However, psilocybin and the larger category of "hallucinogens" are not following the increasing trend.[89] It has been theorized the effects of psilocybin and other hallucinogens are so strong and sometime disorienting that those under the influence are less likely to drive.[90] A more plausible explanation that has been advanced, is individuals do not typically use hallucinogens with much frequency, therefore unlike alcohol and other drugs of abuse, individuals on hallucinogens are statistically less likely to be driving under their influence.[91]

In any event, the numbers speak for themselves. Psilocybin is much safer for both the person consuming it and the general public, than alcohol and other typical drugs of abuse that lead to severe intoxication and extremely poor decision making. While the acute effects of psilocybin are very extreme and sometimes disorienting, it typically does not lead the individual partaking in psilocybin to risk their own life or the lives of others. It is worth note, the numbers related to alcohol and other drug-related fatalities are ascertained by facts gathered at the scene of the accidents and/or shortly thereafter. Unlike survey results, these numbers come with a certain degree of inherent reliability. Again, the numbers speak for themselves.

Despite the proven safety of psilocybin, many in the scientific community continue to voice concern about the safety of its users.[92] Researchers continue to voice their safety concerns, despite the fact that there is only one known death to have occurred due to psilocybin consumption. Apparently their

concerns are due to potential adverse effects of psilocybin, including but not limited to the following: panic reactions, possible precipitation of enduring psychiatric conditions, and long-lasting visual perception disturbances.[93] However, many researchers also admit that those risks can be minimized by control of dose, setting, patient selection and other factors under their control.[94] Ultimately, the majority of psilocybin researchers believe psilocybin can only be safely consumed under their supervision, as they claim to have developed a system for "safe use." It is worth noting again, in regards to "safe use," that only one death due to psilocybin consumption has ever been recorded, which was in a medically compromised individual.

The studies covered in this book reveal that psilocybin holds promise for treating depression, substance abuse, and other mental illnesses. If psilocybin were to effectively treat just ten percent of the depression and addiction cases worldwide, the financial benefit to the public would easily be into the billions of dollars. Unfortunately, the FDA did not even consider the potential public health benefits in the new drug approval process until approximately 2012.[95] However, while this may sound surprising, when one looks at the different schedules and the substances listed therein, it becomes clear that the FDA's risk/benefit analysis is anything but balanced. Drug researchers are adamant that it is very important the public health benefits be fully analyzed in the context of scheduling because it is desirable to avoid unduly restrictive scheduling which imposes barriers to potentially life-saving treatments.[96] What is troubling is that public health considerations were made in the FDA approving nicotine gum[97] and rescheduling hydrocodone plus acetaminophen products.[98]

According to researchers knowledgeable in the subject, the public health risk posed by illicit psilocybin use are lower than most Schedule II and Schedule III drugs.[99] Moreover, if as they

propose, access is restricted through pharmacies or even a central pharmacy then the public health risk would be even lower.[100]

The findings of psilocybin studies discussed in this book are consistent with outcomes reported by large surveys regarding psilocybin use by the general public. In one study, researchers tested the relationships of classic psychedelic use and psilocybin use with psychological distress and suicidality among over 190,000 adult survey participants pooled from 2008 thought 2012.[101] What the study found was that lifetime psychedelic use was associated with reduced odds of past month psychological distress, past year suicidal thinking, past year suicidal planning, and past year suicidal attempt; whereas lifetime illicit use of other drugs was strongly associated with increased odds of those outcomes. Another study that examined psychedelic use and opioid use and abuse found lifetime classic psychedelic use was associated with a reduced risk of past year opioid dependence and past year opioid abuse.[102] The study examined responses from over 44,000 illicit opioid users who completed the survey (National Survey on Drug Use and Health) from 2008 to 2013.

One of the more fascinating studies examined the effects psychedelic use on the criminal justice system.[103] The study's findings suggest that psychedelics provide protective effects for offenders in the criminal justice system that suffer from multiple diagnoses such as depression, anxiety, and drug dependence that exacerbate criminal behavior.[104] More specifically, with regards to recidivism, this study found that naturalistic "hallucinogen" use was correlated with a diminished likelihood of recidivism among over 25,000 individuals on probation and/or parole with as history of substance abuse.[105] The other study here found that naturalistic "hallucinogen" use was correlated with a reduced arrest for intimate partner violence among 302 jail inmates.[106] While the broader definition of "hallucinogen" obviously encompasses more substances than just psilocybin, the effects of

these substances are similar to psilocybin and undoubtedly some reports did involve psilocybin.

Another study of psilocybin and the criminal justice system evaluated classic psychedelic use, which included psilocybin, in relation to particular criminal behaviors. [107] The study examined the relationship between classic psychedelic (including psilocybin) use and criminal behavior in 480,000 respondents from the years 2002 through 2014 (NSDUH).[108] What they found is that lifetime psychedelic use was associated with reduced odds of past year larceny/theft, past year assault, past year property crimes (arrest), and past year violent crime. Again, while classic psychedelics were associated with a decrease in these behaviors, lifetime use of other classes of illicit drugs was associated with an increased in these behaviors. The results of this study, which included 480,000 respondents only leads to the inescapable conclusion that psilocybin (a classic psychedelic) could have a significant and positive impact on our criminal justice system if utilized properly.

The above studies show, to a significant degree of certainty, that psilocybin can not only benefit public health, but also alleviate other problem areas of society, including the criminal justice system. The effects of psilocybin, and other classic psychedelics, tend to permeate the lives of those who consume them in the proper settings. The idea that mystical experiences are religious in nature seems to be at least partially validated in the above criminality studies.

SEVENTH FACTOR: PSYCHIC OR PHYSIOLOGICAL DEPENDENCE LIABILITY

As discussed earlier in this chapter, psilocybin does not cause withdrawal symptoms as has been noted in both human and animal subjects.[109] This was also noted in a study that administered ascending dosages (.15mg/kg to .21mg/kg) of

psilocybin to 19 participants for 12 days with 13 days of monitoring post final psilocybin session.[110] Moreover, it has been observed that tolerance to psychedelics is not commonly seen because they are consumed infrequently.[111] The above study noted participants built a statistically significant tolerance to psilocybin over the course of the 12 day period.[112] However, in another study, it was noted that after several weeks tolerance to psilocybin will decrease significantly.[113] What these studies show is if one takes psilocybin repeatedly, then they will quickly build a tolerance (it will be less and less effective) and they will not experience withdrawal symptoms. Therefore, tolerance and psychical withdrawal traits of psilocybin both point to the inescapable conclusion that psilocybin is safe and not a drug of abuse!

EIGHTH FACTOR: IMMEDIATE PRECURSOR OF SUBSTANCE CONTROLLED

Psilocybin is the precursor to the active substance, psilocin, both of which are currently Schedule 1 drugs.[114]

As a result of the above analysis, psilocybin researchers strenuously advocate that psilocybin should be re-scheduled and placed into Schedule IV of the CSA.[115] In fact, they argue that Schedule IV is the absolute most restrictive schedule warranted by the scientific facts regarding psilocybin.[116] They posit the original placement of psilocybin into Schedule I was "…the result of substantial overestimation of the risk of harm and abuse potential."[117]

Schedule I drugs are reserved for those substances with a high potential for abuse, lack of therapeutic approval, and that cannot be safely used in medicine.[118] According to the study's authors, the proposition that psilocybin has a high potential for abuse is "questionable."[119] They further state the proposition that psilocybin cannot be safely used in medicine is "likely not

true."[120] Whether psilocybin has a lack of therapeutic approval is strictly up to the FDA.[121] Considering the FDA has granted "breakthrough" therapy status to two separate clinical trials,[122] it will likely grant therapeutic approval for psilocybin treatment at least as it relates to depression. Additionally, there are at least two other clinical trials examining psilocybin's effectiveness at treating addiction.[123] Whether those trials will eventually garner therapeutic approval obviously remains to be seen.

Considering the multitude of benefits provided by psilocybin therapy, which have been uncovered since the 1950's, it is my belief that placement into Schedule IV would be more than warranted, if even scheduled at all. As I will discuss below, there is another contingent of psilocybin/psychedelic advocates that are now calling for decriminalization of psilocybin both at the state and local level.

CURRENT DECRIMINALIZATION EFFORTS

In addition to those in the psilocybin research community who seek to place psilocybin into Schedule IV of the CSA, there are activist and political groups calling for the decriminalization of psilocybin at the state and local level. In fact, multiple municipalities in the United States have been successful in decriminalizing psilocybin. The decriminalization efforts have been successful so far in three jurisdictions: Oakland, California, Santa Cruz, California, and Denver, Colorado. The term "decriminalized" in this context essentially means that arrest and prosecution of individuals in possession of psilocybin is placed at the very bottom of law enforcement's priority list. All decriminalization measures need to be viewed with the understanding that psilocybin remains a Schedule I substance under federal law.[124] Therefore, while local authorities will not actively seek arrest and prosecution of those found in possession

of psilocybin, the same is not true for state and/or federal authorities.

DENVER PSILOCYBIN MUSHROOM DECRIMINALIZATION INITIATIVE

In 2019, Denver, Colorado, by a mere 2,000 vote margin, enacted Ordinance 301 which makes the personal use and personal possession of psilocybin mushrooms by persons twenty-one years of age and older the city's lowest low-enforcement priority, prohibits the city from spending resources to impose criminal penalties for the personal use and personal possession of psilocybin mushrooms by person twenty-one years of age and older, and establishes a psilocybin mushroom policy review panel to assess and report on the effects of the Ordinance.[125]

The recitals section of the Denver initiative, which cites to many of the research articles covered in this book, establishes the proposition that psilocybin is: associated with a decreased risk of opioid use and dependence, associated with a reduced risk of certain criminal behaviors, associated with reduced psychological distress and suicidality, safest of all recreational drugs, not known to cause brain damages and is non-addictive, and only accounted for 0.8% of total drug reports.[126]

Another interesting aspect of the Denver Ordinance is that it defines "Personal Possession" as, "…the possession, storage or propagation (growing) of psilocybin mushrooms by an adult for personal use, where the psilocybin mushrooms are not displayed in public; the sale of psilocybin mushrooms for renumeration is not included in the definition of personal possession and is subject to prosecution under existing state laws." Here, possession includes the propagation (growing) of psilocybin mushrooms, but very clearly excludes the sale of psilocybin mushrooms for money.[127]

In order to ensure that psilocybin laws are the lowest on law-enforcement's priority list, the Ordinance clearly states, "…no department, agency, board, commission, officer or employee of the city, including without limitation, county court administrative and clerical employees, probation, pre-trial services and community corrections personnel, shall use any city funds or resources to assist in the enforcement of laws imposing criminal penalties for the personal use and personal possession of psilocybin mushrooms."[128] While this provision seems to ensure local law enforcement and court personnel do not arrest and/or prosecute individuals for violating psilocybin laws, one can't help but wonder what would happen if a federal court order mandated that city officials participate in the enforcement of federal psilocybin laws? As we will see later in this chapter, the proposed statewide initiative in California covers this exact scenario.

Lastly, Decriminalize Denver's website contains a section that warns of the risks of psilocybin.[129] It acknowledges that psilocybin is not without risk and that there is the potential of individuals to act in a way that is harmful to themselves and others. They advise that individuals have an experienced and attentive person present at all times while under the influence of psilocybin. It also states those who might be psychologically or physically compromised should be properly screened before engaging in psilocybin consumption. These risks and precautions are the exact ones advanced by the psilocybin research community, the only difference being the Denver initiative grants access to psilocybin to all persons over 21 years of age, whereas placement in Schedule IV would essentially restrict access to psilocybin to those who receive treatment through a licensed medical professional. Considering the breadth of the Denver initiative, it will be interesting to see the review board's report on the overall effects of the decriminalization measure!

OAKLAND AND SANTA CRUZ'S DECRIMINALIZATION ORDINANCES

In 2019, Oakland, California's city council also passed a measure very similar to Denver's ordinance.[130] One major difference between the two is Oakland's ordinance actually legalized the use and possession of all "entheogenic" plants, which in addition to psilocybin, would include the following: peyote, san pedro cactus, ayahuasca, morning glory, salvia divinorum, mescaline, dimethyltryptamine, ibogaine, etc. The resolution does not cover the commercial sale of entheogenic plants but does cover the purchasing and manufacturing of entheogenic plants. Similar to Denver's ordinance, it also instructs the City Administrator to report, within a year of passage, the community impact and benefits to the city council.

In early 2020, Santa Cruz, California's city council also voted to decriminalize "magic mushrooms" and other natural psychedelics. This measure, like Oakland's, is broader than the ordinance passed in Denver, as it includes all "natural psychedelics."

CALIFORNIA PSILOCYBIN DECRIMINALIZATION INITIATIVE 2020

There are currently two vastly different statewide initiatives being proposed in California and Oregon. The California Decriminalization Initiative 2020 is a wide-reaching and comprehensive decriminalization initiative. The introductory section to the initiative states as follows:

"Decriminalizes under state law the cultivation, manufacture, processing, production of edible products and extracts, distribution, transportation, possession, storage, consumption, and retail sale of psilocybin mushrooms and the hallucinogenic chemical compounds contained in them. Applies to individuals at least 18 years of age, and to individuals under 18 years of age

as prescribed by a doctor. Authorizes dismissal, re-sentencing, and destruction of records for psilocybin-related arrests and convictions. Summary of estimate by Legislative analyst and Director of Finance of fiscal impact on state and local governments: One-time state and local court and law enforcement costs in the tens of millions of dollars primarily related to the identification and destruction of arrest and conviction for psilocybin-related crimes. Reduced costs, not likely to exceed a few million dollars annually, to state and local governments related to enforcing psilocybin-related offenses, handling related criminal cases in the court system, and incarcerating and supervising psilocybin-related offenders. Annual state costs to regulate psilocybin businesses, ranging from minimal to the tens of millions of dollars. Some or all of these costs could eventually be partially or fully offset by fee revenue. Potential increase in state and local tax revenues, not likely to exceed a couple million dollars annually."[131]

I had the opportunity to have an in depth conversation with a gentleman, Ryan Munevar, who is associated with Decriminalize California, an organization supporting the decriminalization effort.[132] Mr. Munevar and I discussed many of the specific provisions of the Initiative, as well as general topics regarding psychedelics and legalization. He did inform me the psilocybin decriminalization movement in California has been informed by the pros and cons of the regulatory structure and taxation of legalized marijuana. According to Mr. Munevar, the initiative reflects the lessons learned from the regulatory and taxation of marijuana in California. Unfortunately, due to the impact of the COVID-19 pandemic, the Initiative will not go to popular vote this year but will be place on the ballot in 2021.

One aspect of the California initiative that is different from other

decriminalization efforts is that it lowers the age of eligibility to eighteen years old instead of twenty-one.[133] However, it does allow for those under the age of eighteen to consume psilocybin if prescribed by a doctor or a licensed therapist.[134] Mr. Munevar indicated this might be raised to 21 before the initiative is put to statewide vote, but couldn't be certain at the time we spoke.

As far as the commercial cultivation and sale of psilocybin mushrooms, the initiative proposes it be regulated no more than non-psychoactive agriculturally produced mushrooms.[135] However, it is proposed those who seek to produce psilocybin mushrooms commercially not sale to minors and submit to testing of the active ingredients for potency.[136] Other than these restrictions however, the California initiative states no regulation should be so excessive or burdensome as to make it impractical for psilocybin mushroom businesses to operate and earn a profit.[137]

The initiative also allows for research into clinical and pre-clinical therapeutic applications of psilocybin mushrooms, as well as allowing licensed healthcare providers to use psilocybin mushrooms for research and treatment purposes.[138] Psilocybin-assisted psychotherapy is also allowed by licensed practitioners and mental health professional who undergo specialized training in psilocybin-assisted therapy and obtain a specialized license to engage in the practice.[139] Furthermore, the California Department of Public Health is called upon to work with education organizations with experience in psychedelic harm reduction to develop non-binding protocols for healthcare workers engaged in psilocybin mushroom therapy and management of psilocybin mushroom therapy. [140]

Absent a court order, the initiative states that any information required to be provided to any State or local governmental agency by the initiative, or information given in connection with

any activity regulated by the initiative, will not be released to any agency of the federal government or agent of the federal government in connection with an investigation or prosecution for activities permitted under the initiative.[141] As stated above, this is a grey area that was not covered by the other ordinances passed in Oakland, Santa Cruz, and Denver. This specific measure seeks to protect California citizens, engaged in lawful conduct pursuant to the initiative, from having state or local officials participate in their investigation or prosecution for acts authorized by the initiative.

The California Initiative mandates the destruction of criminal records related to any arrest or conviction pursuant to the initiative two years after the date of arrest or conviction, except in limited circumstances.[142] Moreover, it gives those currently serving a sentence for acts covered under the purview of the initiative the right to petition the courts to have their convictions dismissed or sentences reduced.[143] Also, those who have already served their sentences are able to file an application with the trial court to have it dismissed and sealed, because the prior conviction is now legally invalid or re-designated as a misdemeanor or infraction.[144] The initiative states no violation thereof shall be considered a felony and shall not be punishable by incarceration or imprisonment.[145]

The California Psilocybin Decriminalization Initiative represents all-inclusive and wide-reaching measure aimed to completely decriminalize all activities as it relates to the consumption, propagation, and sale of psilocybin mushrooms. Unfortunately, due to COVID-19, while the measure will not reach the ballot box in 2020 I was assured that it would be up for popular vote in 2021. It is likely the results of the community impact reports in Oakland and Santa Cruz will inform many of the California voters when the Initiative goes up for vote. Of course, any decriminalization/legalization

advocate will want to examine the community impact reports in all three decriminalized municipalities, as that represents direct evidence of the impact that legal psilocybin has on communities at large. To date, I have yet to see any reports, positive or negative, regarding psilocybin's impact in decriminalized cities.

OREGON PSILOCYBIN SERVICES ACT

In addition to the California Psilocybin Decriminalization Initiative, Oregon as well has a measure being placed before voters in 2020, The Oregon Psilocybin Services Act. This act is much narrower than the California Initiative. The Oregon Psilocybin Services Act only legalizes psilocybin therapy inside regulated establishments.

In the first section of the Oregon Act, it states numerous findings which make a compelling case for passage of the Act.[146] The first section recites the following findings: Oregon has one of the highest prevalence of mental illness among adults in the nation; one in every five Oregon adults are coping with a mental health condition; the Governor declared addiction a public health crisis in the state; the Governor's budget proposed spending over $2.8 billion on mental health and behavioral health services; studies conducted nationally and internationally show that psilocybin is effective, tolerable, and safe treatment for a variety of mental health disorders; the FDA has granted "breakthrough" therapy status to psilocybin depression therapy.

The first two years that the Act is in effect is considered a "program development" period whereby the Oregon Health Authority is to:

"(a) Examine, publish, and distribute to the public available medical, psychological, and scientific studies, research and other

information relating to the safety and efficacy of psilocybin in treating mental health conditions; and,

(b) Adopt rules and regulations for the eventual implementation of a comprehensive regulatory framework that will allow persons 21 years of age and older in this state to be provided psilocybin services…"[147]

In Section 2, the Act lays out the purpose of the Act.[148] In that Section it states the purpose of the Act is to: educate people of Oregon about the safety and efficacy of psilocybin therapy for mental health conditions; reduce the prevalence of mental illness and improve the physical, mental, and social well being of all people in the state; develop a long-term strategic plan for ensuring that psilocybin services will become and remain safe, accessible, and affordable; permit persons licensed, controlled, and regulated by the state to legally manufacture psilocybin products and provide psilocybin services to persons age 21 and older; establish a comprehensive regulatory framework concerning psilocybin products and services under Oregon law.

The psilocybin therapy contemplated by the Act includes three therapeutic sessions: a preparation session, an administrative session, and an integration session.[149] This framework mirrors, to a large extent, the methods employed in the majority of clinical trials and studies examined in this book. As stated above, the act only extends to psilocybin therapy in licensed establishments and is not applicable to personal consumption outside thereof. It is worth note the Act extends to all persons over the age of 21, whether suffering from mental health problems or not. Specifically, in Section 8 it states that, "The authority may not require a client to be diagnosed with or have any particular medical condition as a condition to being provided psilocybin services."[150]

Under the Act, a "psilocybin services facilitator" is an individual that facilitates the provisions of psilocybin services in the state.[151] Essentially, these are the individuals that administer psilocybin and provide therapy services before, during, and after the psilocybin session. The requirements under the Act to qualify as a "psilocybin services provider" are scant, but the Oregon Health Authority is tasked with creating mandatory testing requirements and curriculum which would be a prerequisite to obtaining a service provider's license.

The requirements to qualify as a "psilocybin services facilitator" include, but are not limited to the following: must be 21 years of age or older, been a resident of Oregon for two years or more, have a high school diploma or equivalent, must complete an education and training course, and must pass an approved examination.[152] In no event can the Oregon Health Authority require that a "psilocybin services facilitator" possess a degree from a university, college, post-secondary institution, or other institution of higher education.[153] However, the Act does require that "psilocybin services facilitators" meet any public health and safety standards and industry best practices establishes by the Oregon Health Authority by rule.[154] The Oregon Health Authority will set the maximum concentration of psilocybin that is permitted in a single serving of a psilocybin product.[155]

The Act also contains some disqualifications for those seeking a license pursuant to the Act.[156] These disqualifications include, but are not limited to the following: in the habit of using alcoholic beverages, habit-forming drugs, or controlled substances in excess, has been convicted of violating a federal law, state law, or local ordinance if the conviction is substantially related to the fitness and ability of the applicant to lawfully carry out the activities under the license, if not of good repute and moral character.[157] As far as convictions for federal, state, or local laws, the Oregon Health Authority may not consider the

prior conviction if it is for the manufacture of psilocybin or marijuana if the conviction was more than two years prior to the date of application and the person has not been convicted more than once for the manufacture of psilocybin or marijuana.[158] The Oregon Health Authority also may not consider a prior conviction for possession of a controlled substance or marijuana if the date of conviction was more than two years prior to the date of application or the person has not been convicted more than once for the possession of a controlled substance or marijuana.[159]

In order to manufacture psilocybin, the Act's requirements are less stringent than those placed on "psilocybin service facilitators."[160] In order to manufacture psilocybin one must be 21 years of age or older, establish they are allowed to manufacture psilocybin on the premises location where the license is to be issued, and meet the qualifications in Section 15.[161] Additionally, psilocybin manufacturers must renew their license annually and must submit their products for testing.[162] The Oregon Health Authority will determine the number of servings permitted in a psilocybin product package.[163]

As far as taxation is concerned, the Act is much clearer than the California Initiative. According to the Oregon Act, only retail sales of psilocybin can be taxed[164] via a direct tax on the patient being provided the psilocybin and is 15% of the retail sales price.[165]

Finally, the Oregon Act has provisions that potentially allows for cities and counties to opt out of its provisions. Section 128 allows for the governing bodies of cities or counties to pass ordinances which opt that particular city or county out of the Act.[166] However, once the governing body passes an ordinance that opts their jurisdiction out of the Act, they must then put that ordinance up for popular vote during the following general

election.[167] Therefore, while the Act generally applies statewide, there are provisions that allow for cities and counties to opt out.

If we view psilocybin legalization efforts on a spectrum or continuum, the Oregon Act represents approximately the halfway point between the California Initiative[168] and the Schedule IV proposal of psilocybin researchers.[169] The Oregon Act is more liberal than the Schedule IV proposal in that it makes psilocybin available to all persons over the age of 21 regardless of whether they suffer from mental health issues or not. It will be interesting to see what effect the availability of psilocybin to healthy individuals has on the overall mental healthcare system. Will access to psilocybin prevent healthy individuals from getting depressed or acquiring a substance abuse disorder? The research is clear that healthy individuals do derive positive benefits from ingesting psilocybin.

While the Oregon Act does not place many requirements on the qualifications of "psilocybin services facilitators," it does require that the Oregon Health Authority create educational programs and testing requirements. There is a big movement worldwide, from my understanding, to standardize psychedelic therapy services. While it is slightly surprising the Oregon Act doesn't require any type of formal medical or psychological education or credentials as a pre-requisite to obtaining a facilitator's license, it is likely the educational and testing requirements will be onerous enough to weed out those who are not competent enough to handle administering psilocybin services.

The Oregon Act seems to represent a common-sense approach to decriminalizing psilocybin. First, the Act is likely to be palatable to voters who are either on the fence about psilocybin therapy or who might otherwise be opposed to blanket decriminalization. Next, its' two-year development period will allow the Oregon Health Authority time to further develop the specifics of the

open-ended regulations, as well as collect data and research that could further justify the Act. While the research and history of psilocybin, in my humble opinion, justify complete legalization, such a proposition is not a pill many in our society can swallow all at one time. After all, psilocybin advocates are fighting against over fifty years of soaicl conditioning by the federal government and other fear mongering individuals and entities.

Why do the research and history of psilocybin use justify complete legalization? The research has shown that psilocybin is effective at treating depression, addiction, and reduces the likelihood individuals will engage in criminal behavior and/or recidivate back into the prison system. Furthermore, psilocybin is non-addictive and has a low and almost non-existent potential for abuse. Just like most over-the-counter drugs, psilocybin does come with some risks and psilocybin is not everyone. However, as we have seen, some researchers are of the opinion that psilocybin is less addictive than caffeine.

Despite approximately 10,000 years of recorded use, there has only been one confirmed death related to psilocybin in a medically compromised individual. The number of medicinal products sold openly at the neighborhood pharmacy or convenience store have drastically higher body counts than psilocybin. I encourage anyone who is skeptical to research the number of deaths attributable to any over the counter medicine and compare it to one, the number of confirmed deaths attributable to psilocybin, the lethal dose of which is 1,000 times the effective dose and theoretically impossible to consume.

Psilocybin is not recommended to be consumed by individuals whose mental health is compromised as it can trigger psychosis and other mental conditions. However, this is no different than saying that people who have liver disease or are pregnant should not consume alcohol. Moreover, it is no different than saying that

those with asthma or lung disease should not smoke cigarettes. What is hard to understand at this juncture is why it is still legal for people to consume alcohol and cigarettes but not psilocybin? What costs are we paying as a society because our laws are so incoherent?

The research to date suggests that psilocybin could reduce healthcare costs associated with the consumption of other legal substances like tobacco and alcohol. The addiction studies make a compelling case that psilocybin can assist individuals in overcoming addictions which cost society, in the aggregate, billions of dollars a year. While substances such as tobacco and alcohol cost society, psilocybin could assist in putting those dollars back in the taxpayer's pockets. Moreover, psilocybin's ability to treat depression could lessen the burden on society, as depression is the number one cause of disability worldwide.

As far as history is concerned, ancient peoples across several continents have consumed psilocybin mushrooms as religious sacraments for thousands of years. It has been posited, perhaps convincingly, that sacred mushroom use goes back much further than what archeology can confirm.[170] In either event, there has been no notable individual or societal harm that has ever materialized due to the consumption of psilocybin. Therefore, any restrictions placed on the consumption of psilocybin should be minimal, if restricted at all.

In the United States there are several jurisdictions that have successfully decriminalized psilocybin mushrooms. While these jurisdictions are some of the most progressive in the country, it does seem that a larger and larger segment of our society is beginning to turn the corner on the issue. This seems natural, as public opinion is swaying towards more sensible regulations as the research progresses.

The California Initiative represents the least restrictive of all the

proposed decriminalization laws. Essentially, it allows for the use, sale, and propagation of psilocybin mushrooms by any individual over the age of eighteen years old. It will be interesting to see if the Initiative passes in 2021. Perhaps this will pave the way for more states to decriminalize psilocybin in the future, much like the domino effect that is still taking place over marijuana's legalization.

The Oregon Act is another measure aimed at decriminalizing psilocybin use and propagation. While it is admittedly more restrictive and controlled than California's Initiative, it represents a reasonable middle ground between outright legalization and the restrictions recommended by leading psilocybin researchers who propose psilocybin be moved from Schedule I to Schedule IV. Furthermore, the leading psilocybin researchers propose that psilocybin therapy only be administered by licensed professionals under controlled conditions with psilocybin being held in a centralized pharmacy or pharmacies. This represents the most restrictive of proposals outside of the current Schedule I situation.

It is obvious that many leading psilocybin researchers speak out of both sides of their mouths. While on the one hand they conduct and cite to research which evidences the safety and efficacy of psilocybin, on the other hand they advocate for the most restrictive of regulations. The research cited by these researchers would lead any other rational thinker to believe the least restrictive of measures would be warranted, if any measures be warranted at all. However, when asked what measures would be appropriate, those same researchers assert that placement in Schedule IV and tightly controlled dissemination of psilocybin is warranted. Many in the psychedelic community believe this viewpoint is expressed in order to protect the pecuniary interests of the companies which have funneled money into psilocybin research over the last twenty years. It has been further posited

that these companies want to see a return on their investment, which can only be done by implementing tight regulations and controlling the therapeutic supply of psilocybin in the marketplace.

In either event, we all must still be grateful for those that have devoted their time and resources developing the research. While I believe the scientific and historical evidence justifies complete legalization, I do realize a couple of salient points. First, there are millions of people in the United States and worldwide suffering from depression and addiction. Second, perhaps the only and best treatment available for many of those suffering is psilocybin therapy. Third, it is likely the FDA will grant treatment status to psilocybin in the near future, which will be tightly controlled. Lastly, this is the quickest way psilocybin therapy will become available to those who need it the most. Realistically, it will be decades before all fifty states legalize psilocybin, if ever. Therefore, I believe the Schedule IV proposal is sensible and will benefit the most people in the shortest amount of time.

The mystical psilocybin experience has been found by researchers to mediate positive changes. Yet to date, leading researchers have been unable to pinpoint its exact biological mechanisms or psychological underpinnings. My anecdotal research has revealed the mystical experience to be existential in that it defies scientific explanation and many components of the experience likely emanate from outside of the mind. While scientific researchers will never admit the mystical experience is nothing outside the purview of rational scientific explanation, many believe that if researchers keep prodding long enough, science will meet the divine! Much Love!

NOTES

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6. PSILOCYBIN'S CURRENT AND FUTURE LEGAL STATUS

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165. Oregon Psilocybin Services Act § 114(2) (Imposition of Tax on Retail Sale of Psilocybin Products).
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167. Oregon Psilocybin Services Act § 128(2) (Adoption of Ordinances; Referral to Electors for Approval).
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