Universidade de Aveiro
Ano 2014/2015
Secção Autónoma de Ciências da Saúde

PEDRO MIGUEL SÁ MACHADO

AS FRONTEIRAS DA PSICOTERAPIA PSICADÉLICA – A PSILOCIBINA COMO NOVA OPÇÃO DE TRATAMENTO

THE FRONTIERS OF PSYCHEDELIC THERAPY – PSILOCYBIN AS A NEW TREATMENT OPTION

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Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica do Professor Doutor Bruno Gago, Professor Auxiliar Convidado da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro.

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agradecimentos

As meus pais, por todo o apoio, carinho e atenção que me prestam todos os dias e pela felicidade de os ter na minha vida.

Ao Professor Doutor Bruno Gago, pela forma como acompanhou o desenrolar deste trabalho e pela sua orientação que foi um instrumento fundamental na concretização da tese. As suas palavras de incentivo, apoio e crítica construtiva, motivaram-me a tentar melhorar continuamente.

Aos meus colegas de mestrado, com os quais partilhei momentos especiais e que guardarei com afeto na memória.

palavras-chave Psilocibina, psicadélicos, psicoterapia psicadélica, alucinógenos, serotonina, LSD, ensaios clínicos, biomedicina farmacêutica.

resumo O presente trabalho propõe fornecer uma visão geral sobre o estado atual da investigação clínica utilizando psicadélicos clássicos, com especial relevo nos ensaios clínicos com a substância psilocibina que constitui o princípio ativo dos "cogumelos mágicos". Este trabalho aborda o legado deixado pela pesquisa inicial nos anos 60, mas explora em profundidade a pesquisa conduzida na última década, após várias décadas de supressão devido ao panorama político e legal, evidenciando a evolução dos ensaios clínicos de forma a cumprir os padrões aceites atualmente. A psilocibina tem sido utilizada em ensaios clínicos em conjunto com intervenção psicológica com o intuito de estabelecer a sua segurança, dose e eficácia em aliviar problemas como a ansiedade, dependência do álcool, dependência do tabaco e transtorno obsessivo-compulsivo. Os resultados da pesquisa clínica são promissores, no entanto os ensaios são de pequena escala e apresentam limitações, o que torna necessária a realização de mais e maiores ensaios clínicos para que se possa entender melhor o valor desta terapia.

keywords Psilocybin, psychedelics, psychedelic therapy, hallucinogens, serotonin, LSD, clinical studies, biopharmaceutical medicine.

abstract The current work intends to offer a global outlook of the state-of-the-art of clinical research using classic psychedelics, with a special focus on clinical studies using psilocybin, which is the active ingredient in “magic mushrooms”. This thesis approaches the legacy of the research conducted during the 60s, but goes further in depth into the research carried out during the last decade, after several decades of suppression due to the political and legal panorama, evidencing the evolution of clinical studies to comply with currently accepted standards. Psilocybin has been used in clinical studies together with psychological intervention aiming at assessing its safety, dosage and efficacy in alleviating problems such as anxiety, alcohol dependence, tobacco dependence and obsessive-compulsive disorder. The results from clinical research are promising, however, these are small-scale studies with limitations. Therefore, more and larger trials are necessary to better understand the value of this therapy.

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Abbreviations

5-HT2A – 5-Hydroxytryptamine (Serotonin) Receptor 2A

5D-ASC – Five-Dimensional Altered States of Consciousness

AMRS – Adjective Mood Rating Scale

BDI – Beck Depression Inventory

CBT – Cognitive Behavioral Therapy

DIA-X – Computerized Diagnostic System

DMT – N,N-Dimethyltryptamine

DSM-IV – Diagnostic and Statistical Manual of Mental Disorders

ECG – Electrocardiogram

HPPD – Hallucinogen Persisting Perception Disorder

ICD-10 – International Classification of Diseases

LSD – Lysergic Acid Diethylamide (Lysergsäurediethylamid)

MAPS – Multidisciplinary Association for Psychedelic Studies

MDMA – 3,4-Methylenedioxy-N-Methylamphetamine

NMDA – N-Methyl-D-Aspartate

OCD – Obsessive-Compulsive Disorder

PET – Positron Emission Tomography

POMS – Profile of Mood States

PTSD – Post Traumatic Stress Disorder

SCL-90 – Symptom Checklist-90

SEM – Standard Error of the Mean

STAI – State-Trait Anxiety Inventory

TQD – Target Quit Date

YBOCS – Yale–Brown Obsessive Compulsive Scale

Introduction

Psychedelics have been known to mankind for millennia and have been employed in spiritual practice, most commonly in shamanistic rituals, as a vehicle to come in touch with deities. The negative connotation and prohibitive laws attributed to this class of drugs that is currently evident in the western society goes back to the 1960s and 1970s as a response to the counterculture movement that embraced the usage of psychedelics in often uncontrolled and unsafe settings [1]. Lysergic Acid Diethylamide (LSD) and related drugs were increasingly associated with cultural rebellion and were popularized as drugs of abuse and producing harmful effects. The term drugs of abuse is often associated as synonymous of illegal drugs, however this connotation is erroneous as there is large evidence of many prescription and over-the-counter drugs being abused both for recreational purposes or for self-medication. Moreover, the types substances being abused by the population do not only comprise mind-altering substances but also medicines pertaining to many classes (e.g. laxatives).

Criminalization of psychedelic substances occurred, therefore, on the grounds of a political and societal response to a fragment of the society that was clashing with the conventional mainstream culture. These substances were placed in the most restrictive categories in most countries, making it very difficult for scientists to conduct research on their benefits and harms. Along with a change in policy, most funding for this area of research was cut off or greatly reduced and political issues and government agendas influenced many of the studies that followed.

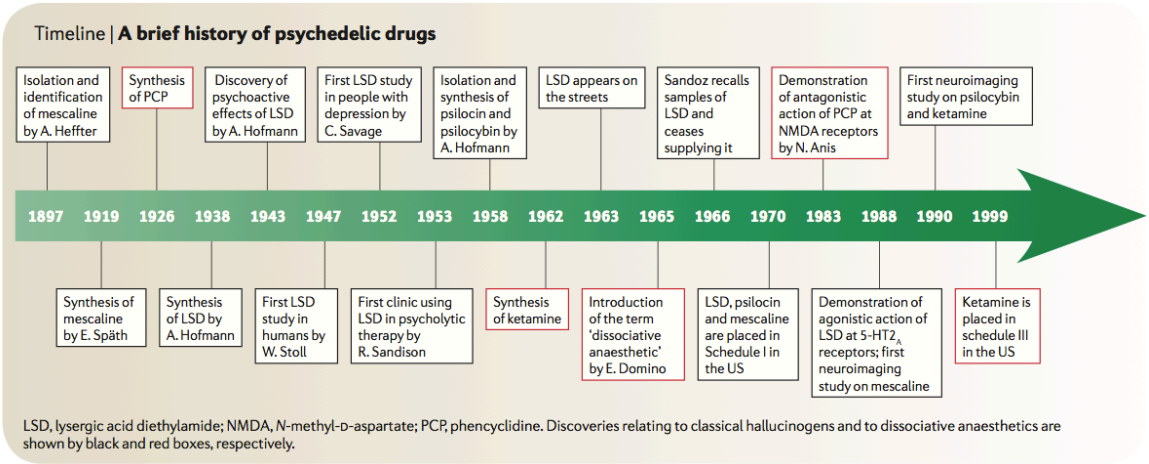
Hence, we can argue that current policies do not reflect a clear scientific rationale and are not based on evidence of pharmacological danger posed by psychedelics [2].

Psychedelics hold a fair charge of mysticism, fascination and fear, as they are known to produce altered states of consciousness, including visions, perceptual distortions, ecstasy, dissolution of self-boundaries and the experience of union with the world. Those that come from plant material have been used since ancient ages by diverse indigenous cultures, however scientific research dates

back to a quite recent past, having begun in the 1950s with the breakthrough discovery of the classical psychedelic LSD by Albert Hofmann (**Figure 1**) [3].

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is an indoleamine or serotonin-like psychedelic and the main active compound of a group of psychedelic fungi of the genus Psilocybe, also often referred to as "magic mushrooms" [4]. Psilocybin is a prodrug that is rapidly metabolized into its active metabolite psilocin. The latter is also present in the mushroom but in smaller amounts. Both psilocybin and psilocin resemble the neurotransmitter serotonin (5-hydroxytryptamine or 5-HT). Albert Hofmann was also responsible for the identification of both of these compounds in the mushrooms and invented their chemical synthesis, giving birth to the product marketed as Indocybin® that consisted of synthetic psilocybin and was used for basic pharmaceutical and therapeutic clinical research. Psychophysiological and pharmacological studies showed that the effects of psilocybin last for about 4-6 hours, whereas LSD has a larger duration of 8-12 hours. Despite the difference in duration of action, both drugs were found to have a very similar pattern of effects and psilocybin usually produced less anxiety, panic reactions, affective disturbances, and milder vegetative side effects than LSD [4].

Figure 1. Summarized timeline of the history of psychedelic drugs. Transcribed from [3].



The effects that characterize the psychedelic experience are qualitatively very varied. They are dependent upon the individual taking the drug, the expectations the individual has (this is often referred to as the "set" and characterizes the internal expectations and mindset of each individual), the external environment that comprises the physical and social environment (this is called the "setting") and finally the dose being administered.

Despite the vast amount of anecdotal reports that psychedelics can be useful in the treatment of several disorders, its therapeutic potential remains largely unexplored by scientific studies. The prohibitionist political paradigm poses major obstacles to the conduct of in-depth research on the characteristics, potential benefits and harms of psychedelics.

The neuropharmacology of psychedelics continues to be largely unknown [3]. In order to create further insight into the functioning of this class of drugs, we need more quality driven studies and it has been argued that the scientific community should be in the forefront of creating the knowledge that enables the change in drug laws, as current policy lines greatly hinder scientific exploration of both neurobiological mechanisms and clinical effects that may prove valuable in the understanding of consciousness and mental illness, and offer novel therapies [5].

We have chosen purposefully the term psychedelics to refer to this certain class of compounds as a preferred term to hallucinogens, as the latter is not accurate representation of their effects. This is because subjective effects of psychedelics are more precisely described as perceptual alterations of real stimuli rather than true hallucinations, which are not always present in the psychedelic experience. Nonetheless, "hallucinogens" remains a very popular term in the literature and can be understood interchangeably [6]. Other frequent terms used to refer to the same class of substances are "psychotomimetics" that emphasizes the model of psychosis and "entheogens" that refers to the mystical-type character of the subjective experience.

Besides classical psychedelics, several other agents have been described as provoking hallucinations, such as the psychotomimetic N-Methyl-D-Aspartate (NMDA) receptor antagonist ketamine, the stimulant 3,4-Methylenedioxy-N-Methylamphetamine (MDMA) or the dissociative opioid-κ agonist salvinorin A. However the effects induced by these drugs seem to be mediated by different

pathways and interaction with different receptors. The subjective effects as well as the pharmacological actions are distinct and discernible from those of classical psychedelics. Table 1 summarizes classical psychedelics divided in three groups according to their biochemical structure [2].

Table 1. Classical psychedelics.

Tryptamines	**Lysergamines**	**Phenethylamines**
Psilocin / Psilocybin	**LSD** (lysergic acid diethylamide)	**Mescaline**
DMT (*N,N*-dimethyltryptamine)	**LSP** (lysergic acid 3-pentylamide)	**DOI** (2,5-dimethoxy-4-iodoamphetamine)
5-MeO-DMT (5-methoxy-*N,N*-dimethyltryptamine)	**ETH-LAD** (6-ethyl-6-*nor*-lysergic acid diethylamide)	**DOB** (dimethoxybromoamphetamine) **2C-B** (4-bromo-2,5-dimethoxyphenethylamine)
DET (*N,N*-diethyltryptamine)	**AL-LAD** (6-allyl-6-*nor*-lysergic acid diethylamide)	**2C-E** (2,5-dimethoxy-4-ethylphenethylamine)
5-MeO-DALT (*N,N*-diallyl-5-methoxytryptamine)	**ALD-52** (*N*-acetyl-LSD)	**25I-NBOMe** (4-iodo-2,5-dimethoxy-N-(2-methoxybenzyl)phenethylamine)

Note: Classical psychedelics are divided into the three biochemical classes of tryptamines, lysergamines and phenethylamines. Psilocin, DMT and mescaline are naturally occurring, the rest are synthetic: this table is illustrative, and many other compounds have been discovered. Transcribed from [2].

The effects induced by psychedelics share commonality with those experienced in naturally occurring psychoses and this perspective has suggested that psychedelics can be useful research tools for the comprehension of the neuronal mechanisms inherent to psychotic disorders such as schizophrenia spectrum disorder [7-11].

Classical psychedelics are known to act primarily as agonists of serotonin 5-HT2A receptors and simulate mainly the positive symptoms of schizophrenia (hallucinations and thought disorders) [7].

It is worth mentioning that, on the other hand, dissociative anesthetics mimic the positive and the negative symptoms (social withdrawal and apathy) of

schizophrenia through antagonism of NMDA (N-methyl-d-aspartate) glutamate receptors.

Psychedelics can increase self-awareness and can lead to the resurfacing of suppressed memories and this feature raised interest among psychiatrists as a form of facilitating the psychodynamic process throughout psychotherapy sessions. An article published in 1971 elaborates on the acute adverse reactions to LSD and treats data that covers, in round figures, 49,000 LSD sessions administered to 4,300 patients, which indicates that this form of treatment was actively being used [12]. LSD and psilocybin have been reported to be beneficial in the treatment of anxiety and Obsessive-Compulsive Disorder (OCD), depression, sexual dysfunction and alcohol addiction, and to relieve pain and anxiety in patients with terminal cancer [13-15]. However, many of these older studies have serious methodological flaws and are not acceptable according to current standards. Most specifically, they lack adequate control groups and follow-up measurements and present vague criteria for therapeutic outcome, which makes it hard to justify whether the success of treatment was achieved through the therapy alone or if the drug was a contributing factor. It is also hard to conclude on the long-term efficacy [3].

The emergence of new technology that allows for brain mapping and neuroimaging, led to a new comprehension of the mechanisms of action of psychedelics in animals models, which opened doors for a revivalism of basic human research and clinical research with psychedelics [3]. This has been steadily increasing since the 1990s even if only at slow pace and a fair deal of resistance from some government bodies.

The resurgence of psychedelic human research began with the work of Rick Strassman, who explored the subjective, pharmacological and biological effects of DMT in healthy subjects [16-18].

Subsequently, investigators in the United States and Europe have conducted studies with other psychedelics. Many of these studies use psilocybin as a vehicle to research the roots of psychotic symptoms, ego disorders and hallucinations [19-21]. Others have investigated the effect of psilocybin on cognitive and visual processes [22, 23]. One study assessed the effects of varied doses of psilocybin in the perception of time [24]. Another study investigated the acute and long-term

subjective effects of psilocybin in psychedelic-naïve healthy subjects and found in a follow-up that 14 months after the experiments about two-thirds of participants still rated the experience as among the most personally meaningful and spiritually significant of their lives [25, 26].
Although there is a considerable amount of data on the physiological safety of psychedelics and that they don't produce dependence [6, 27], there is less literature on the acute tolerability and potential long-term psychological effects of psilocybin. Adding to this, a lot of the early studies on psilocybin and other psychedelics where conducted with poor or outdated methodology and don't compare results against appropriate control groups nor did they apply follow-up measures. Samples were often small and unrepresentative and for these reasons it is hard to take solid conclusions regarding their findings.

First we will discuss the historical context of psychedelic use, namely in sacramental settings by indigenous cultures. Next we will provide an outlook of the characteristics and risks of human psychedelic research and the advised guidelines to conduct research with this class of compounds. Finally we will attempt to summarize the basic human research and clinical research that has been conducted with psilocybin and the knowledge that has been gathered so far.

Methods

This work analyses data from several published clinical studies and peer-reviewed literature about psychedelics, psilocybin and psychedelic therapy.
All of the basic human research studies and the clinical studies included in this review were found through PubMed (US National Library of Medicine National Institutes of Health), using the search term: "psilocybin clinical trial".
Some of the articles used to support the introduction chapter, were found through other search terms such as: "psychedelics", "psychedelic therapy" and "hallucinogens". Adding to this, some of the articles consulted were also found

using the references of the articles that came directly out of the search performed using the aforementioned search terms.

Most of the papers that were analyzed in depth pertain to research conducted during the last decade, due to the relevance of contemporaneous research to the future of psychedelic research. The comprehensive list of clinical studies ongoing or recently published was built after consulting clinicaltrials.gov, which is a web-based platform that provides easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions.

The findings presented here are a summary of the relevant aspects of several articles in an attempt to shed some light over what has been done in terms of psychedelic research with psilocybin and what kind of outcomes and limitations have been found. Furthermore, the attempt of this work is to understand some of the paths to follow to continue conducting research with psilocybin in order to bring it to the market as an approved therapy.

Historic sacramental and healing use of psychedelics

Indigenous cultures have used naturally occurring psychedelics for over 5000 years [28]. These cultures have restricted hallucinogen use to sacramental and healing contexts, with these two often being inseparably intertwined. Such cultures regarded psychedelic plants and fungi as divine and restricted their consumption to controlled ceremonial contexts including taboos against improper use [29]. These rituals include rites of passage, or to set the occasion for divination and spiritual or physical healing. In some cases where use can be seen as more recreational without the presence of a shaman, the preparation of the psychedelic drug and the ceremony are nevertheless highly ritualized [29, 30]. Modern, urban syncretic religions, such as the União do Vegetal, which have developed in South America and have been influenced by indigenous use of

ayahuasca, also incorporate a high degree of structure and guidance into their *ayahuasca* use, which may minimize adverse reactions [27].

Despite this, the use of psychedelics by indigenous cultures cannot serve as a model for modern human research. While some of the ancient knowledge may be valuable to help understanding how to use psychedelics, such cultures also engaged in practices that are regarded as immoral and unethical in our society. For example, the Aztecs, who used psilocybin mushrooms and morning glory seeds (containing LSD-related agents), practiced human sacrifice, and even incorporated hallucinogen use into sacrificial rituals [31]. Other indigenous cultures have used psychedelics for both healing and malevolent purposes as bewitching [32].

Moreover, the risk-benefit balance that is considered acceptable by other cultures may not be acceptable by modern scientific standards. Nonetheless, many of the features of current human research have emerged from what has been learned from indigenous use, more specifically, structured use (expressed as ritual in indigenous use), restrictions on use including the need for guidance, and appreciation of hallucinogens' powerful psychological effects (expressed as reverence in indigenous use) [27].

Guidelines for safety in human psychedelic research

Human research with drugs that fall into the most restricted category of controlled substances and that are generally considered to have high addiction potential and no approved therapeutic benefits raises ethical questions that can be a barrier when trying to get approval from ethical committees and regulatory authorities. More importantly, all research conducted in humans should consider in the first place the protection, wellbeing, rights and interests of the subjects.

Fischman and Johanson, described the ethical and practical issues involved in behavioral pharmacology research that administers drugs of abuse to human volunteers. These topics range from keeping track of drugs to selecting subjects and designing ethical studies [33].

Johnson and colleagues, complemented the previous recommendations by laying down a proposal of the guidelines for conducting high-dose psychedelic research in human subjects were they addressed several domains including volunteer selection, study personnel, physical environment, preparation of volunteers, conduct of sessions, and post-session procedures [27]. We will make a detailed analysis and summary of the important domains, as they have been described in these guidelines.

The authors' guidelines are specifically written to provide guidance in the safe administration of high doses of psychedelics (e.g., ≥ 25 mg psilocybin or 200 μg LSD), but many of the recommendations are also applicable to research using lower doses. As with other drug classes, with higher doses the probability of adverse events is larger and therefore extra caution is necessary.

Selection of volunteers

The selection of volunteers should reflect the nature of the study and the specific questions being explored. For exploratory studies without therapeutic purpose, participants must be in good general health as assessed by detailed medical history, physical exam, 12-lead Electrocardiogram (ECG), blood chemistry profile, hematology, and urinalysis. Pregnant women or women in child bearing age that are not using contraception should be excluded.

Because psychedelics have moderate cardiovascular effects (increase in blood pressure and heart rate, subjects with high blood pressure should also be excluded.

Some medicines can interact with psychedelics and alter their effects. As such, individuals under the following medications should be excluded: tricyclic antidepressants lithium, serotonin reuptake inhibitors, monoamine oxidase inhibitors and the antipsychotic medication haloperidol. Some dietary supplements are also of concern, as they can act on the serotonin system, e.g. 5-hydroxytryptophan and St. John's Wort.

Possibly the most concerning problem derived from drug interaction is the serotonin syndrome, which can be a serious reaction.

Individuals with psychiatric disorders are at higher risk of suffering adverse effects, because psychedelics may trigger underlying mental issues. Therefore, individuals with a past or family history of schizophrenia or other psychotic disorders or bipolar I or II disorder should be excluded. These are the most concerning conditions but other psychiatric disorders (e.g. history of alcohol/drug dependence, major depression, and volunteers with current OCD, dysthymic disorder, panic disorder, dissociative disorder, anorexia nervosa and bulimia nervosa) or individuals with high personality traits of rigidity and emotional liability can also be more prone to adverse reactions.

Despite this, there have been recently studies where psychedelics were used in some of these conditions to assess their therapeutic potential and have shown promising results. Hence, the conditions that should be avoided when conducting basic human research in healthy volunteers can be targeted in therapeutic studies.

Study personnel

Psychedelics can produce very strong psychological experiences and the nature of the subjective effects is greatly influenced by the interpersonal connection with those around the subject. The monitors, the part of the staff who will be in the room during the sessions, should be knowledgeable about the potential adverse effects of the drug, the subjective effects that can be expected and should have good interpersonal skills to facilitate rapport. Psychologists and social workers are good fits for this role, but more important than their formal education is the aptitude to build trust and communicate with people.

It is good practice to have two monitors present during each session, so that the participant is never left alone in the case that one of the monitors has to leave the room. Another aspect that has been suggested is that having both genders present can elicit a feeling of security [32].

All of the study personnel involved that has some level of interaction with the subject can affect their experience. Some members may be involved in meeting with the participants to receive them at the study site or to administer questionnaires. Therefore investigators should work with all the members to ensure that participants are treated with courtesy and respect.

In all human research it is part of the ethical conduct to treat subjects respectfully, however in research involving psychedelics this is certainly even more of paramount importance due to the influence that human relations may play out in the outcome. As such, in this area of research, investigators are encouraged to take extra care in fostering rapport beyond what is usual in other human research.

Physical environment

The physical environment where sessions take place is very important for the wellbeing of the participants. An environment with pleasant aesthetics is likely to create a feeling of comfort and minimize psychological adverse reactions. It is better to use a room decorated in a welcoming, cozy and hospitable manner than a room resembling of a hospital or medical office setting because the latter may be suggestive of an environment that typically creates some anxiety (Figure 2).

Figure 2. The living room-like session room used in the Johns Hopkins psychedelic research studies. Transcribed from [27].

1a

1b

Likewise, having monitors wearing regular clothing is better than monitors wearing white lab coats. However, in some types of studies, like those involving brain scans, the type of setting required may be different.

Besides setting up a comfortable and relaxing environment, another aspect of crucial importance is the physical safety of the site. Perceptual changes caused by psychedelics can lead to disorientation. Thus, dangerous objects or unnecessary obstacles should be kept out of the room. Phones must be switched off and other distractions avoided. If possible, it is advised to have a restroom near the session room.

In short, aesthetics and physical safety are very important factors to consider when preparing the setting.

Preparation of subjects

In line with other human research, there should be a thorough review of the consent form. This document should explain in a straightforward language the variety of experiences that may result from psychedelic administration, including changes in perception, sense of time and space, and emotion (possibly including anxiety, fear, panic, and paranoia), the duration of action of the drug, the current knowledge of its toxicity and inform that the drug is experimental. The consent form should also mention the small risk of adverse effects that last for hours to days after the psychedelic session. These include mood disorders (such as depression), psychotic disorders, and anxiety disorders. Furthermore it should state the rare possibility of manifestation of psychoses or persisting visual perceptual abnormalities, more specifically “flashbacks” and Hallucinogen Persisting Perception Disorder (HPPD).

The next step in volunteer preparation is to conduct a series of meetings between the monitors and volunteer in order to build rapport and trust. Some of the subjects usually addressed during the meetings are childhood, romantic life, current relationships with family and friends, and the philosophical/spiritual beliefs of the volunteer. The relationship between the monitors and the volunteers should be well established by the time of the first session.

One of the meetings should take place in the room where the sessions will happen to familiarize the volunteer with the study room.

These meetings not only help building trust between the monitors and the volunteer but they also help the monitors understand better the personal history and worldview of the volunteer which is important to provide support in case of difficult experiences and personal psychological/emotional issues arising during the sessions.

It should be kept in mind that this connection built between both parts must not be used to coerce the volunteer to remain in the study. The volunteers should not feel that they are obliged to continue the study at any time.

Another affair to be approached is the study logistics (e.g. timings, dietary restrictions that may be required, drug interactions and concurrent medication). This discussion should also include thorough descriptions of study procedures, to the degree allowable by blinding issues. This comprises assessment tools, questionnaires and physiological measurements. It should be explained in depth to the volunteers the possible physical, psychological and emotional effects that they may experience.

Conduct of psychedelic administration sessions

A physician should be available during the sessions for the event of any medical complications such as high blood pressure outside of pre-established limits. In this case, medication should be promptly available as well. Usually, even high doses of psychedelics do not produce significant motor disturbance, however the monitors should be available to help the participants in case they need assistance to walk, for instance to use the restroom. This is one of the reasons why at least one of the monitors should be of the same gender as the participant.

The only people that should interact directly with the participant should be the monitors, because they are the ones with whom the participant developed trust earlier during the preparation sessions. Other study staff that is required to have

some level of intervention, like a nurse taking blood pressure measurements, should have met with the participant previously at least once.

A restroom should be near the study room. Due to the long course of action of most classic psychedelics, it is likely that the volunteer will need to use it at some point.

The participant should not be allowed to exit the research site because it may not be safe for that person to face certain everyday life situation under the influence of a drug or it may be that a participant suffering from significant psychological distress may attempt to do something dangerous.

For studies that investigate potential therapeutic effects the employment of eyeshades and headphones playing supportive music may contribute to safety by reducing the distractions of environmental stimuli and social pressures to verbally interact with research staff.

After the effects of the drug have subsided, the participant should either be released into the care of a friend or family member or required to stay overnight at the research site for monitoring and should be advised not to drive that day.

Post-session procedures

The primary monitor and the participant should have post-session meetings to monitor the safety of the participant in terms of psychological stability. This is also a valuable opportunity for the participant to discuss and integrate the experience. High doses of psychedelics often elicit very strong psychological and emotional reactions and usually subjects feel the need to talk them through with someone they can trust. Given the intimate personal content of the feelings and thoughts that occurred, subjects may not feel comfortable discussing them with family members, friends or people they have no connection with. The monitors, who were present during the course of action of the drug, have a better insight on what the subject went through and are therefore the best people to provide reassurance and guidance.

This follow-up is also useful to determine the presence of any adverse effects.

Basic human research

The purpose of basic human research with psychedelics is to provide information about the acute, sub-acute and long-term subjective effects of psilocybin in healthy humans. These studies provide early data about some of the psychological and physiological effects of psilocybin in a controlled environment. They not only generate a better understanding of how humans are directly affected by the psychedelic experience, but they also allow for a better understanding of the human brain chemistry, by studying the binding to the receptors in our brain and how the interaction with certain receptors affects cognitive functions, attention, memory and working.

Basic human research lays the ground for future clinical research by establishing some of the data that is needed about key aspects such as: safety, tolerance, adverse effects and dosage.

These studies can sometimes elicit new clues about potential therapeutic applications, even though this is not their intention. Furthermore, they can be used to define exclusion and inclusion criteria, to understand the incidence and relevance of idiosyncratic reactions, to assess the appropriateness of different psychological measuring tools and tests and even to create new methodologies of rating and quantifying the psychedelic experience.

The Zurich studies

A group from the University of Zurich, carried out several studies in their research facility, from 1999 to 2008 and afterwards published a pooled analysis of their findings to enlighten about the acute, sub-acute and potential long-term subjective effects of the administration of psilocybin to healthy subjects under controlled experimental settings [4]. Their analysis was based on 8 clinical studies using a double-blind placebo-controlled within-subject design and comprises a total of 227 individual psilocybin sessions in 110 subjects. Data was treated using validated tools to investigate the various aspects of consciousness, mood, psychological and physical side effects.

Table 2. Summary of psilocybin studies by the group of researchers from the University of Zurich. Transcribed from [4].

Study description	**Psilocybin dose condition**	**Number of administered psilocybin doses**				
		Subjects receiving at least one dose of psilocybin	Very low dose (45 µg/kg)	Low dose (115-125 µg/kg)	Medium dose (215-260 µg/kg)	High dose (315 µg/kg)
1) Dose-effect study on acute psychological and physiological effects of psilocybin [34].	1) 45 µg/kg 2) 115 µg/kg 3) 215 µg/kg 4) 315 µg/kg	8	8	8	8	8
2) Acute effects of psilocybin on cognitive functions and subjective experience (publication in progress).	1) 115 µg/kg 2) 215 µg/kg 3) 315 µg/kg	16		16	16	16
3) Effects of psilocybin on brain activity using H2O-PET (publication in progress).	260 µg/kg	12			12	
4) Effects of psilocybin on prepulse inhibition of startle in healthy human volunteers [35].	1) 115 µg/kg 2) 215 µg/kg 3) 315 µg/kg	20		17	17	18
5) Effects of psilocybin on the rate and rhythmicity of perceptual rivalry alternations [36].	1) 115 µg/kg 2) 250 µg/kg	12			12	12
6) Investigation on the relationship between attention, working memory, and the serotonin 1A and 2A receptors using psilocybin and ketanserin [37].	1) 215 µg/kg 2) 215 µg/kg after ketanserin pretreatment	10			10	
7) Effects of psilocybin on visual processing: An EEG study (publication in progress).	1) 125 µg/kg 2) 250 µg/kg	21		21	18	
8) Serotonin 5-HT2A receptor dynamics in the human brain following psilocybin stimulation: A PET study (publication in progress).	250 µg/kg	11			11	
Total number of subjects		110	8	74	104	42

Testing of subjects occurred on 2 to 5 experimental days, depending on the study, and those days were separated by periods of at least 14 days, to avoid carry-over effects. Volunteers received placebo and 1 to 4 different doses of psilocybin, administrated orally in a randomized order. There was one study where subjects were pretreated with ketanserin, a 5-HT2A and placebo to evaluate the effects of this antagonist on the hallucinogenic effects of psilocybin.
The doses of psilocybin administrated were variable, ranging from 45 μg/kg to 315 μg/kg body weight, this translated to absolute doses: 2-28 mg. Before the sessions, subjects were advised to have a light breakfast. The investigators measured the blood pressure and heart rate before the sessions and monitored every hour throughout the day. The sessions ended roughly 7 hours after ingestion of the psilocybin and the principal investigator examined the subjects before letting them out and advising them not to carry on demanding work for the remainder of the day.
Recruitment of subjects was made recurring to advertising from the local universities and hospitals. Participants were asked to give written consent for their participation in the studies, after being informed through a written and oral description of the goals of the studies, the procedures involved, possible effects and risks. The subjects were reimbursed for their time and were aware that they could withdraw freely from the study at any time.
As a matter of health and to avoid unintended potential risk factors for adverse reactions to the test drug, the subjects were screened using the following procedures: structured psychiatric interview, the DIA-X computerized diagnostic expert system [38], a physical examination including ECG, and detailed clinical-chemical blood analysis, as well as a psychological assessment with standard psychometric instruments and the Symptom Checklist-90 (SCL-90) [39]. The exclusion criteria used were: personal or family (first-degree relatives) histories of schizophrenia, major depression, bipolar disorders, borderline personality disorder, neurological disorders, or regular alcohol or substance abuse. Subjects with high emotional liability, as measured by the Freiburg Personality Inventory were also excluded, as this is a predictor of negative experiences during altered states of consciousness. People with high scores of emotional liability are more

prone to problems and conflicts and often have psychosomatic symptoms; are overly sensitive and anxious; and often feel overwhelmed by events.

The psilocybin used in the studies was obtained through the Swiss Federal Office for Public Health and both placebo and psilocybin were prepared using identical gelatin capsules.

All the studies used as measuring tools the Five-Dimensional Altered States of Consciousness (5D-ASC) and 6 studies also used the Adjective Mood Rating Scale (AMRS) to assess acute and sub-acute subjective drug effects.

The sub-acute side effects were measured in 6 studies, 24 hours after drug intake, using a methodology called List of Complaints, which is a self-rating scale comprising a list of 65 common somatic and psychological ailments, which can be summed to a global score of general discomfort. Subjects were asked to rate whether each symptom is present or not at the time of assessment.

The long-term follow-up of psilocybin effects was assessed using a questionnaire built by the investigators that comprised the following aspects:

1. Ratings of acute drug experiences in retrospect:

Subjects were asked the following question: “How do you rate the acute drug experience during the experiment in retrospect?” For each of six adjectives (pleasant, enriching, frightening, unpleasant, influential, and nothing special), subjects had to choose one of three possible answers (very much, medium, or not).

2. Changes in values and attitudes:

Subjects were asked the following questions: Did the experiment with psilocybin cause changes in (a) worldview, (b) values, (c) awareness of personal problems, (d) the relationship to your body, (e) relationships to other people, (f) professional relationships, (g) the relationship to the environment/nature, (h) aesthetic experiencing, and (i) in the attitude to ASC? For each item, subjects had to choose from three possible answers (positive change, negative change, or no change)

3. Changes in drug consumption habits:

Subjects were asked whether they had changed their consumption habits of any psychoactive drug after the experiments. For each drug that was consumed either more or less often than before, subjects were asked to give further details on frequency of use, dosages, route of administration, and setting of use. Subjects were also asked whether they considered the described changes as a consequence of their drug experience during the experiments.

4. Spontaneously occurring ASC before and after the experiments and flashbacks: Subjects were asked to describe frequencies, durations, circumstances, and symptoms of ASC that spontaneously occurred before and/or after the experiments and whether they interpreted these ASC as a flashback-like re-experiencing of acute drug effects.

5. Negative changes in psychological wellbeing and/or mental functions:
Subjects were asked to report the intensity, duration, and frequency of any experienced negative change in wellbeing and/or mental functions after the experiments. Sleeping, memory, and concentration problems, as well as mood swings, anxiety, and reactivation of old problems were directly listed in the questionnaire, but the subjects if necessary could describe further symptoms.

The total of doses administered, listed by strength, was as follows: 8 very low doses (45 µg/kg body weight), 74 low doses (115-125 µg/kg), 104 medium doses (215-260 µg/kg), and 41 high doses (315 µg/kg) of psilocybin. The number of subjects who received at least one dose of active psilocybin was 110 (59 males and 51 females). Subjects were between the age of 20 and 47 and exclusively Caucasians. 56% of subjects were university students and 33% were university graduates. 60% of subjects had no prior experience with a classical psychedelic (LSD, psilocybin, DMT, or mescaline); 20% had consumed it 1-10 times during their lives. 20% had consumed it more than 10 times in their lives but in a maximum of 6 times per year. 90% of subjects had smoked cannabis at least once in a lifetime.

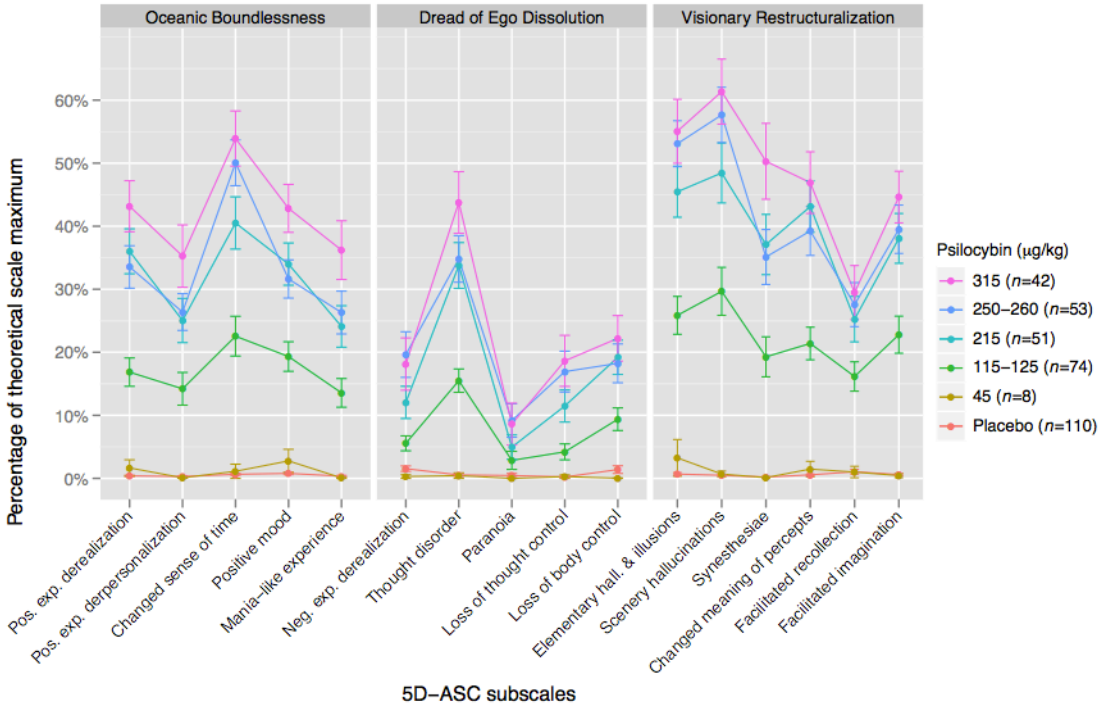
Of the 110 subjects included in the pooled analysis, seven subjects had prematurely dropped out after having received at least one dose of active psilocybin. In two cases, drop-outs were due to technical reasons and unrelated to drug effects. In the remaining five cases, two subjects had an unusually intense

reaction to a low dose of psilocybin and were therefore excluded by the study manager due to safety considerations. Another subject experienced a transient hypotonic reaction (systolic and diastolic blood pressure: 86/63 mm/Hg) with dizziness, fainting, and vomiting after having received 115 µg/kg of psilocybin and was therefore also excluded from further psilocybin experiments.

The remaining two subjects prematurely terminated the study of their own accord after the high dose psilocybin session. Both subjects reported having had experiences of strong anxiety, fear of loss of ego control, emerging negative memories, and thoughts during acute drug effects and were therefore not willing to participate in further psilocybin sessions. All five adverse drug reactions leading to a premature termination of the study were limited to the acute phase of drug effects and were completely resolved by the end of the experimental day.

Psilocybin had a positive effect on the scores of all the scales of the 5D-ASC, having shown to be dose dependent and statistically different from the placebo, except for the very low dose of 45 µg/mg, which was similar to placebo. The results are illustrated in Figure 3.

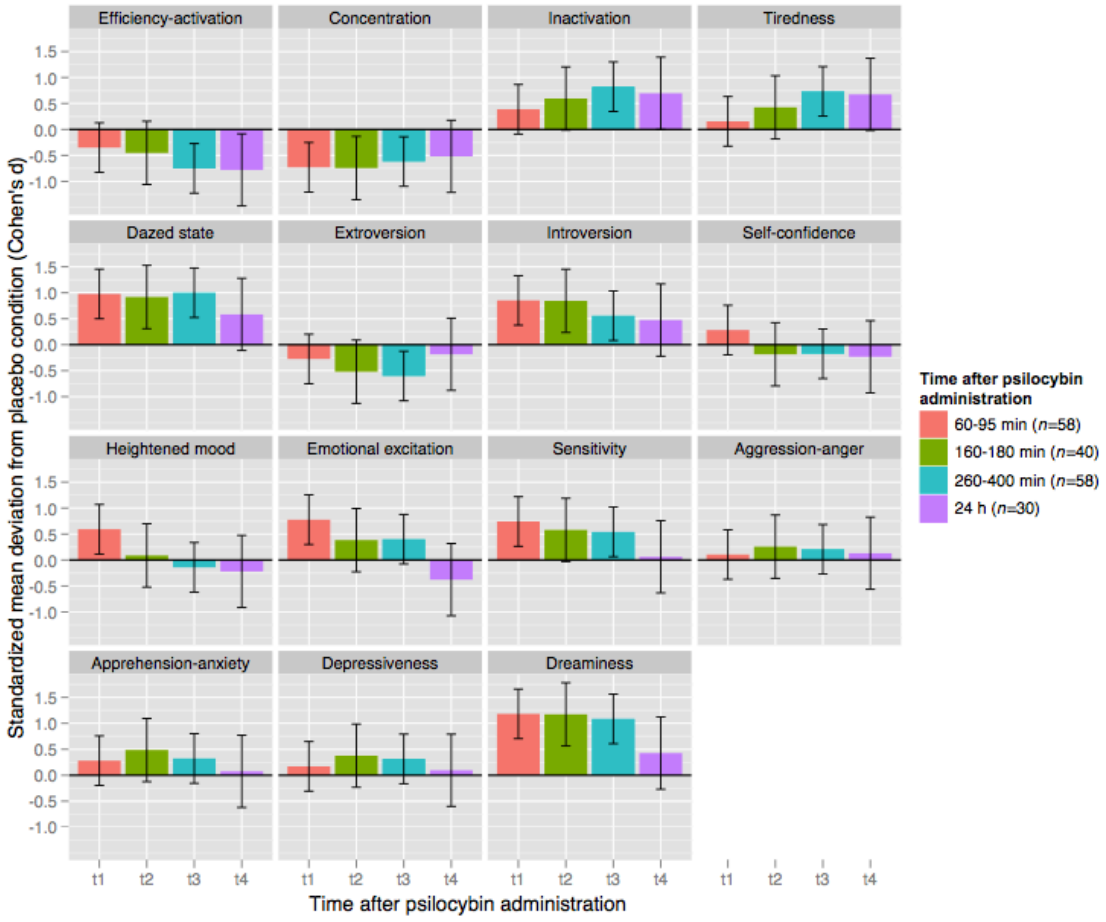
Figure 3. Dose-dependent percentage scores of item clusters from the 5D-ASC.



Note: Error bars represent standard errors. Ratings were obtained during peak drug effects. Transcribed from [4].

The measurement of the changes in affective mood states and conditions over four different time periods was performed using the AMRS and is represented in Figure 4. The stronger interaction effects on early time points are a reflection of the stronger effects of the dose during those time periods. The effects that were significantly stronger were: emotional excitation, dreaminess, heightened mood, dazed states, sensitivity and concentration. For tiredness, the interaction effect is more prominent at a later time point, which is representative of an after effect of psilocybin. The effects that were independent from time were: introversion, inactivation, efficiency-activation, extroversion and apprehension-anxiety. Since these drug-effects were independent of measurement time, they represent longer-lasting psilocybin effects.

Figure 4. Time-dependent effects of medium dose psilocybin (215-260 µg/kg) on mood sates and condition as measured by the AMRS.



Note: Paired differences between placebo and psilocybin conditions for each time and variable combination were divided by their standard deviations in order to express psilocybin effects in units of Cohen's d effect size. By convention, Cohen's d of 0.2, 0.5, and 0.8 are termed small, medium, and large effect sizes, respectively. Error bars denote Bonferroni-corrected 95% confidence intervals of mean differences. Thus, mean differences between placebo and psilocybin are significant, where error bars do not include zero. Transcribed from [4].

The short-term side effects were measured according to another test applied to subjects, the List of Complaints. The most pronounced side effects were fatigue, exhaustion, lack of energy, difficulty concentrating, and "gone feeling" after psilocybin administration. Serious complications, such as fear of death, shortness of breath, feelings of suffocation, vomiting, and fainting, which were also covered by the questionnaire, were not reported by any of the subjects.

Long-term follow-up of the Zurich studies

A long-term follow-up was conducted using questionnaires. This follow-up assessed several parameters. One was the change in drug consumption habits, which was found, remained stable for most subjects. For those who reported changes, these were in a trend of decreased consumption.

Regarding spontaneous alterations of consciousness and flashbacks, these were reported in a similar frequency, duration and intensity both before and after the experiments. These include out-of-body-experiences during meditation and sleep, trance-like states while deeply concentrating, euphoric experiences in nature, perceptual alterations in very dark or bright environments, lucid dreams, hearing voices under high fever, and hypnagogic hallucinations. All these alterations lasted a few seconds to no more than one hour, occurred a few times in a lifetime to no more than once per month, and were limited to specific triggers such as listening to music, meditating, falling asleep, deep concentration or being in a sensory deprived environment. They were not experienced as

threatening and they did not interfere with the daily lives of the subjects. For this matter, they were not considered as psychopathological symptoms.
11 subjects (12%), reported negative changes in psychological wellbeing and/or mental functions. From these, 4% considered those changes were unrelated to the experiment. For the remaining subjects, the problems reported were the following: Concentration problems, mood swings, reactivation of old problems, memory problems, and being pensive and introverted. In all these subjects, symptoms were described to be of low intensity and frequency, non-interfering with everyday life, and only occurring in the first few weeks subsequent to the experiments. One subject experienced a strong reaction with irritability, anxiety, and depressive feelings and required psychotherapy, after which he completely stabilized with no relapse.

The studies performed demonstrate that psilocybin induces altered states of consciousness defined by marked alterations in all mental functions, including perception, mood, volition, cognition, and self-experience. The most relevant features of this altered state are alterations in visual perception, followed by oceanic boundlessness (a positive effect) and dread of ego dissolution (a negative effect).
The way visual perception was affected included increased visual imagery with closed eyes, optical illusions, elementary hallucinations, and synesthesia to picture-like scenery hallucinations. However, the experienced hallucinations were almost always recognized as unreal and therefore are more accurately described as pseudo or nonpsychotic hallucinations.
The increase in the oceanic boundlessness scale was due to the feelings of pleasurable experiences of depersonalization, derealization, and a changed sense of time to phenomena allegoric to experiences of mystical nature.
The less prominent increase in the dread of ego dissolution scale was mostly due to unpleasant disturbances of cognitive functions and somatesthesia and not so much due to suspiciousness or paranoid ideation. The auditory alterations experienced were only moderate and comprised primarily occasional intensification of music and sounds or misperceptions of real auditory stimuli, with true auditory hallucinations, such as hearing voices remaining rare.

The variability in individual responses was very pronounced, with some subjects experiencing strong effects with low doses while others experienced minor effects with large doses. The inter-study variability was moderate. Such differences indicate dose is a poor indicator of psilocybin effects and other variables such as plasma levels of the active metabolite psilocin, expectations, personality structure, interpersonal support, and environment may play an important role.

Retrospectively, the majority of subjects who responded to the follow-up questionnaire, rated the experience as very enriching and 90% rated it as enriching to at least a medium degree. Many thought the experience was influential as well. Curiously, several of those who had felt considerable distress during the acute phase rated the experience as very enriching.

There were no reports of HPPD symptoms according to the diagnostic criteria established in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) or flashbacks in the International Classification of Diseases (ICD-10). Furthermore, the absence of severe prolonged adverse reactions in the study population suggests that these are rare when psilocybin is given in a safe controlled setting. It is worth noting that recruitment bias may have played a role in the outcome, as subjects who were potentially more prone to suffering adverse events were excluded and those who responded to the adverts were more likely to have a positive attitude and personal experience with psychedelics. The studied population is not representative of the general population.

The spiritual significance studies

In 2006, Griffiths and colleagues published one interesting study and its follow-up were they evaluated the acute and longer-term psychological effects of a high dose of psilocybin relative to a comparison compound administered under comfortable, supportive conditions [25, 26]. This was the first study carried out following current accepted scientific methodologies to provide evidence that psilocybin can occasion experiences similar to spontaneously occurring mystical

experiences and this finding brought about a new insight that opened ground for the most recent human research with this compound.

Among other problems with the early psychedelic clinical research, was the unimportance given to the mindset of participants and physical setting where studies would take place. This would be often not taken into consideration by investigators and could have been a confounding factor contributing for the variability of outcomes reported.

Following a review of the literature, Griffiths et al, concluded that when there was more preparation and support of subjects, the adverse psychological reactions decreased. Therefore in this study, investigators sought to carefully control set and setting.

The recruitment was made through flyers in the local community announcing a "study of states of consciousness brought about by a naturally occurring psychoactive substance used sacramentally in some cultures". 36 participants were included in the study, 16 of which were males. All were physically and mentally healthy, without family records psychotic disorders and had never taken psychedelic drugs. The age ranged from 24 to 64 and education levels were high with 35 participants having college degrees. Over half of the participants were affiliated with a religious or spiritual community, such as a church, synagogue, or meditation group and all participants were engaged at least moderately in some kind of spiritual activities.

There was no monetary compensation offered to participants on behalf of their participation. The main motivation that compelled them to participate was their curiosity about the effects of psilocybin and the opportunity for extensive self-reflection in the context of both the daylong drug sessions and the meetings with the monitors that occurred between sessions.

The study was designed to compare a high dose of psilocybin (30 mg/70 kg) and a high dose of methylphenidate hydrochloride (40 mg/70 kg) using a double-blind between-group, crossover design that involved two or three 8-hour drug sessions conducted at 2-month intervals.

36 volunteers were randomly assigned to receive either two sessions (N=30) or three sessions (N=6). Each element of the group of 30 volunteers was then randomly assigned to receive psilocybin or methylphenidate on the first session

(15 per group), with the alternative drug administered on the second session. The other 6 volunteers received methylphenidate on the first two sessions and unblinded psilocybin on the third session. The purpose of this condition was primarily to obscure the study design to the participants and monitors, because expectancy in known to play a role in the qualitative effects. While some of the expectations are inescapable, the authors pursued to minimize this by choosing psychedelic-naïve participants, conducing individual instead of collective sessions, and creating the expectation that the sessions could involve other drugs, some of which have effects overlapping with those of psilocybin. Furthermore, it was hidden from participants and monitors who and how many would have a final unblinded session.

The methylphenidate was used as the comparison condition because it has an onset and duration of subjective effects similar to psilocybin, and it produces some subjective effects overlapping with those of psilocybin.

The primary monitor had four meetings with each participant before the sessions and four meetings after each session. This was to foster communication and trust, which as mentioned earlier, increases safety.

On the day of the sessions, participants were advised to eat a low-fat breakfast. The sessions lasted 8 hours and took place in a nicely decorated room. Two monitors accompanied each participant during sessions, while the participants where encouraged to lie down on the couch, use an eye mask to block external visual distraction, direct their attention inwards, and use headphones through which a classical music program was played. The same music program was played for all participants in all sessions. At the 7-hour time point, when most of the effects had subsided the subjects completed several questionnaires.

One of the most curious parameters measured in this study was the integrity of the blinding procedure, in which the monitors guessed which drug had been administered. The rate of failure was 23%, most often due to rating a methylphenidate session as psilocybin. On two of the three occasions in which this occurred, the participants subsequently rated their experiences as among the five most meaningful and spiritually significant experiences of their lives. These observations suggest that the experiences reported during psilocybin sessions were not merely artifacts of monitor expectation or suggestion.

At the end of the study, both the primary and assistant monitors guessed on the study design through a questionnaire and they believed that psilocybin had been administered in varying doses and that an array of other active drugs and placebo had been used. Thereby, the blinding procedure was at least partially successful.

The blood pressure increased moderately for both drugs about 30 minutes after administration, with psilocybin reaching higher levels than methylphenidate and peaked at the 90-180 minutes marks subsiding to baseline values over the rest of the session. Heart rate also increased by about 10 bpm for both drugs and sustained those values throughout the session.

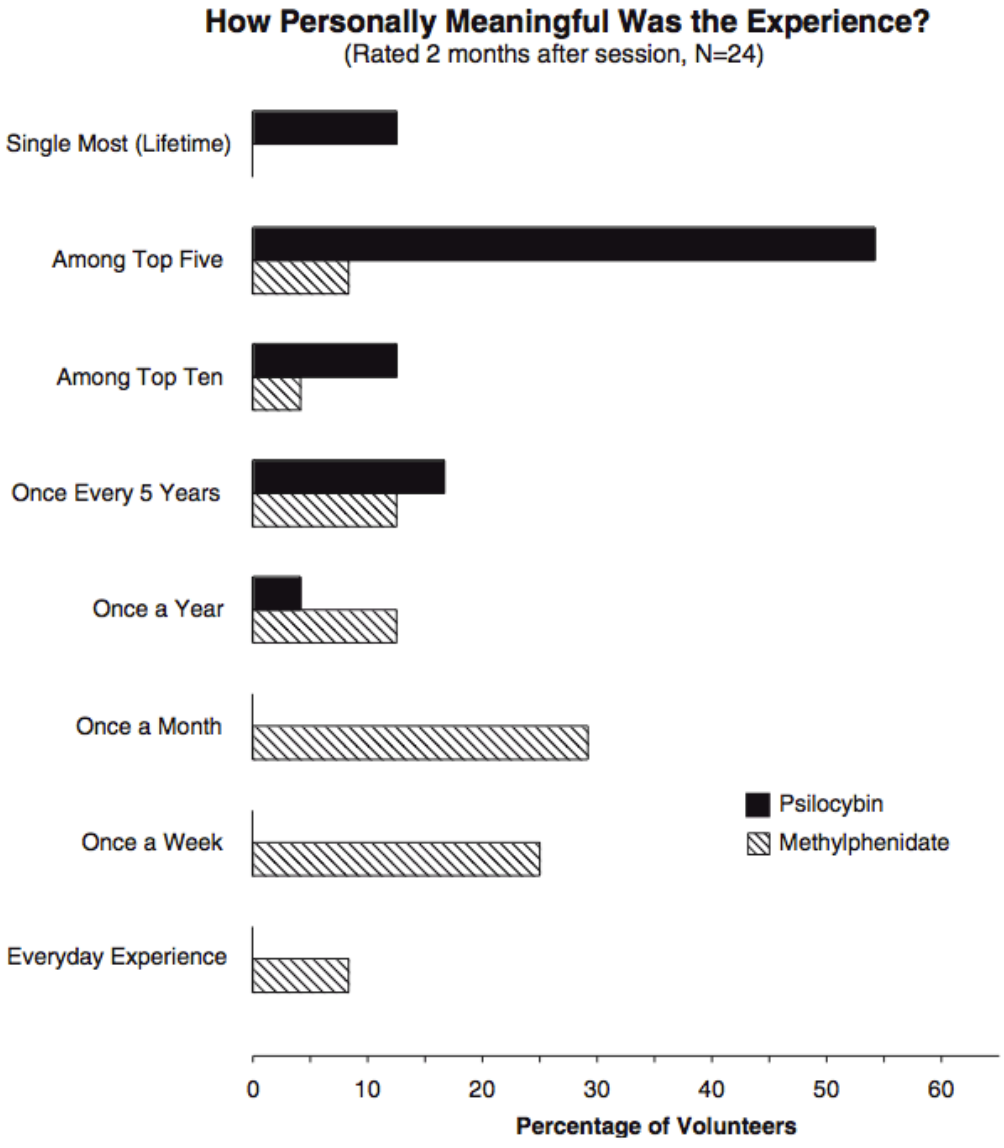
Subjects answered three questionnaires designed to assess the sensitivity to psychedelic drugs. These showed differences between both drugs, with psilocybin consistently rating higher, which indicates that after psilocybin, the participants experienced alterations in mood, affect, and cognition typical of psychedelic drugs. These included perceptual changes (e.g., visual pseudo-hallucinations, illusions, and synesthesia), labile moods (e.g., feelings of transcendence, grief, joy, and/or anxiety), and cognitive changes (e.g., sense of meaning and/or ideas of reference). In terms of euphoria, the levels induced were similar for both drugs.

At the 7-hour time point, participants filled out two questionnaires to assess primary mystical experiences based on classic phenomenological descriptions from the psychology of religion. The result was again consistently higher for psilocybin, with 22 volunteers having had a complete mystical experience after psilocybin and only 4 after methylphenidate.

At the 2-month time points, psilocybin produced significantly greater elevations in ratings of positive attitudes, mood, social effects, and behavior, compared to methylphenidate. A total of 67% of the participants considered the psilocybin experience to be either the single most meaningful experience of his or her life or among the top five most meaningful experiences of his or her life (Figure 5). In their own words, the volunteers judged the meaningfulness of the experience to be similar, for example, to the birth of a first child or death of a parent and valued the experience as having a sense of unity without content (pure consciousness) and/or unity of all things.

At the beginning of the study, subjects were asked to appoint 3 community observers with whom they would have close contact. These observers rated the behavior and attitudes of the subjects after their experiences. Compared to methylphenidate, psilocybin sessions were associated with small but significant positive changes in the participants' behavior and attitudes.

Figure 5. Percentage of volunteers who endorsed each of eight possible answers to the question "how personally meaningful was the experience?" on a questionnaire completed 2 months after the session (N=24). Transcribed from [26].



Many participants reported mild to moderate anxiety before the beginning of the session as result of their anticipation. Another report in 31% of participants was that at some point during the psilocybin session they felt strong or extreme fear. This was not seen once with the control drug. For 11% of participants, the predominant feeling in psilocybin session was anxiety or unpleasant psychological struggle. Mild transient ideas of paranoid thinking were felt by 17% of participants and these occasions were handled by reassurance from the monitors. Despite these psychological struggles, most of these participants rated the overall experience as having personal meaning and spiritual significance and no volunteer rated the experience as having decreased their sense of wellbeing or life satisfaction.

Although there is some body of empirical evidence about psychedelics being able to elicit mystical experiences, there have been no other studies following currently accepted methodological scientific approaches to study this phenomenon. Given the selection bias of this study, where participants were religiously active, psychedelic-naïve and well educated, it is impossible to extrapolate the results to the general population. It is possible that the religious character of the subjects may have increased their propensity for having a mystical experience and for attributing a personal meaning to it. Also, the fact that subjects had never taken psychedelics before may have contributed for a higher intensity of the experience.

The authors concluded that a high dose of psilocybin can be administered safely in a clinical environment following appropriate preparation of the subjects and adequate monitoring. The experience achieved under these conditions can manifest mystical characteristics and be perceived as highly valuable.

Furthermore, psilocybin did not produce compulsive drug seeking behavior as the classical drugs of abuse nor did it exhibit the level of euphoria associated with these drugs. These findings are in line with previous results indicating that psilocybin and other psychedelics do not exhibit profiles of compulsive drug self-administration in animal models [40, 41].

As a cautionary note, it is worth noting that the risks of dealing with psychedelics should not be underestimated. Controlled environments and close monitoring

reduced the likelihood of adverse events but even in these conditions 31% of participants experienced significant fear.

Follow-up 14 months later of the first spiritual significance study

The authors of the previous study on the mystical effects of psilocybin conducted a follow-up study at the 14-month time point to investigate the wellbeing of the participants and whether the effects formerly reported were sustained over time [25].

For this assessment, the participants once again responded to the questionnaires that had been used in the study and the same standardized measurements were used. Moreover, participants were asked to complete a Retrospective Questionnaire and to participate in a clinical interview reflecting on study experiences and current life situation.

The most important finding highlighted by the authors is that a large proportion of volunteers rate their psilocybin session as among the most personally meaningful and spiritually significant of their lives. For 58% it was the most single most meaningful experience and for 67% it was the single most spiritually significant experience. Likewise, 64% of the participants thought that the experience increased their sense of wellbeing or life satisfaction moderately or very much, and no one considered that the experience had decreased their wellbeing or life satisfaction. Compared to the measurements performed previously at the 2-month time point after the psilocybin session, the magnitude of the ratings at the 14-month time point remained the same.

The selection bias used in recruiting the study population in the study has been analyzed before and as mentioned, these results cannot be extrapolated for the general population. Nevertheless it is noteworthy 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.

This uplift in the wellbeing and life satisfaction of participants appears to be caused by the psychological effects of psilocybin that can be compared to those of spontaneously occurring classical mystical or religious experiences.

At the 14-month time point there was no traced evidence of adverse effects deriving from the previous administration of psilocybin, however the authors caution against potential risks, namely:

- Panic or fear reactions resulting in dangerous behavior during the time of drug action;
- Precipitation or exacerbation of enduring psychiatric conditions;
- Long-lasting perceptual disturbances;
- Development of a pattern of abuse or dependence on psychedelics.

The long lasting positive results evidenced in the study suggest that it is worth furthering research with psychedelics in human subjects both for therapeutic purposes and to deepen our understanding of human consciousness and cognitive processes. It raises questions about the origins of mystical and religious experiences, the factors that can trigger them, and what role they may have in our inner wellbeing and our perception and interaction with the world.

Dose-effect study using ascending and descending sequences

In 2011, Griffiths and colleagues published a second study that further explores the acute and persisting effects of psilocybin [42]. They used essentially the same methodology, including preparation of subjects and same measuring tools, but this time, they characterized the effects of a range of ascending doses against a range of descending doses.

The recruitment screening involved 279 individuals, of which 18 were selected to participate. One participant had previously taken psilocybin mushrooms on two occasions, while the rest were completely inexperienced with psychedelics. Again in this study, the population had a high level of education and half were affiliated with a religious or spiritual community and all had some level of religious or spiritual practice.

The study used a double-blind, between-group, crossover design with five sessions lasting 8 hours each and separated by 1-month intervals. A follow-up was conducted after 14 months. The participants were randomly split in two groups of 9 and received the psilocybin dose range (0, 5, 10, 20, 30 mg/70 kg) in

ascending or descending order. All participants received placebo once, however, in each group the placebo condition occurred twice on sessions 1, 2, 4, and 5, and once on session 3. The purpose of this quasi-random scheduling of placebo was to obscure the dose sequence to the participants and monitors.

At the conclusion of the study, the monitors, who were blind to the ascending/descending design, were inquired and did not demonstrate to have been aware of this nature of the study.

The cardiovascular measurements found that blood pressure increased in a dose and time dependent manner, peaking within the first two hours after administration. In general the blood pressure rose modestly but there were some high values. These did not require pharmacological treatment.

The monitor assessments of the overall drug effects and joy/intense happiness peaked within the first three hours.

As measured by the States of Consciousness Questionnaire, 72% of participants had a complete mystical experience with either or both the 20 and 30 mg/70 kg doses and the likelihood of having such an experience was dose-dependent.

Extreme fear was reported by 39% of the volunteers and the onset of these episodes was unpredictable, occurring at different time points, not necessarily correlated with the peaking of the effects. Paranoia or delusions occurred in 44% of participants in the higher dose session, except in one case were it occurred in the 20 mg/70kg session. These struggles did not affect the meaningfulness of the experience as rated by the volunteers.

According to the Persisting Effects Questionnaire, that was applied 1 month after each session and before the next one, psilocybin produced increasing effects as a function of dose in positive ratings of attitudes about life, attitudes about self, mood, social effects, and behavior. 61% of volunteers considered the psilocybin experience during either or both the 20 and 30 mg/70 kg sessions to have been the single most spiritually significant of their lives. Almost all participants considered that the experiences with psilocybin increased their wellbeing or life satisfaction and had a positive impact on their behavior.

At the 14-month follow-up, patient reports show that the positive effects measured earlier were sustained and undiminished. None of the participants reported having been affected negatively or having significant persisting

perception phenomena sometimes attributed to psychedelic use. Neither did participants report having taken psychedelics any time outside of the study.

However, the ascending dose condition was more beneficial than the descending dose condition in terms of wellbeing and positive mood.

This study showed, in accordance with the previous study by the same authors describe above, that psilocybin causes dose-related increases in blood pressure and heart rate.

A novel aspect of the study is that the lowest dose (5mg/70 kg) was attributed to significant, physiological effects, subjective effects reported by the participants and effects rated by the observers. A previous study that used a dose range including a similar dose (45 μg/kg) did not show the same significance [34]. Another important innovation was the design of the study that used ascending and descending dose sequences and compared the results against each other. The acute effects reached the same magnitude at each dose independently from the sequence, however, the positive changes in attitude and behavior rated by participants at 1 month after each session reflected that the ascending dose sequence rated higher and was hence more beneficial. This suggests that using an ascending dose sequence may be more likely to elicit long-lasting positive effects, possibly meaning that having been exposed to lower doses of psilocybin can facilitate the integration of a mystical experience occurring at a subsequent session with a high dose.

The study also offers a comparison of adverse subjective effects at different doses, where the likelihood of feelings like anxiety, delusions or paranoid thinking increases with increasing doses. These effects were promptly managed by the monitors and did not require pharmacological treatment. Aside from these unwanted side effects of psychological struggle, which were transient, the study did not find other problems associated with psilocybin exposure.

However, the study population is not representative of the general population, as group of participants had a high level of education and were engaged in spiritual or religious activities. They also received preparation and monitoring during the course of the study. These results cannot be used to assess the safety of psilocybin in real-life recreational settings.

The authors raise the question of whether persons who identify as atheist or agnostics have the same likelihood of having a mystical experience and what kind of meaning they would attribute to that. Another question is whether being psychedelic-naïve contributes to the long-lasting effects of the experiences, therefore it would be interesting to compare these results to those that would be obtained in people that have had previous experience to psychedelics.

The occurrence of mystical experiences is a very rare phenomenon in the general population. These findings of 70% of participants having had a mystical experience suggest that most people are capable of having such an experience under the right conditions.

Current therapeutic studies

In the past decade, there have been a small number of clinical studies using psilocybin and LSD for the treatment of different conditions. These are all small-scale studies that focus primarily on assessing safety, defining dosage and preliminary efficacy. Table 3 shows some of the potential therapeutic uses and scientific interests that researchers are looking at. Table 4 shows a list of studies that are undergoing or have recently been published.

Table 3. Potential therapeutic uses and interest for neuroscience. Adapted from [5].

Drug	**Potential therapeutic uses**	**Neuroscience research interests**
LSD	• Cluster headaches • Anxiety associated with terminal illness • Pain syndromes • Alcoholism	• Model of psychosis • Nature of consciousness • Perceptual processes • 5-HT receptor function
Psilocybin	• OCD • Cluster headaches • Anxiety associated with terminal illness • Depression • Tobacco addiction	• Nature of consciousness /mystical experiences • Perceptual processes • Model of psychosis and mood • 5-HT2 receptor function

Table 4. List of recent clinical studies using psilocybin or LSD.

Location	Substance	Indication	Treatment	Number of patients	Status / Reference
Harbor-UCLA Medical Center, Los Angeles, California	Psilocybin	Existential anxiety related to cancer	two experimental sessions a few weeks apart, one with psilocybin and one with placebo	12	Published in 2011 [43]
Private practice in Solothurn, Switzerland	LSD	Anxiety in patients with life-threatening disease	Psychotherapy, including two sessions on LSD	12	Published in 2014 [44, 45]
New York University, New York City	Psilocybin	Existential anxiety related to cancer	Nine preparatory psychotherapy sessions; two dosing sessions (one psilocybin, one placebo)	32	Ongoing since 2009
Johns Hopkins University, Baltimore, Maryland	Psilocybin	Existential anxiety related to cancer	Several psychotherapy sessions, including one on psilocybin	44	Ongoing since 2009
Johns Hopkins University, Baltimore, Maryland	Psilocybin	Nicotine addiction	Several preparatory sessions, then three day-long sessions with psilocybin	15 in an open-label pilot	Published In 2014 [46]
Imperial College, London	Psilocybin	Depression	Psychotherapy with two sessions on oral psilocybin	12 in an open-label pilot; 60 in a controlled trial	Expected to start by the end of 2015
University of Alabama, Birmingham	Psilocybin	Cocaine dependence	Several preparatory sessions, then one day-long session with psilocybin	40	Recruiting
University of New Mexico, Albuquerque	Psilocybin	Alcohol dependence	One or two sessions psilocybin sessions, Motivational Enhancement Therapy and psychotherapy sessions	10	Published in 2015 [47]
University of Arizona, Tucson	Psilocybin	OCD	Up to four single-dose psilocybin sessions in an outpatient clinic	9	Published in 2006 [48]

Tobacco addiction

One of the areas where it has been hypothesized that psychedelics may be useful is in the treatment of addictive behaviors. Within this purview is the treatment of tobacco addiction. Current approved methods have a low degree of success, especially in the long-term, because relapses are common. As is of common knowledge, smoking-related illnesses cause a large number of deaths and constitute a big burden for the healthcare system.

Based on the aforementioned, Johnson and colleagues conducted an open-label pilot study to determine the safety and feasibility of psilocybin-facilitated smoking cessation treatment [46]. The moderate (20 mg/70 kg) and high (30 mg/70 kg) doses of psilocybin were administered concomitantly with a tobacco smoking cessation treatment protocol that included sessions of Cognitive Behavioral Therapy (CBT). Psilocybin was administered at weeks 5, 7 and 13.

Due to the lack of similar studies, this pilot study was conducted without a control condition as a first step to evaluate both the safety of the approach, and whether efficacy rates would be promising enough to warrant the investment of resources necessary for a randomized trial.

The recruitment occurred through advertisements offering a novel treatment for smoking cessation (Figure 6).

A total of 15 volunteers were recruited (10 male). The inclusion criteria were: smoke a minimum of 10 cigarettes per day, be healthy as determined via medical interview, electrocardiogram, blood and urinalysis laboratory tests, have multiple unsuccessful past quit attempts, and still desire to quit smoking. Individuals with drug dependence, personal or family history of psychotic or bipolar disorders were excluded. Not all participants were psychedelic-naïve, with 10 reporting to having taken a psychedelic drug in the past. No monetary compensation was offered.

Figure 6. Tobacco study flyer.

Approved May 12, 2014

Cigarette Smokers

interested in a new approach to quitting smoking at no cost to you?

Johns Hopkins University School of Medicine is seeking cigarette smokers who would like to quit smoking for participation in a scientific research study. The study involves free counseling and treatment provided in a comfortable, supportive setting. Transdermal nicotine patches, an FDA approved smoking cessation treatment, may be provided in the study. Cognitive behavior therapy and ongoing interpersonal support will be provided in order to help volunteers quit smoking. Questionnaires, interviews, MRI scans, and biological measures of smoking will be used to assess the treatment's effects on mood, and smoking.

Volunteers must be right handed, must be between the ages of 21 and 65, and must live within travel distance of the Hopkins Bayview campus in Baltimore.

If you would like to discuss the possibility of volunteering, please call 410–550–1972 and ask for Albert, the study's research coordinator or go to www.smoking-insight.org. Confidentiality will be maintained for all applicants and participants.

Principal Investigator: Matthew W. Johnson, Ph.D., Protocol: NA_00016166

Participants were enrolled in four preliminary meetings to prepare themselves for the psilocybin intervention and to complete several CBT modules and subsequent support meetings after the psilocybin sessions to discuss their experiences and support abstinence (Table 5).

Table 5. Summary of treatment meetings and content.

Meeting (duration)	**CBT modules**	**Psilocybin session-related topics**
Prep. Mtg.[a] 1 (90 min)	Assign Target Quit Date (TQD) Sign contract to quit NURD [b] program Smoking diary introduction	Introduction to overall approach Discuss childhood / early family life
Prep. Mtg. 2 (90 min)	Smoking diary review Reasons to quit vs. continue smoking Develop brief motivational statement WEST-D [c] program Health effects of smoking Smoking financial costs	Discuss childhood / early family life
Prep. Mtg. 3 (90 min)	Smoking diary review Discuss previous quit attempts Weight gain and quitting smoking Withdrawal framed as "recovery"	Discuss work, hobbies, and other important activities
Prep. Mtg. 4 (90 min)	Smoking diary review Dealing with urges after TQD Preparing to quit	Discuss worldview (philosophical and/or spiritual beliefs) What to expect in psilocybin sessions
Psilocybin Ses.[d] (8 hrs)	-	-
Integration Mtg.[e] (1 hr)	-	Participant narrative of session
Support Mtg.[f] (45 min)	Support smoking abstinence Review CBT techniques	Discuss session experiences

Legend: a) Preparation meetings were held weekly for 4 weeks prior to TQD. Approximately half the duration of each meeting was spent conducting CBT, and half preparing for psilocybin sessions.

b) NURD program card was to be read each time a cigarette was smoked: "This

cigarette is giving me *No* satisfaction; This is an *Unpleasant* experience; This cigarette is making me feel *Rotten;* I am losing the *Desire* to smoke."

c) WEST-D program card was to be read each time participants noticed an urge to smoke: "What's the trigger? *Each* time I feel like smoking, *Stop, Think, Deprogram."*

d) Psilocybin sessions were introspective and contained no formal treatment content other than listening to a music program.

e) Integration meetings occurred the day after each psilocybin session. Participants' experiences of the preceding day's psilocybin session were discussed.

f) Support meetings were conducted weekly after TQD for 10 weeks.

Transcribed from [46].

The first psilocybin session used the moderate dose and was established as the Target Quit Date (TQD). Subsequent sessions two and three were meant to reinforce the abstinence in those who quit after the first session and were an additional opportunity to quit for those who had been unsuccessful. These sessions were predetermined to use the high dose but participants were allowed to take the moderate dose if they preferred. Previous research has suggested that after psychedelic administration there is an afterglow effect associated with decreased substance use, elevated mood and energy, decreased anxiety, and increased capacity for close interpersonal relationships [49]. Based on this premise, this study used a multiple-session design, which could work by extending the "afterglow" period through the time of greatest relapse risk, or by increasing the probability of a transformative mystical experience. The selected doses followed the rationale suggested by previous research on psilocybin and mystical experiences showing greater prevalence of mystical experience at 20 mg/70 kg and 30 mg/70 kg over other lower doses and supporting ascending doses rather then descending doses [42]. The way of conducting the sessions was also identical to that described in previous mystical experiences research done by Griffiths and colleagues [26, 42], except that here participants repeated their brief motivational statement for smoking cessation before each psilocybin

administration, and participated in a guided imagery exercise at the resolution of psilocybin effects on the first psilocybin session.

Several measures were used in participants to evaluate the effects and outcomes of this study. Two measures of recent smoking, exhaled carbon monoxide (CO) and urinary cotinine level, were assessed at intake, weekly throughout the intervention, and at 6-month follow-up. Participants also filled out a self-report calendar on their cigarette consumption and their experiences were evaluated using the Mysticism Scale Questionnaire, the States of Consciousness Questionnaire and the Persisting Effects Questionnaire. These questionnaires intended to assess the subjective effects of the experience and try to correlate them with the obtained outcomes, as well as look at potential adverse effects.

From the 15 volunteers, 12 completed three psilocybin sessions. 3 participants did not undergo a third session, but completed the study. One participant chose a moderate dose on the second psilocybin session and all other participants chose the default.

The adverse effects detected in the study were modest acute increases in blood pressure, heart rate, transient anxiety and dysphoria and headaches. Overall, the administration of psilocybin was considered to show safety. The authors point out that other medication for smoking cessation like bupropion and varenicline can cause more prolonged side effects that include nausea, insomnia and abnormal dreams.

The great majority of participants attributed substantial personal meaning to their psilocybin experiences and considered them to be among the 10 most meaningful experiences of their lives. They also reported that their personal wellbeing or life satisfaction had increased very much as a result of at least one psilocybin session.

The rate of abstinence at a 6-month time point was 80%, which is very encouraging, however this study had a small sample size, used an open-label design and had no control group. An open-label study is liable of being distorted by the placebo effect, observer bias and experimenter bias. Another liability was the lack of racial heterogeneity in the study population and the high education level of all participants. It is worth mentioning that in this study the level of

interaction and support provided by the research staff was higher than the ordinary for a smoking cessation treatment.

The study design was unable to discern differential benefits of moderate-dose (20 mg/70 kg) and high-dose (30 mg/70 kg) sessions. All participants who quit smoking did so after their initial moderate-dose session, and those who did not quit were unable to do so even after their subsequent high-dose sessions.

No drug seeking behavior was detected. Supporting this is the fact that 2 participants declined the third session.

The mechanism of action of psilocybin in smoking cessation is not clear but results suggest that it may be linked with the increase in psychological wellbeing of participants and their self-report of altered life priorities.

Online survey on psychedelic-facilitated smoking cessation

Due to the results obtained in the aforementioned study, the authors are conducting an online survey to understand if psychedelics used in real-life settings may have an impact on quitting or reducing of smoking.

The survey is ongoing and data gathered to date from 164 completers indicates that the psychedelics more commonly related to smoking cessation are LSD (49%) and psilocybin (32%). The mean of cigarettes smoked was 12 per day for a mean of 8 years. After their psychedelic experience, 38% of participants reported total abstinence and another 41% reported persisting smoking reduction to less than 1 cigarette per month. The remaining reported temporary reduction. In terms of withdrawal symptoms, the participants reported that while most symptoms were as severe as in previous attempts to quit, depression, irritability, anxiety, and craving were less marked. 86% of the surveyed had no aforethought intention to quit or reduce smoking [50].

While online surveys are generally unreliable and present biased data that doesn't provide scientific evidence, they can serve as a stepping-stone to prompt serious scientific research and shed light on which paths to follow.

Obsessive Compulsive Disorder

Moreno and colleagues analyzed anecdotal reports suggesting that psychedelic agents might have a role in the relief of symptoms of OCD [48]. They conducted a small phase I, double-blind study, aimed at investigating the safety, tolerability and clinical effects of psilocybin on 9 subjects with OCD as defined by DSM-IV, without concomitant psychiatric disorders. All of these subjects were refractory to at least 1 other previous treatment. They used up to 4 single-dose exposures to psilocybin and the dose ranged from sub-psychedelic to frankly psychedelic. Low (100 μg/kg), medium (200 μg/kg), and high (300 μg/kg) doses were assigned in that order, and a very low dose (25 μg/kg) was inserted randomly and in double-blind fashion at any time after the first dose. There was a minimum time gap of one week between sessions. Each session lasted 8 hours under a controlled environment. The severity of symptoms was measured using the Yale–Brown Obsessive Compulsive Scale (YBOCS) and a visual analog scale at 0, 4, 8, and 24 hours post-ingestion. The Hallucinogen Rating Scale was administered at 8 hours, and vital signs were recorded at 0, 1, 4, 8, and 24 hours after ingestion. This study was carried out during a 3-year period. The only significant adverse reaction observed was transient hypertension without relation to anxiety or somatic symptoms that occurred in one subject. The analysis of YBOCS score showed marked decrease in symptoms for all subjects and this usually lasted beyond 24 hours (Figure 7).

The dose-response relationship was not significant, as the dose or the perceived intensity of the experience did not greatly correlate with the reduction in symptoms.

5 of the subjects felt that the experience was very enriching psychologically and spiritually. In the high dose session, 4 subjects reported profound positive transcendental experiences such as exploration of other planets, visiting past-life reincarnations, and interacting with deities.

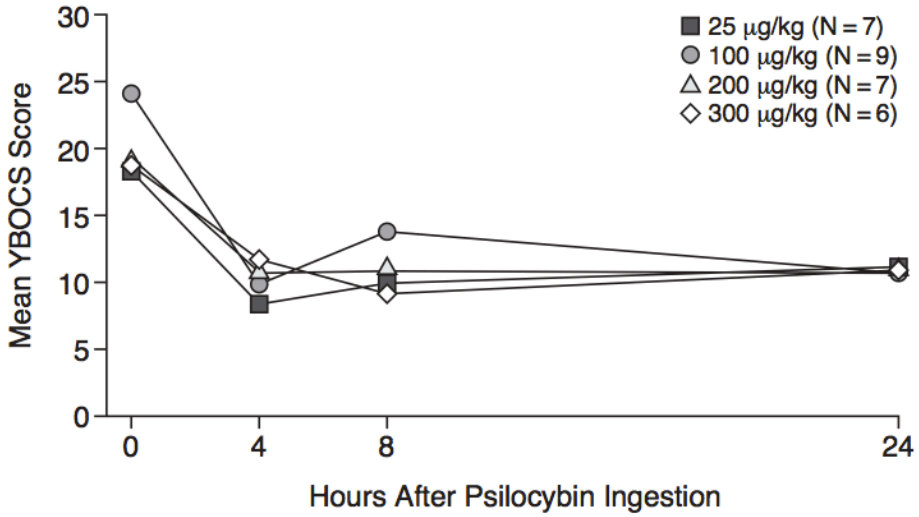
The smaller dose (very low dose) was meant to be a placebo comparator in the study, and was thought it would have negligible psychedelic effects. However the response it elicited was much greater than expected both in terms of subjective perception by the subjects and in clinical effects. This response eliminates the

possibility of using the very low dose as a placebo comparator and consists of a methodological limitation in the study, which poses an obstacle when trying to explore the real clinical effects obtained as a cause of drug administration.

Another problem with the study was that the order of the doses was escalating, aside from the very low dose, which was inserted randomly. This study design could have influenced the expectations of both the subjects and the raters.

The authors concluded that in a controlled clinical setting, psilocybin was administered safely and was linked with an overall acute reduction in OCD symptoms in several subjects. Despite the methodological limitations and the reduced sample size, the results encourage further exploration. It is also worth mentioning that the fact that symptom reduction persists much after the effects of the drug have worn off raises interesting questions. This lingering effect might be due to a continued feeling of wellbeing associated with a pleasurable experience or it can be driven by pharmacological activity. There is evidence that psychedelic administration leads to down-regulation of 5-HT2A receptors in animal models [51]. These speculations require further investigation.

Figure 7. Effects of Psilocybin on Obsessive-Compulsive Symptom Severity.



Note: Mean YBOCS scores immediately prior to ingesting psilocybin (T-0) and 24 hours after ingesting psilocybin (T-24) for each dose were as follows: 25 µg/kg,

T-0 = 18.29, T-24 = 11.14; 100 µg/kg, T-0 = 24.11, T-24 = 10.67; 200 µg/kg, T-0 = 19.57, T-24 = 11.00; 300 µg/kg, T-0 = 18.83, T-24 = 11.33. Transcribed from [48].

Treatment for Anxiety in Patients With Advanced-Stage Cancer

Studies carried out from the late 1950s to early 1970s showed promising evidence on the use of psychedelics for the treatment of anxiety, despair and isolation in patients suffering from terminal illness, most commonly advanced-stage cancer. Those studies described critically ill individuals undergoing psychospiritual epiphanies, often with powerful and sustained improvement in mood and anxiety as well as reduced need for narcotic pain medication. Due to the subsequent shutdown on psychedelic research, there was no follow-up research.

Based on this preliminary data, Grob and colleagues conducted a phase I clinical trial to examine the safety and efficacy of psilocybin for the treatment of anxiety in patients with advanced stage cancer [43]. This study was the first of its kind in over 35 years to assess the potential of psilocybin in patients with terminal illness. The study enrolled 12 subjects (11 of which were women) with advanced-stage cancer and a DSM-IV diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety. The aim was to assess the safety and efficacy of psilocybin in the treatment of psychological distress associated with the existential crisis of terminal disease.

The design was within-subject, double-blind, placebo-controlled. One of the potential limitations of this type of study is that, because all participants have advanced-stage illness, they may not survive long enough to complete all assessments. In this case, eight subjects completed the 6-month follow-up assessment, 11 completed at least the first 4 months of assessment, and all 12 completed at least the first 3 months of follow-up. The study ran for almost 4 years, from June 2004 to May 2008. Most of the subjects had some previous experience with psychedelics: LSD (7 subjects), psychedelic mushrooms (5 subjects), peyote (2 subjects), and ayahuasca (2 subjects); whilst 4 subjects were

completely naïve. Researchers met with subjects previously to the sessions and informed the subjects about the purpose of the study which was to determine whether psilocybin could ameliorate the anxiety associated with their advanced-stage cancer and also informed them about the spectra of emotional reaction that might be experienced while under the influence of psilocybin, including challenging psychological issues. These meetings were also used to create trust between the participants and research personnel, reviewing each patient's life history and their current concerns.

The sessions took place in a room situated inside a hospital that was decorated to create a pleasant environment. Each subject participated in 2 experimental treatment sessions, and acted as his own control. In one of the sessions they received active psilocybin (0.2 mg/kg) and in the other session the placebo, niacin (250 mg). Subjects were aware they would receive placebo in one of the sessions. The choice of niacin as placebo was because it often induces a mild physiological reaction (e.g., flushing) without altering the psychological state. Both session lasted for 6 hours and the team remained at the subject's bedside, while the subjects were encouraged to lie in bed with eyeshades and listen to preselected music using headphones.

Every hour, the treatment staff took measurements for heart rate and blood pressure and inquired the subjects to check if they were feeling well. Aside from that, subjects were mostly left undisturbed. When the session was completed, discussed the subjective aesthetic, cognitive, affective, and psychospiritual experiences they had during the session and filled out rating instruments.

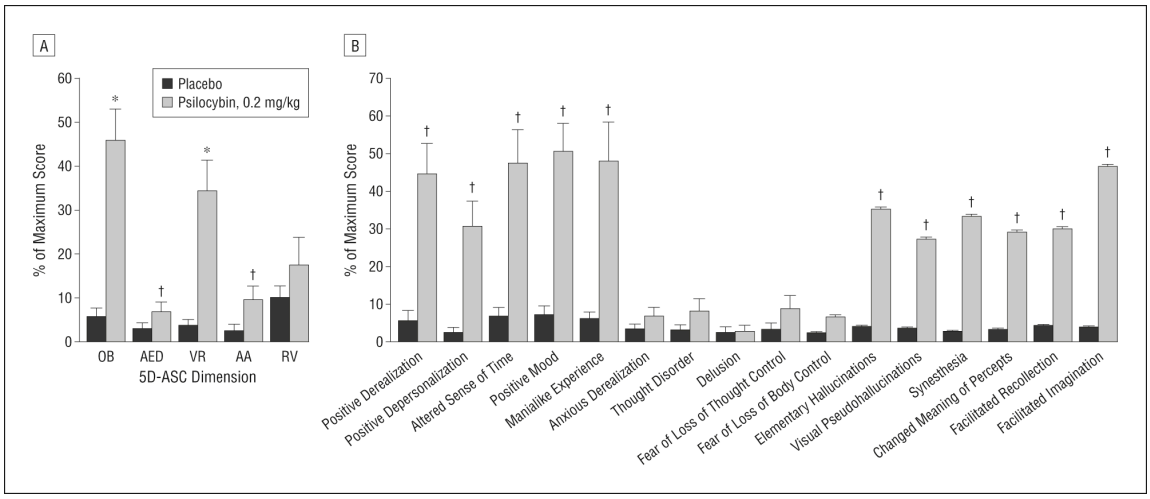
Before each session, the following measuring instruments were used: the Beck Depression Inventory (BDI), Profile of Mood States (POMS), and State-Trait Anxiety Inventory (STAI). After each session, subjects completed to following assessments: The POMS, STAI, 5D-ASC, and Brief Psychiatric Rating Scale. The day following the session, the BDI, POMS, and STAI were readministered. As follow-up measurements, the instruments chosen for assessments after 2 weeks and then at monthly intervals until the 6-month time point were: the BDI, POMS, and STAI.

Both heart rate and blood pressure suffered a mild but statistically significant elevation that mutually peaked 2 hours after ingestion. For heart rate, the mean

peak effect was 81.5 beats/min compared to 70.4 beats/min for the placebo session. For blood pressure, the mean peak systolic pressure was 138.9 mm Hg compared to 117.0 mm Hg for the niacin (placebo) sessions.

When analyzing the psychological measures, the 5D-ASC showed significant subjective differences. The most affected measurements were the oceanic boundlessness and visionary restructuralization. There were also effects on anxious ego dissolution and auditory alterations but these were less prominent (Figure 8).

Figure 8. Subjective effects of psilocybin as measured by the 5D-ASC.



Legend: A – Five main 5D-ASC dimensions are shown: oceanic boundlessness (OB), anxious ego dissolution (AED), visionary restructuralization (VR), auditory alterations (AA), and reduced vigilance (RV).

B – Item clusters comprising the OB, AED, and VR dimensions are shown. Values are the Standard Error of the Mean (SEM) percentages of the total possible score. *P < .01, †P < .05 for psilocybin vs niacin placebo control (1-way analyses of variance were used to compare niacin and psilocybin effects on individual 5D-ASC dimensions and 5D-ASC item clusters). Transcribed from [43].

The BDI did not change significantly with the placebo, but observed a decrease for the psilocybin, dropping by almost 30% from the first session to 1 month after the second session, this difference was sustained and became significant at

the 6-month follow-up point. Hence, there was a positive trend in the reduction of depression as measured by this tool.

The POMS equally revealed a reduction in adverse mood tone from 1 day before treatment with psilocybin to 2 weeks later. This was not seen with the placebo.

There were no significant changes in the STAI until 2 weeks after treatment but a sustained decrease in STAI trait anxiety score was observed for the entire 6-month follow-up having achieved significance at the 1-month and 3-month points after the second treatment session.

The Brief Psychiatric Rating Scale at the end of the experimental session revealed no appreciable difference between psilocybin and placebo administration. This scale is used to measure symptoms such as depression, anxiety, hallucinations and unusual behavior.

This study intended to lay down the feasibility and safety for a psychedelic treatment model in patients with advanced-stage cancer and anxiety and the dose chosen as agreed with the regulatory bodies was modest (0.2 mg/kg of psilocybin). This dose is hardly comparable to those stronger doses that were administered to patients before the shutdown of the first wave of psychedelic research but is still capable of inducing an altered state of consciousness as corroborated by the tests that were administered to subjects. Therefore, this dose was believed to be appropriate in investigating the potential benefit of psychedelic therapy whilst optimizing patient safety. In order to carry on further research it was necessary to more clearly understand the safety scope of this novel treatment.

In line with former research, this study showed that the cardiovascular effects provoked by psilocybin are mild and do not pose a considerable risk.

There were also no adverse psychological effects arising from the treatment and the subjects did not report severe anxiety or the event of a “bad trip”. The fact that psilocybin produced only modest effects on the anxious ego dissolution scale of the 5D-ASC confirmed this conclusion.

During the 1960s and 1970s, when psychedelics were given to terminal cancer patients, the therapeutic outcome was bound to the occurrence of a profound psychospiritual experience [52]. This kind of transcendent experience is linked

with higher doses and therefore the author's expectations of demonstrating efficacy were limited.

In this particular study, subjects reported common themes of how their illness had impacted their lives, relationships with family and close friends, and sense of ontological security. They also reported a highly empathic cathexis towards their loved ones and discussed how they wished to address their limited life expectancy. During the monthly follow-up meeting, subjects expressed their insights and new outlooks achieved during the psilocybin sessions.

Previous studies, using the higher dose model, produced reports of more marked therapeutic effects but this lower dose also revealed some level of benefit. More specifically, the STAI trait anxiety revealed a sustained reduction in anxiety that reached significance at the 1-month and 3-month points after treatment, which might be caused by a decrease in the stress and anxiety charges over time.

Another improvement observed was in the mood, which was better after 2 weeks of the psilocybin session and maintained improvement according to the BDI becoming statistically significant at the 6-month time point.

Likewise, the POMS also indicated improved mood 2 weeks after the psilocybin session. This was not statistically significant but showed a tendency towards positive outcome.

Having a bigger number of subjects and using a stronger dose of psilocybin, it seems possible that the selected assessment tools would give out more prominent results.

The study also investigated the somatic symptoms of a 0.2 mg/kg dose of psilocybin, more specifically in regards to pain perception. Contrarily to previous studies, there was no pronounced reduction in pain perception or reduced necessity for narcotic pain medication. In the 2 weeks that followed the experimental treatment sessions, some subjects reported pain reduction whilst others did not, independently of having received the placebo or the psilocybin. Despite the lack of efficacy in reducing pain attained with this dose of psilocybin, in the light of remarkable past reports [53] by earlier researches, this criterion should nevertheless be included in future studies.

The study was designed as double-blind and placebo controlled, notwithstanding, the drug order was almost always evident to both subjects and

the research team. Subjects critiqued the placebo sessions as being less fruitful and suggested that forthcoming research offered the chance for a second psilocybin session. The underlying idea was that a second session with psilocybin would strengthen and extend the perceived therapeutic effects of the first session.

Due to the severity of the illness and limited life expectancy of the subjects, the study authors decided to give all subjects the opportunity to experience the experimental medicine and to serve as their own control. This choice was made on the belief that it would be the most ethical behavior, nonetheless it is acknowledged that it created some limitations to the study protocol.

In forthcoming research the problem of controlling for a placebo effect that might otherwise be attributed to the active treatment should be addressed. One option would be to incorporate an independent control group, receiving only either placebo treatment or a conventional psychopharmacological intervention.

Undoubtedly, the extensive care given to patients impacted on the outcomes, still the unparalleled characteristics of the psilocybin experience in favoring strong bonds and improving the psychological demoralization are worth deeper exploration.

The extent of contact with the subjects was another variable that posed a limitation to the study. Despite having established a minimum contact of 1 hour per month, the needs and desires of each subject were different and some were close to death while others were more functional.

Taking into account all of the aforementioned limitations of the study, it generated evidence that the controlled use of psilocybin may allow for an alternative model for conditions that are frequently minimally responsive to conventional therapies, such as the deep existential anxiety and despair that often emerge in advanced-stage cancers.

Alcohol dependence

A meta-analysis published in 2012 of randomized controlled trials, found that LSD-facilitated treatment of alcoholism approximately doubled the success rates of control conditions at the first follow-up [54].

A small proof-of-concept (phase II) study by Bogenschutz and colleagues, attempted to determine the safety and efficacy of psilocybin for the treatment of alcohol dependence [47]. The study used a single-group, within-subjects design.

Participants received 12 psychosocial interventions throughout the study and 2 psilocybin sessions (at week 4 and 8).

The distribution of the psychosocial sessions was the following: 4 psychosocial sessions occurred before the first psilocybin session, 4 sessions between the first and second psilocybin sessions, and 4 sessions after the second psilocybin session.

The investigators collected data over the course of 36 weeks to assess the outcomes.

Volunteers were recruited using advertisements and flyers in the local community. A total of 70 participants were screened of which 10 enrolled in the study. Family or personal history of psychiatric disorders like schizophrenia and bipolar disorder were part of the exclusion criteria, as well as showing dependence of cocaine, psychostimulant, or opioid drugs.

The population was mixed-gender, aged 25-65 and all participants met the DSM-IV criteria for the diagnosis of active alcohol dependence and had at least 2 heavy drinking days in the past month.

At the time of the psilocybin sessions, the volunteers had to be abstinent and not in alcohol withdrawal.

The psychosocial intervention was used for three purposes: Motivational Enhancement Therapy, preparation for the psilocybin sessions and debriefing after the latter sessions.

A regime of two escalating doses was used for the psilocybin sessions, except for one case. First session, used a 0.3 mg/kg and was completed by 10 participants. 7 participants completed the second session, of those 6 received the higher dose of 0.4 mg/kg. 1 participant received a second dose of 0.3 mg/kg because of

having met the criteria for a “complete mystical experience” in the first session. These sessions took place in a decorated room and participants where encouraged to lie on a couch with eyeshades, use headphones to listen to a preset playlist and focus on the internal experience. Monitoring occurred during 8 hours and at the 7-hour time point, when most of the drug-effects had subsided, participants completed the questionnaires and assessments.

The acute physiological effect noticed was modestly increased blood pressure for both dosages. Heart rate was not significantly elevated. Five participants reported mild headaches that resolved within 24 hours. One had nausea and one episode of emesis. There was also one case of insomnia in the night following psilocybin and one case of diarrhea in a patient with irritable bowel disease.

The self-reported intensity of effects varied markedly from patient to patient. On average, acute effects on the Mystical Experience Questionnaire and Hallucinogen Rating Scale are numerically lower in magnitude than those seen at comparable doses in healthy subjects of the mystical study [42].

During the first 4 weeks, when subjects received only counseling, there was no statistical significance in the reduction of drinking habits, however, after the first psilocybin session, both drinking days and heavy drinking days suffered a considerable reduction that was sustained until the end of the study. The reduction in drinking, craving and abstinence was positively correlated with the intensity of effects felt by the participants.

Subjective effects varied highly among subjects and were also lower in average than those reported by Griffiths and colleagues for healthy subjects [26, 34, 42]. This supports early evidence coming from studies in the pre-prohibition era that alcoholics required larger doses of LSD to have a strong effect [55].

The authors also point out that some alcohol-dependent patients may be relatively insensitive to the effects of psilocybin, although larger samples will be necessary to confirm this. There was also no significant difference between both doses, possibly due to the small sample size, however, because most participants received two doses, it is impossible to say if the same results could have been obtained with just one dose and if there is a dose-dependent difference in the outcomes.

Some of the limitations of this study are: small sample size, lack of a control group or blinding, and lack of biological verification of alcohol use. However, the study indicated that it is safe and feasible to pursue research in this area and the positive outcomes observed in drinking behaviors support the idea that randomized pivotal studies could be conducted in the future to clarify about the efficacy and pertinence of this approach to treating alcoholism.

Furthermore, the high inter-subject variability raises questions about the genetic response to psilocybin and whether understanding this parameter could help choosing appropriate patients for this therapy.

Discussion

Psychedelic research has come a long way since the first studies that were conducted in the late 1950s and early 1960s. During this period, numerous researchers carried out human research with classic psychedelics, often focusing on the effects of the drug itself and paying little attention to the external environment and the mindset of the subjects. This early research spanned from studies conducted in clinical settings by physicians and psychologists to experiments made by psychedelic enthusiasts and proponents that bear little to no scientific value, aside from the anecdotal evidence that they can provide on the potential harms and benefits of using this class of substances. During this period, self-experimentation among researchers was also a common occurrence and even today it is deemed important that researchers in this area have themselves self-experience or at least are familiar with the possible subjective effects of psychedelics.

For psilocybin, there is no approved training program were therapists can receive the drug themselves and become familiar with its effects. However, in the case of MDMA-assisted psychotherapy, the promoter Multidisciplinary Association for Psychedelic Studies (MAPS) has achieved approval for a therapist-training program, which acts at the same time as a phase I clinical study. This therapist training is a placebo-controlled, double-blind, randomized, cross-over study that allows MAPS to administer a single MDMA-assisted psychotherapy session to therapists as part of their training to conduct MAPS' MDMA/Post Traumatic Stress Disorder (PTSD) studies, while also conducting a series of evaluations of the psychological effects of MDMA administered to healthy volunteers in a therapeutic context [56].

Irresponsible use of psychedelics and a clash between the subgroups that used psychedelics and mainstream society were certainly factors that contributed to the beginning of the prohibitionist era that followed.

After the scheduling of the most commonly used psychedelic drugs, including LSD and psilocybin, under the United Nations Convention on Psychotropic Substances, in 1971, most research was shutdown by the government and it was

practically impossible to attain grants for new studies, especially when it came to clinical applications. A lot of research was still carried out in animal models and some research was done in humans but it focused mostly on pharmacological and toxicological aspects, to better understand the functioning of the neurotransmitter serotonin and its biochemical pathways.

Following a decades-long period of obscurity with very little human research, psychedelics surfaced again in the scientific ground during the 1990s. This occurred partly because of the new technology that allowed scientists to explore the brain using non-invasive techniques such as Positron Emission Tomography scans (PET).

As discussed before, opening way to a new era of psychedelic research, a team in the University of Zurich carried out an important set of studies that provided new insight about the acute, sub-acute and long-term subjective effects of psilocybin in healthy subjects, as seen through a scientific lens. These studies allowed scientists to focus on the mental effects produced by psilocybin instead of studying only its pharmacological properties.

Backed by the knowledge generated by the Swiss team and other previous studies, other teams of scientists started carrying out research in humans. A team at Johns Hopkins Hospital conducted two studies in healthy humans to determine if psilocybin could cause mystical-type experiences in humans. In both studies, the methodologies used to assess the subjective results of the psilocybin experience, revealed that most subjects met the criteria for a mystical-type experience and that the positive effects that arose out of the psilocybin sessions were long-lasting, as measured in follow-up assessments that took into account the personal reports of the subjects, the ratings of the study monitors and of community observers which are people that live in close contact with the subjects.

Furthermore, the Johns Hopkins team also wrote a valuable article laying down the guidelines for safety in conducting human research with psychedelic substances, especially in high doses. In these guidelines, the authors focus on the aspects of subject selection and preparation, requirements for study personnel, the importance of the physical environment were sessions take place, the

appropriate ways to conduct the sessions and important post-sessions procedures.

Besides the basic human research studies, there have been a small a number of clinical trials with psilocybin used in combination with psychological intervention to address problems like OCD, anxiety related to advanced-stage cancer, tobacco addiction and alcohol dependence.

All of these studies have shown promising results and point towards better results when compared to the currently used therapies and it must be highlighted that psilocybin treatment is based in a small number of sessions using the drug, whereas common treatments for these problems are usually based in chronic medication that may have long-term side effects and usually only alleviates the symptoms without tackling the root cause of the problem. Another important issue to take into consideration is that current treatments for addiction have a low success rate and high relapse rate.

From all the studies analyzed, psilocybin seems to show potential as an alternative treatment option, especially in cases where conventional treatment has failed. The clinical studies with psilocybin used volunteers that had been unsuccessful in finding relief from previous treatments, in all studies, at least one previous treatment failure was a required criteria.

The clinical studies that have been conducted to date used small samples of subjects that are not representative of the general population and they present several limitations. Although the researchers took measures to minimize and tackle the identified limitations in each study, some limitations can only be solved by using larger sample sizes and trying different treatment plans, such as using higher psilocybin doses (as suggested in the alcohol dependence study) or a higher number of psilocybin sessions (as suggested by some subjects in the anxiety in terminally-ill cancer patients study).

One of the limitations that is common across studies using mind-altering substances is the fact that the double-blind design is easily broken because the subjects become aware that they are under the influence of the substance and often the monitors accompanying the session do as well. Some of the studies use an active placebo (i.e. methylphenidate, niacin), which bears some of the characteristics of psychedelics, but it is still not perfect in recovering the double-

blind effect. Especially subjects that have had previous experience with psychedelics will know when they are under their influence. This can seen as a confounding factor that may have impact in the outcome because it may interfere with the double-blind design. Subjects that have had previous positive experiences with psychedelics and that show a positive attitude towards this kind of substances may be more likely to take interest in volunteering for studies and in benefiting more from the intervention than a randomized population. Hence, for some studies it may be useful to rule out subjects that have previously experimented with psychedelics using this as an exclusion criterion. However, conducting research with experienced psychedelic users can also help understand if the positive/negative effects change over time with usage and also if the psychedelic experience is stronger in naïve subjects, with the effects becoming less marked in subsequent sessions. For this matter, it may or may not be adequate to use subjects that have had previous exposure to psychedelics, depending on the nature of the study. For human basic research studies that explore the effects of high doses of psychedelics using equipment such as a PET scan machine it may be useful to recruit subjects that are familiar with the effects of psychedelics because they may be more suitable to endure the uncomforting sensation of standing immobile inside a narrow space with loud sounds. This experience can be overwhelming for many and is more prone to elicit anxiety and panic than a supportive and cozy psychotherapy room.

Regarding adverse effects, none of the studies found any event of major concern. Most adverse effects were mild to moderate in nature, which indicates that psilocybin, even in high doses, has an acceptable safety profile that validates the possibility of continuing research using this substance. The most profound effects of the substance occurred on a psychological level, while physiological measurements did not exhibit strong changes.

Because each clinical study focused on a different condition, it is hard to determine if the dose range for psilocybin treatment should vary considerably according to the problem being treated or if the effective dose will be similar to treat different conditions. However, preliminary data suggests that for alcohol dependence it may be that higher doses are needed or that psilocybin is not so effective for this disorder. Furthermore, the variability in the sensitivity to

psilocybin among different subjects also raises questions about whether dosage should be adjusted depending on the subject and how to predict optimal dosage for a certain patient and for a certain condition. The clinical studies analyzed here use very small populations and therefore it is hard to understand how certain parameters (such as: age, gender, ethnicity, level of education, previous experience with psychedelics, religious beliefs, metabolism, previous drug consumption experience) affect the outcome. Only larger study populations can generate enough data that can be statistically treated and indicate what role those and other factors have in the result. For now, all we can say is that the results seem to be promising but inconclusive and that research is still at an early stage. The fact that studies use subjects that have been refractory to other therapeutic interventions means that psychedelic therapy is using worst-case scenarios to assess its efficacy.

Overall, the results and more importantly the questions raised by the research that has been carried out to date bring encouraging challenges for future investigation to tackle.

Conclusion

The resurgence of human psychedelic research under controlled clinical settings is a somewhat recent event. Scientists are now resuming work based on early scientific evidence generated in the first era of psychedelic research and on anecdotal evidence collected over time, which can date as far as millennia ago.

Understanding the mistakes that were made in the past and also the limitations that outdated scientific models have is key to setting the grounds for current research that can bring value and insight about the potential therapeutic applications of psilocybin and other classic psychedelics and also about how to use them as tools to better understand the functioning of the human brain and the nature of consciousness.

It is very important that a first set of guidances for human research with psychedelics have already been drafted by a team of experts and that these can be worked upon to set the standards of high quality research where the wellbeing and safety of the volunteers and patients are of the utmost importance.

The basic human research studies that have been described show very interesting aspects of the unique nature of psychedelics and their action on the human mind.

The clinical studies analyzed in this work are small-scale and show encouraging results regarding the therapeutic potential of psilocybin in patients refractory to conventional therapies. Nevertheless, they do present many limitations that will have to be addressed by future larger trials. The next phase of clinical research should use samples that are more representative of the population that it is trying to study and the necessary number of subjects in order to give it statistical and clinical significance.

It is possible that, during the following decades, we will have fewer stigmas and barriers associated with psychedelic research and a better understanding of the potentials and limitations of this intriguing class of compounds.

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