

UNIVERSITY OF PADOVA  
Department of General Psychology

Bachelor's Degree Course in  
PSYCHOLOGICAL SCIENCE



Final Dissertation  
Psychedelic Assisted Psychotherapy for Treating Substance Use Disorders

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Academic Year 2022-2023

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## Chapter 1- Introduction:

Despite the great strides made in the field of mental health in recent decades many people still suffer from a variety of mental ailments. According to the World Health Organization mental health conditions are increasing worldwide. Mental health problems now cause 1 in 5 years lived with a disability and about 20% of the world's children and adolescents now have a mental health condition. Suicide is the second leading cause of death among 15-29 year olds (World Health Organization, 2019). This decrease in mental health is further highlighted by the increase in substance consumption as a way to cope with stress. Despite the decline in smoking in recent years smoking still causes an estimated 480,000 mortalities annually in the US alone (US Department of Health and Human Services, 2014), and 5 million worldwide (WHO, 2011). Alcohol use is also very common (around 2.6 billion people are current drinkers). In 2016 the harmful use of alcohol caused around 3 million deaths which adds up to 5.3% of all deaths worldwide (WHO, 2018). 3 out of 10 US adults drink at levels that increase their risk of physical problems and of these heavy drinkers, a quarter has alcohol abuse or dependence problems (Willenbring et al., 2009).

Even with the rapid growth in the field of mental health, therapists still have relatively limited options when it comes to treating mental disorders. The last major advancement in psychotherapy was 30 years ago with the introduction of SSRIs for depression treatment (Johnson, 2018). According to some, psychopharmacology which is essential to psychiatry came to a halt in 2010 (Schenberg, 2018). Even with these available medications relapse rates are high and the need for improvement is severe (Schenberg, 2018). In response to this concern a promising field of study in recent years has been the research conducted on psychedelics as a treatment for mental health issues. Research on these substances has been supported by a variety of organizations ranging from government agencies such as the United Kingdom Medical Research Council to non-profit organizations like the Multidisciplinary Association for Psychedelic Studies (MAPS), Heffer Research Institute, and the Beckley Foundation. Current Psychedelic research has been conducted by leading academic research universities such as John Hopkins University, New York University, University of California, Imperial College London, University of Zurich, and University of Basel just to name a few (Reiff et al., 2020). Many studies have been conducted in such universities, some reaching

and completing phase 2 clinical trials. Based on these results both Psilocybin and MDMA have been granted "breakthrough therapy" status for treatment-resistant depression and PTSD respectively by the FDA. According to these findings, psychedelics could potentially become a useful tool for therapists in the near future.

Even though there have been many papers published on psychedelics during this so-called "psychedelic renaissance", there have been relatively few papers published on using psychedelics to treat substance use disorders. A look at the current state of psychedelic research can be important for informing and encouraging any future researchers with an interest in this treatment. Some studies show promising results especially when it comes to smoking cessation (Matthew W. Johnson, 2014), and alcoholism (Bogenschutz et al., 2015). An advancement in this field is not only important but necessary to combat substance abuse more effectively in the future. Therefore, the purpose of this literature review is to evaluate the safety and feasibility of psychedelics assisted psychotherapy in treating substance use disorders (focusing on smoking and alcohol use in particular), looking at the readily available scholarly resources.

## **What are psychedelics ?**

Psychedelics, also referred to as hallucinogens are psychoactive substances that alter perception and mood alongside numerous cognitive processes. The term psychedelic is more common in recent literature due to the misleading nature of the term hallucinogen. The word psychedelic comes from the Greek words "psyche" meaning soul and "deloun" meaning to reveal or to manifest. So a rough English translation could be "soul-revealing substances" (Carhart-Harris & Goodwin, 2017). We can divide psychedelics into classic psychedelics and non-classic psychedelics.

Classic psychedelics, also called serotonergic psychedelics are LSD (Lysergic Acid Diethylamide), Psilocybin, Ayahuasca (DMT), and Mescaline. Many of these substances have been used traditionally for millennia as they're found in a variety of plants and fungi such as the ergot fungus (*Claviceps purpurea*) and the peyote cactus (*Lophophora williamsii*) (Tupper et al., 2015) while others like LSD were synthesized at the beginning of the 20th century. These serotonergic psychedelics function as 5-HT 2A agonists, binding to 5-HT A2 receptors.

Classic psychedelics can be further divided into phenethylamines and tryptamines. The tryptamines include LSD, psilocybin, and DMT which all share their core structure with the neurotransmitter serotonin (Reiff et al., 2020). It should be noted that in this article the word "psychedelic" will be used to refer to these classic psychedelics.

Other non-classic psychedelics are MDMA (Methylenedioxymethamphetamine) which is an entactogen. It has partially overlapping effects with classic psychedelics while still being distinct from them. It should be noted that street drugs known as "ecstasy" or "molly" are often adulterated by other substances and may not contain pure MDMA which increases the likelihood of adverse effects. Other substances sometimes classified as psychedelics are Ketamine and Ibogaine which are both beyond the scope of this literature review.

## **History of psychedelics**

Although psychedelics have been used in spiritual rituals and traditional healing ceremonies in some cultures for thousands of years (Nichols, 2016), these substances and their effects remained unknown in the Western world until the 20th century. LSD was synthesized by the Swiss chemist Albert Hofmann in 1938 (Dos Santos & Hallak, 2020). The psychedelic effects of the substance were discovered in 1943 when Hofmann came into physical contact with the substance resulting in "an uninterrupted stream of fantastic pictures, extraordinary shapes with an intense, kaleidoscopic play of colors" (Hofmann, 1979).

The 1950s were a significant period for psychedelics. Aldous Huxley published his "The Doors of Perception" (Huxley, 1954) where he documented his psychedelic experience with mescaline. Following this, the term "psychedelic" was coined by Humphrey Osmond (Carhart-Harris & Goodwin, 2017). In 1955 an amateur mycologist R. Gordon Wasson and his wife became the first Westerners to experience a Mazatec ritual in Mexico using psilocybin mushrooms. Wasson published his findings in Life magazine in 1957 under the name "Seeking the Magic Mushroom" (Wasson, 1980). These publications led to an increase in both public and scientific interest in psychedelic substances. LSD began to be widely used in "psycholytic" and "psychedelic" therapies for mood disorders and alcoholism during this time (Gardner et al., 2019). It's estimated that tens of thousands of patients were given LSD over a period of around 15 years (Grinspoon, 1981 as cited in Johnson, 2018).

In 1960, Harvard psychologist Timothy Leary started working on the Harvard Psilocybin Project but became a polarizing figure after promoting the use of psychedelics outside of the clinical setting as a result of experimenting with the drugs himself. He was dismissed from Harvard alongside his friend Richard Alpert (who later became known as Ram Dass). Recreational LSD usage famously flourished amongst the counterculture movements of the 1960s which caused a severe political backlash. The opinion of the general public shifted towards a more anti-psychedelic sentiment which led to these substances becoming illegal in the US in 1965. This made it very difficult to conduct scientific research with these substances. After President Nixon signed the Controlled Substances Act of 1970 the already slowed-down research on psychedelics stopped entirely (Gardner et al., 2019). Substances such as LSD and psilocybin were classified as Schedule 1 which meant a high abuse potential and no medical use despite a lack of evidence. The following year Richard Nixon declared the "War on Drugs" thus pushing psychedelic research underground which spread throughout the US. Today this war on drugs is generally considered to be unsuccessful.

After 20 years in hibernation, the field of psychedelic research came back in the early 1990s. These early studies led to more studies as the safety and the potential efficacy of clinical psychedelic therapy were shown. While the Schedule 1 restriction remains, the attitude and the political climate towards these substances have shifted. This is partly due to the realization that more effective treatments are desperately needed (Johnson, 2018). Also, the preliminary evidence in the second phase trials looks very promising which reminds us that we should conduct these experiments with the utmost scientific rigor to avoid past mistakes. In this article, some of these experiments will be looked at.

## **How to Conduct Psychedelic Assisted Psychotherapy ?**

The two most commonly used types of psychedelic assisted psychotherapy are "psycholytic therapy" and "psychedelic therapy". Historically psycholytic therapy involves the digestion of low to moderate micrograms( $\mu\text{g}$ ) of LSD (30-200 $\mu\text{g}$ ) over multiple sessions to allow easier access to the subconscious. This type of talk therapy developed in Europe and was used between the 1950s to 1970s (Garcia-Romeu & Richards, 2018). Simultaneously Psychedelic therapy was developed in the US. It involved a non-psychedelic preparatory session followed by a high dose LSD (>250 $\mu$ ) session to create a "overwhelming and transcendent experience",

to gain insight into the patient's condition. The more recent experiments with psilocybin used versions of the psychedelic therapy which has been closely aligned with transpersonal psychology.

Psychedelic assisted psychotherapy usually involves three types of sessions. Preparatory sessions where the patient is given insights and education about the upcoming psychedelic experience. The therapists guide the patient to turn inwards, to understand their intentions, and to be open to new emotional experiences. The medication sessions where ideally the patient is accompanied by a male and female therapist team. The importance of this should not be undermined considering the sexual abuse that occurred in the 1980s with psychotherapy using MDMA (Passie, 2018). And finally integration sessions where the therapist works with the patient to interpret the experience into meaningful long-term change by identifying insights that occurred during the psychedelic experience.

The context (set and setting) is of the utmost importance. It's argued that the neglect of context could render the psychedelic experience ineffective and potentially hazardous. The set refers to the psychological expectations of the patient and the setting refers to the physical environment (Carhart-Harris et al., 2018). The medication session is conducted in a comfortable room, decorated to look familiar. After the ingestion of the drug, the patient lays on a reclining chair or a bed and is offered the option to listen to music and wear eye shades. For the following 6-8 hours the therapist remains with the patient to facilitate a sense of openness and trust (Pollan, 2018). It is thought that a therapeutic set and setting can help the patient when challenging experiences arise during the treatment. Challenging experiences are considered to be one of the most beneficial parts of psychedelic therapy and should not be considered as a negative occurrence, that being said the safety of the patient should still be the top priority.

## **Mechanisms of Action**

It must be stated that despite the growing interest in psychedelic research the biological and psychological mechanisms of action of psychedelics remain largely unknown. From a biological perspective, it's been demonstrated that the mind-altering effects of psychedelics result from 5-HT A2 agonism (Dos Santos & Hallak, 2020). It's also been hypothesized that

the enhanced neuroplasticity induced by psychedelics may be involved in their beneficial effects. Another biological observation related to psychedelic use is the decreased activity in functional connectivity in key hubs such as the Default Mode Network (Carhart-Harris et al., 2012). It's thought that the resulting "unconstrained" cognition style causes alterations in self perception and an increase in the connectivity of normally distinct brain networks. It's been suggested that this destabilization may provide an opportunity to alter brain network activity in a persisting manner.

From a psychological perspective, PAP can be considered a return to the roots of psychological therapy before biology and the brain took center stage. PAP shares many elements with psychodynamic models like a focus on the patient's sense of self, personal history, and environment. A unique aspect of psychedelic therapy is that patients seem to be doing their own psychological "heavy lifting" during these sessions. It's worth mentioning that this "homecoming" should now have a more empirically grounded approach to bridge the gap between psychology and neuroscience.



## Chapter 2- Methodology:

The scholarly sources obtained for this literature review were mainly obtained from the Scopus database which was used as the primary source of information, these findings were supplemented with articles previously obtained from the google scholar database which served as a secondary source of information.

The primary keywords used in the search of these articles were "psychedelics", "psychotherapy", "smoking cessation" and "alcohol dependence". The combination of the keywords "Psychedelics" and "psychotherapy" yielded a total of 845 results. When further combined with the keywords "smoking cessation" and "alcohol dependence" these results were reduced to 10 and 80 respectively.

42 articles from Scopus and 9 articles from google scholar were identified for a total of 50 articles after 1 duplicate was removed. After the screening procedure, 20 articles were included in the review after 4 eligible full-text articles were removed with reasons. The selection was done based on the research questions 1 (Potential efficacy of psychedelic assisted psychotherapy for treating substance use disorders) and 2 (Safety of psychedelic assisted psychotherapy for treating substance use disorders) as well as general information on psychedelics including historical use and potential integration with pre-existing treatments.

After the backward reference searching, also known as chain searching, the total number of articles was increased to 32. Once selected these 32 papers were reviewed and relevant information was extracted to create the current literature review.

## Chapter 3- Findings:

The findings section is divided into two separate sections, one for alcoholism and one for tobacco addiction. These findings are ordered chronologically with the exception of the online surveys. The meta-analysis, proof of concept and pilot studies, qualitative content analysis, and randomized clinical trials are taken into consideration to assess the safety and potential efficacy of these substances in the treatment of substance use disorders. Proposed synergies with other treatments are mentioned when relevant.

### **Alcoholism**

As mentioned before LSD was widely used to treat alcoholism in the past. Unfortunately, not all of these experiments satisfy the modern standard when it comes to scientific study design. A meta-analysis of randomized control trials that used LSD to treat alcoholism was done by Krebs and Johansen (Krebs & Johansen, 2012) where they managed to identify six eligible randomized control trials that included a total of 536 adults after the screening process. Volunteers with medical complications such as psychiatric complications, a history of schizophrenia, or overt psychosis were removed. The remaining participants were randomly assigned to receive LSD or a control condition. Ultimately 325 (61%) participants received LSD while 211 (39%) received a placebo. There was a significant beneficial effect of LSD on alcohol misuse for the medium term (6 months) and on abstinence from alcohol for the short term (3 months). These findings were not statistically significant in the long term (12 months and above). None of these trials reported any adverse effects of LSD on social functioning.

The authors comment on the findings saying "Given the evidence for the beneficial effect of LSD on alcoholism it is puzzling why this treatment approach has been largely overlooked" (Krebs & Johansen, 2012). According to these findings, a single dose of LSD is comparable with the effectiveness of daily ingested drugs such as naltrexone, acamprosate, or disulfiram. They also mention comments of previous researchers like Bowen stating that it was not uncommon for patients to become much more self-accepting and to show greater openness, adopting a more optimistic view of their capacities to solve future problems. Another comment worth mentioning is that according to Albaugh and Anderson, the regular consumption of the psychedelic peyote cactus and ayahuasca have been claimed by

indigenous groups to help maintain sobriety from both alcohol and other addictive substances (Bowen et al., 1970; Albaugh and Anderson, 1974 as cited in Krebs & Johansen, 2012). The article concludes with a recommendation for future researchers to use a shorter-acting psychedelic such as psilocybin as an alternative to LSD since they are similar in many aspects.

The promising results shown by the meta-analysis led to a proof of concept study by Michael P. Bogenschutz (Bogenschutz et al., 2015). The study consists of 14 sessions during a 12 week period, 2 of these sessions being psilocybin sessions. The study participants had to be diagnosed with active alcohol dependence using the DSM-IV. They had to have at least two heavy drinking days in the past thirty days before the screening procedure, concerned about their current drinking and not in treatment. Heavy drinking days were defined as five or more standard drinks (14g) for men and four or more for women. The remaining twelve sessions consisted of three preparation sessions, seven sessions of Motivational Enhancement Therapy (MET), and two debriefing sessions. During the psilocybin sessions interactions with the patients were non-directive and supportive. For safety reasons, the vitals were obtained at every visit and were checked regularly during the psilocybin sessions. Medication against possible adverse effects was present.

After the first psilocybin session, there was a significant decrease in drinking and heavy drinking days compared with the baseline. A large correlation was observed between the intensity of the experience and the positive change in drinking behavior. The intensity was determined by using the Mystical Experience Questionnaire. There were no serious adverse effects but headaches and nausea were common. This proof of concept study supported the idea that psilocybin can have long-lasting benefits for people dealing with alcohol use disorders when administered under supervision to carefully screened patients. Despite the positive impressions of this proof-of-concept study, the study itself was very limited. A very small group of people completed the second psilocybin session (only seven people), there was no control group, no blinding, and no way to biologically verify abstinence. In the following debriefing sessions seven common themes emerged (Nielson et al., 2018). These were "mysticomimetic" experiences (unity, noetic quality, sacredness, positive mood, transcendence of time and space and ineffability), ego dissolution, relationship to alcohol, motivation for change, stigma, commitment to change, dysphoric experiences and their resolution.

In the light of these promising results but severe limitations another study was conducted by Bogenschutz (Bogenschutz et al., 2022). Similarly to the previous study the participants had to meet the alcohol dependence criteria defined by the DSM-IV and had to have at least 4 heavy drinking days before the screening to join this randomized clinical trial. After the screening, the participants were randomly assigned to either the psilocybin group or to the active placebo group and took diphenhydramine instead of psilocybin. All participants had the option of attending twelve psychotherapy sessions alongside the psychedelic therapy during the 36 weeks. Four before the first psilocybin session, four between the first and second psilocybin sessions, and four after the second psilocybin session. The psychotherapy included Cognitive Behavioural Therapy (CBT) for alcohol use disorder (AUD) as well as motivational interviewing. All the study staff (except the pharmacist) and the participants were blinded during the trial.

Participants who were treated with psilocybin were more likely to have a lower percentage of heavy drinking days (PHDD) and to have a lower WHO risk level compared with the participants who were treated with diphenhydramine. The psilocybin group also showed moderate to large reductions in many categories of drinking-related problems compared with the active placebo. Three serious adverse effects were reported during the study all in the active placebo group, no serious adverse effects were reported in the psilocybin group but headaches, anxiety, and nausea were fairly common. This randomized clinical trial is the largest to date with 95 randomized participants (originally the sample size was even larger but recruitment was cut short due to COVID-19). This randomized clinical trial demonstrates that psilocybin administered in combination with psychotherapy shows a strong and sustained decrease in drinking which were greater than the active placebo. The biggest limitation of the study was the inefficacy of the blinding condition as it is very hard to create an active control group against psychedelics.

Another question worth asking is whether psychotherapy is necessary at all to see the benefits of psychedelics against AUD. An anonymous online survey done by Albert Garcia-Romeu (Garcia-Romeu et al., 2019), looked at the reduction in alcohol use following psychedelic use in non-clinical settings. All the participants had to be at least 18 years old, read and write English fluently, retrospectively met DSM-5 criteria for AUD, and had used a classic psychedelic outside of school or a medical setting followed by a reduction or cessation in alcohol use. The final sample was made up of 343 adults mostly male (78%) and from the US

(60%). Prior to their Reference Psychedelic Experience (RPE) most respondents (72%) met the criteria for severe AUD while the rest met the criteria for moderate or mild AUD. Also, respondents had been dealing with their drinking problem for around seven years on average and reported feeling distressed related to their alcohol consumption ranging from "a moderate amount" to "a lot". Most people in the study (approximately three-quarters) used either psilocybin (36%) or LSD (38%) in their RPE, using a mild (54%) or high (29%) dose. Most participants also reported that it has been at least one year since their experience with the substance (75%).

After their RPE participants reported "a change in values or life priorities", "orientation towards the future", and "an increase in their belief in their ability to abstain from alcohol". Despite experiencing withdrawal symptoms many reported that these symptoms were less severe compared with prior attempts. The majority (83%) of the participants did not meet the criteria for AUD at the time of responding to the study. Many showed improvements in personal relationships, diet, exercise, and work. According to this anonymous online survey, even naturalistic psychedelic use outside of treatment settings can be followed by a severe and enduring reduction in AUD. The paper suggests it may be plausible to think that serotonin 2A agonist psychedelics may possess some inherently anti-addictive properties. It must be noted that these findings are preliminary and more research must follow.

Another thing worth mentioning is that according to some there are potential synergies between psychedelic therapy and twelve-step programs (Yaden et al., 2021). Many people who struggle with AUD join Twelve Step Facilitation (TSF) programs like Alcoholics Anonymous (AA). These programs have traditionally rejected medication in favor of a pharmacotherapy-free approach focused on spirituality. Bill Wilson, the founder of AA, reported remaining alcohol-free for the rest of his life following a spiritual experience. He found AA to help others through spiritual awakening. What many don't know is that later on Bill had a psychedelic experience with LSD. Bill reported that "all of the assurances of my original experience were renewed and more" after the experience. AA is criticized in academic and clinical settings for its philosophical approach but it's the most widely used treatment for AUD with over 120,000 AA groups across 180 countries and around 2 million members ([www.aa.org](http://www.aa.org)). A unification of these two approaches may help millions of people in need of therapy. An AA/TSF group called Psychedelic in Recovery has already embraced this synergy and it'll presumably be followed by many more in the future.

As demonstrated, the clinical evidence for the efficacy and safety of psilocybin assisted therapy for AUD gets stronger with time and merits further study. Considering the adverse effects associated with psychedelics and the political nightmare in the 1960s it might be safe to say that psychedelic assisted therapies should be conducted in a clinical setting at least for the near future. That being said a unification with pre-existing treatments such as the TSF programs can potentially help millions of people around the globe.

## **Tobacco Addiction**

The results of the previously mentioned meta-analysis (Krebs & Johansen, 2012) inspired another study looking at the efficacy and safety of using psilocybin for treating tobacco addiction (Johnson et al., 2014). The pilot study itself lasted for around 15 weeks with three separate psilocybin sessions at weeks 5, 7, and 13. The Target to Quit Date (TQD) was the first psilocybin session in week 5. The inclusion criteria for the study included smoking a minimum of 10 cigarettes per day, being physically healthy, having multiple unsuccessful quit attempts in the past, and having a desire to quit. The screening was performed to exclude participants with either personal or family history of psychotic disorders, bipolar disorders, or drug dependence (excluding tobacco addiction). After the screening procedure, a total of 15 participants were enrolled in the study. These participants were discouraged from using other smoking cessation therapies during the study. During the non-psilocybin sessions cognitive behavioral therapy (CBT) was conducted for smoking cessation and to prepare the participant for the psilocybin sessions. For safety reasons, all participants vitals were monitored and emergency medication was present during the sessions. After the first psilocybin session, a staff member called the participants daily for 2 weeks to offer brief (<5min.) encouragement to not smoke. 12 of the 15 participants completed all three psilocybin sessions while the remaining three completed two sessions. Common symptoms during the study were increased blood pressure and heart rate, anxiety, and headaches. No serious adverse effects occurred during the study.

Biologically verified results demonstrated that 12 out of 15 (80%) of the participants showed abstinence at 6 months follow-up. Also, even though the remaining participants resumed daily smoking they had greatly reduced their levels of smoking compared with the baseline. When asked about the mechanisms that helped them to quit the most common answers were

"changing orientation towards the future", " increasing belief in their ability to quit", and " a change in life priorities and values". This study demonstrates significantly higher abstinence rates than other smoking cessation treatments. Around 34% for varenicline treatment and around 25% for bupropion treatment at six months post-TQD (Jorenby et al., 2006; Gonzales et al., 2006 as cited in Johnson et al., 2014). Efficacy was also higher than in other studies employing similar CBT-based support. It's worth mentioning that the fact that two participants voluntarily declined a third psilocybin session can be interpreted as further proof that psilocybin does not cause compulsive-seeking behavior.

As mentioned in the secondary analysis of the study (Garcia-Romeu et al., 2015) abstainers scored higher on measures of psilocybin-induced mystical experience. According to the fact that no significant differences were found in the intensity of the drug's effects among the participants, it is thought that the mystical-type subjective effects may have been responsible for the smoking cessation. Also, the magnitude of the mystical qualities of the psilocybin experience measured with the State of Consciousness Questionnaire (SOCQ) seemed to predict a subsequent decrease in tobacco craving and use. Having lasting beneficial effects from a single experience is highly unusual in the modern biomedical paradigm. That being said trauma seems to work similarly, resulting in long-lasting negative effects from a single adverse event. Considering this it does not seem trivial that psychedelics may produce a similar long-lasting positive effect on people. For this reason, Garcia-Romeu et al. describe these long-lasting results as "PTSD-like".

The long-term follow-up of the study (Johnson et al., 2017) showed that 10 participants (67%) remained smoking abstinent at 12 months follow-up and 9 participants (60%) remained smoking abstinent at long-term (over a year) follow-up. Although limited by the small sample and a lack of control conditions these findings indicate that psilocybin treatment may be around twice as efficient as currently available medications for smoking cessation. The authors are currently conducting a randomized comparative efficacy trial with a larger sample size that's estimated to be completed around December of 2023 (ClinicalTrials.gov Identifier NCT01943994).

According to the qualitative analysis of participant accounts (Noorani et al., 2018) which was done to help identify the perceived mechanisms of change leading to smoking cessation. Participants described smoking as offering a time and space for experiencing and processing

their emotions, others described it as an unthinking compulsive habit and finally, some described cigarettes as "friends" providing comfort and companionship. Among the participants, one went as far as to describe his connection to cigarettes as stronger than his relationship with his wife. A common theme among the participants was a sense of connection, using the cigarettes as tools to connect with their feelings or with other people that also smoke. The factors contributing to smoking cessation reported in the study can be divided into psilocybin factors and non-psilocybin factors. Psilocybin factors contributing to smoking cessation included Insights into self-identity and smoking behavior, the experience of interconnectedness, feelings of awe and curiosity, and reduced withdrawal and cravings. The non-psilocybin factors contributing to smoking cessation included preparatory counseling, rapport with the study team, momentum gained by the first 8 hours of abstinence, and therapeutic intent. These two factors were viewed as working together to create a coherent therapeutic structure that benefited from the synergy created among the separate elements.

Participants were asked whether they thought psilocybin was addictive in a similar manner to tobacco. All 12 participants stated that according to them psilocybin was not addictive and that there was no similarity between the addictive nature of cigarettes and their experience with psilocybin. This is in line with the widely held view reported by participants that psychedelic experiences provide a confrontation with one's problems rather than an escape from them (Noorani et al., 2018). Interestingly quitting smoking was often reported as one of the least important effects of the study for the participants. Other long-term changes included increased aesthetic appreciation, heightened altruism, and increased pro-social attitudes. For the majority of the participants, the study created an insight into their self-identity and smoking behavior that resulted in smoking no longer being appealing. Furthermore, these insights were generally not considered new but seen as the "remembering" or "returning" of something that was already known.

The same researchers also conducted an anonymous online survey to see whether people's experience in a non-laboratory setting would lead to a similar decrease in smoking (Johnson et al., 2017). Only classic psychedelics were taken into account for the survey. The participants had to be over 18 years old and be able to speak, read and write English fluently. Only the reference psychedelic experiences that occurred over a year ago were taken into consideration to emphasize longevity. Participants were divided into three separate groups



according to their smoking cessation outcome. The quitting group, the reducing group, and the relapsing group. A total of 358 participants were included in the study after the screening process. Some withdrawal symptoms were rated as similar in severity to previous quit attempts while some others such as restlessness, depression, irritability, and craving were rated as "much less severe" when compared with prior quit attempts. It's worth noting that participants in the relapse group rated their RPE as less personally meaningful and spiritually significant than those in the quitting and reducing groups. This also supports the idea that spiritual experiences have a mediating role in promoting long-term smoking abstinence as previously mentioned (Garcia-Romeu et al., 2015).

Results showed that a total of 137 (38%) quit smoking after their reference psychedelic experience (RPE), 100 participants (28%) showed a significant reduction in smoking, and 121 (34%) individuals reported a temporary reduction before relapsing back to their baseline smoking. These results indicate that even naturalistic psychedelic use can lead to a decrease in smoking. In addition to smoking 152 (42.5%) participants reported a reduction in alcohol consumption and 100 (28%) participants reported a reduction in the consumption of other drugs. The majority of the participants did not report any negative effects from their RPE and the reported adverse effects were not serious. The results also support the hypothesis that psychedelics may provide a general benefit in treating a variety of SUD (rather than just tobacco addiction).

The reasoning behind the pilot study was that despite the hugely detrimental impact of smoking on our society most behavioral interventions and pharmacotherapies show only a modest success rate (<35%) at six months follow up (Cahill et al., 2014). Findings indicate that psychedelic therapy is around twice as effective. These results while preliminary, due to the strong limitations of the study, are impressive. The results discussed here indicate that 5-HT 2A agonists may hold therapeutic potential in treating a variety of SUD in a structured treatment program. It's also worth mentioning that while psilocybin sessions themselves are not really "spiritual" in nature, participants regularly attributed a high level of spiritual significance to their psilocybin experience which in turn seems to be associated with better treatment results. Considering the safety profile and the efficacy of these substances in the treatment of smoking It's fair to expect to see this approach in clinical practice soon.

## Chapter 4- Discussion:

The discussion section includes some common concerns regarding the use of psychedelics for therapeutic purposes such as safety, ethics, and stigmatization. The importance of research integrity is underlined and the optimization of rigor and transparency in future research regarding psychedelics is discussed.

### **Safety**

Psychedelics seem to have an excellent safety profile considering the lack of serious adverse effects in contemporary clinical research. Furthermore, according to a UK-based multicriteria analysis comparing the overall harm of various drugs psychedelics are among the least harmful drugs in terms of both harm to self and harm to others (Nutt et al., 2010).

Psychedelics such as Ecstasy (MDMA), LSD, and Mushrooms (Psilocybin) were considered to be even less harmful than Cannabis not to mention alcohol, tobacco, and opioids. This does not mean however that psychedelics are completely risk-free substances. There are many adverse effects associated with psychedelic use and certain precautions must be taken to ensure the safety of the participants. Luckily today there are robust guidelines in place to help guide researchers on psychedelic research safety (Johnson et al., 2008).

### Historical Lessons

As mentioned previously these substances were used by indigenous cultures for millennia. That being said these substances were not used casually as they were considered to be of divine origin. Their ingestion was often restricted to sacramental and healing contexts under controlled ceremonial guidelines. Some common themes between modern psychedelic use safety and psychedelic use by indigenous cultures include structured use (rituals), restrictions on use, and a need for guidance and appreciation of the powerful psychological effects of psychedelics.

### Potential Risks

Unlike other drugs such as opioids or sedatives, the primary safety concerns associated with psychedelics are mostly psychological rather than physiological.

*Physiological Toxicity:* There is no evidence of neurotoxicity in classic psychedelics, that being said MDMA has been shown to have neurotoxic effects at high doses but is still considered to be generally safe. Some readers might have concerns about chromosomal damage associated with psychedelic use. These concerns stem from an anti-LSD media campaign done by the U.S. government in the late 1960s. Further investigations and follow up studies refuted the hypothesis that LSD or any other psychedelics causes chromosomal damage.

*Abuse and dependence:* Psychedelics are not typically considered drugs of dependence because they do not cause compulsive drug-seeking behavior. Furthermore, there are no withdrawal symptoms associated with psychedelic use (O'Brien, 2008). These findings are in line with the observations that they are not reliably self-administered in non-human animals (Fantegrossi et al., 2004).

*Psychological Distress and Dangerous Behaviour:* The most likely risk associated with psychedelics is commonly referred to as a "bad trip" which includes experiencing anxiety, panic, dysphoria, and/or paranoia under the influence of the substance. These feelings may disorient the user causing potentially dangerous behaviors such as aggression against self or others. Although very rare it must be mentioned that there have been instances of individuals ending their lives by acts such as jumping from a building while under the influence of psychedelics.

*Prolonged Psychosis:* The possibility of prolonged psychosis is the reason for the exclusion of participants with a personal or family history of schizophrenia or any other psychotic disorders. No such case has been reported in modern studies thanks to careful screening procedures but rare cases have been reported in the past. It's worth mentioning that psychedelics are not considered to cause psychosis but to "reveal" it in specially susceptible individuals.

*Lasting Perceptual Abnormalities:* Probably the rarest adverse effect mentioned thus far is the possibility of the onset of Hallucinogen Persisting Perception Disorder (HPPD). This condition is sometimes also referred to as "flashback" and involves re-experiencing perceptual effects similar to those experienced during the psychedelic experience. To be diagnosed with this disorder these perceptual effects must be distressing or must impair

functioning. Not much is known about the disorder due to how uncommon it is apart from the fact that it's mainly observed in the illicit users of psychedelics.

### Guidelines for Safety

*Participant Selection:* To minimize the risk of adverse effects the participant must be in general good health. This is assessed by their medical history, physical examination, hematology, and urinalysis. Since psychedelics increase both heart rate and blood pressure participants with resting blood pressure higher than 140 systolic and 90 diastolic (mmHg) are excluded. Participants that use certain medications that might interfere with the effects of psychedelics such as antidepressants or lithium should be excluded. As previously mentioned participants with current or past history of schizophrenia or any other psychotic disorders should be excluded. Even if the participants themselves don't meet the criteria for these disorders if they have a first or second-degree relative that does they should still be excluded since these disorders are considered to be genetically hereditary.

*Study Personnel:* The staff members who are also sometimes referred to as the monitors accompany the participants during psychedelic therapy. The staff members should be familiar with the altered states of consciousness induced by psychedelics. They should have significant knowledge about the potential medical and psychological markers of adverse reactions to the drug. Furthermore and possibly even more importantly they should have good social and communication skills.

There's usually a primary monitor and a secondary "assistant" monitor, this ensures that the participant is never left alone in case the primary monitor has to use the bathroom for example. Having a male-female team of monitors may boost feelings of security, whenever this is not possible both monitors should be the same sex as the participant. There must be a positive social rapport between the participants and the monitors to minimize the risk of adverse reactions to emotional stimuli. At no point should the participant be made to feel inhuman (like a guinea pig) or isolated.

*Physical Environment:* It's believed that a comfortable and aesthetically pleasing environment may reduce the probability of psychological distress during the psychedelic session. An overly "clinical" looking environment (white walls, lab coats, medical equipment, etc.) may increase anxious reactions (Strassman, 2000). In fact, there are reports of patients having hallucinations of extraterrestrials experimenting on them while under the influence of psychedelics in a laboratory setting. A room resembling a living room is generally preferred for conducting psychedelic therapy.

When it comes to the physical safety of the environment certain potentially dangerous objects such as breakable glass and furniture with sharp corners should be avoided. If there is a window in the session room the study staff must make sure that the patient can't open it in a delusional state. The session room should not have a phone (Including the phone of the participant) as it might be distracting or become a potential safety risk if the participant tries to call someone in a delusional state. Having a private restroom near the therapy session room that cannot be locked from the inside would be ideal. If that is not possible the staff members should accompany the participant while gently offering support and wait outside the bathroom to make sure no one else enters.

*Preparation of the Participants:* It's highly recommended that all participants carefully review the consent form. Multiple preparatory sessions should take place before the psychedelic session to familiarize the patient with the staff members and the room where the session will take place. The main purpose of these preparatory sessions is to build rapport with the patient to minimize the risk of fear or anxiety during the psychedelic session. These preparatory sessions should include a detailed discussion of the potential range of experiences (ego dissolution, interconnectedness, etc.) that may be encountered after the ingestion of the psychedelic substance. During these sessions, the participants should be provided with guidance on how to handle difficult psychedelic experiences. It is said that the best way to deal with such difficult experiences is to surrender to them instead of resisting the experience.

*Safety During the Psychedelic Therapy:* A physician and emergency medication should be available in case of acute adverse effects. The staff should be the only people the patient interacts with during the psychedelic session. Any attempt of the participants to leave the session site should be met with a compassionate but firm direction to return to the session room. In the case that the participant becomes anxious, emotional support should be provided. If verbal support is not sufficient then simply holding the patient's hand also called "interpersonal grounding" can be greatly beneficial. According to patient reports this provided a strong sense of stability and connection during the session. This practice of holding the hand of the patient should be demonstrated during the preparatory sessions to normalize hand holding. Participants' psychological well-being should be periodically (every hour or so) checked by the staff members to make sure that the participant is not in need of support.

*Post-session procedures to ensure safety:* After the completion of the psychedelic therapy session participants must be reminded not to drive or engage in any other potentially dangerous activity. After the psychedelic therapy session, one or more post-session meetings should be done (ideally the next day) to ensure the psychological well-being of the patient and to provide an opportunity for the patient to express their thoughts and feelings regarding their psychedelic experience. This follow-up session also allows the staff members to check for any potentially persisting adverse effects such as HPPD.

## **Ethical Concerns**

It's said that despite the popularity of contemporary psychedelic research it has received little attention from medical ethicists. William R. Smith and Dominic Sisti published a paper to attempt to fill this gap in ethical analysis (Smith & Sisti, 2021). In this paper, it is stated that the unusual features of psychedelics warrant an enhanced informed consent process that is more comprehensive than what may be typical for other medications. These unusual features include shifts in values and personality, mental health risks, and concerns regarding therapeutic touch.

### Shifts in Values and Personality

The observed effect of psychedelics to cause experiences regarded as "spiritual" creates many ethical problems. For example, a non-spiritual or atheist patient may take the development of

a newfound sense of spirituality or belief in god to be detrimental to his life if it's disruptive towards his prior values or relationships with others. Similarly, a religious person who believes that spiritual experiences can only occur as a result of intensive spiritual work or as a divine gift might feel distressed after the experiment if they come to see this process reduced to a biochemical reaction.

Also, a significant increase in the personality trait openness has been found in participants who had a complete mystical experience following a high dose (30mg/70kg) psilocybin session (MacLean et al., 2011). These effects were enduring, lasting for over a year. These findings are quite interesting considering that personality domains remain relatively stable throughout adulthood. The personality domain openness includes greater aesthetic appreciation, sensitivity, imagination, fantasy, and tolerance. To some, these might seem like positive changes but according to others they might be considered undesirable. The potential outcome of increased openness should be shared with the participants before the psychedelic session as a change in personality trait is a significant thing that can alter a person's life in several ways.

#### Risk of Trauma Re-Exposure

The possible psychological adverse effects of psychedelics have already been addressed but an area that has not been addressed is the potential re-exposure to trauma. As stated previously psychedelics provide a confrontation with one's problems which might include past experiences that the patient doesn't want to revisit. The possibility of reliving traumatic experiences should be carefully discussed with the participant before the psychedelic session.

#### Therapeutic Touch

There are certain ethical complexities with using therapeutic touch such as holding the patient's hand while they're under distress. An obvious example is that a patient might initially decline therapeutic touch during the consent process but then change their mind when experiencing distress during the psychedelic session. Here the therapists will have to carefully make an ethical choice based on the situation.

## **Stigma**

Despite the attitude change towards psychedelics in recent decades, there's still a high amount of stigma surrounding these compounds. A quasi-experimental survey study that explored the attitudes of clinical psychologists toward psychedelic substances found that although the general interest in using psychedelics in mental health treatment is growing it's still not widely accepted (Davis et al., 2022). These results demonstrate that misinformation and a lingering cultural stigma towards psychedelics remain even among highly educated mental health professionals. This demonstrates a need to better educate not just the general public but also the therapists on the safety profiles of psychedelics in comparison to other mind-altering substances. This is important considering social stigma could affect the cultural setting negatively, influencing the participants' expectations and increasing the probability of adverse effects such as anxiety during the psychedelic therapy session. Another demonstration of this stigma is the fact that certain governments such as the Australian government intentionally make it difficult to conduct experiments with psychedelics as it's considered risky (Gardner et al., 2019). This conservative "better safe than sorry" attitude might be relished by some but it undoubtedly slows down scientific innovation.

## **Rigor and Transparency**

The excitement for psychedelic research is growing which puts researchers under the spotlight. It must be remembered that in the past over-enthusiasm has caused research on psychedelics to go into dormancy for over 20 years. Careless research would not only endanger the participants taking part in psychedelic research but it could jeopardize any potential future research about these compounds. Considering this fact getting the science right must be the top priority. A research checklist has been proposed to optimize the rigor and transparency of psychedelic research (Petranker et al., 2020). In the paper it's stated that following a standard psychedelic research checklist may provide several benefits such as creating robust and transparent science held to a high scientific standard, protecting scientists from both skeptical policymakers and institutional gatekeepers who'll question their research, clearly communicating any limitation present within the study to overzealous readers while maintaining an excitement for the future of psychedelic research. Such a checklist would include a pre-registration, open materials and data, replication, and limitations.



### Pre-registration:

To avoid Questionable Research Practices (QRP) scientists should set out to study the true effects of these substances whether for good or ill. Pre-registration means planning and uploading a complete, date-stamped experimental design and analysis plan ideally before data collection begins. This may sound daunting to some but it protects the researchers from hypothesizing after the results are known.

### Open materials and data:

Open material means all questionnaires, tasks, and stimuli used in the methods section of a paper are made available to the public. This would make it possible to replicate the study without having to contact the researcher. Open data refers to researchers sharing all the data collected as a part of their study. This would have to be shared alongside their first publication to ensure no one uses their data to publish before them. Even in the case of large data sets it's recommended that the data is not kept private for over 2 years to ensure that all data sees the light of day.

### Replication:

Replication is the cornerstone of the scientific method and ensures that the research is solid while providing the opportunity of working as a community of researchers. It's hard for researchers to get approval for using Schedule 1 substances such as psychedelics but hopefully, we'll see a lot more replication studies on these substances in the near future.

### Limitations:

It should be reminded that reporting the limitations of a well-designed study does not undermine its findings but serves to give other researchers context.

Integrity must be maintained while conducting research on psychedelics. Psychedelic research must protect itself from private interests that wish to bend regulations to get fast results or market advantage. Working within legal frameworks is necessary to not repeat the mistakes done in the past. This way psychedelic science will become a credible and durable science that's able to shape legal and medical policies in the years to come.

## Chapter 5- Conclusion:

While the results discussed in this paper are preliminary they are encouraging. The safety profile and efficacy demonstrated by psychedelic assisted psychotherapy in contemporary studies for treating substance use disorders are remarkable. That being said we must take care not to get overzealous or fanatical as history shows us the potential dangers of such behaviors regarding these substances. Our top priority should be to do good science with integrity while putting the safety of the patients first.

There are many potential benefits of psychedelic assisted therapy in comparison with other available treatments for substance use disorders, the most obvious being the relatively low amount of sessions needed to see long-term benefits. This is important as it can help people who are not in favor of traditional pharmacotherapy and who don't want to self-medicate daily. Also, fewer sessions could lead to a monetary benefit for people by creating a cost-effective alternative to daily ingested pharmaceuticals.

Mental therapists are in urgent need of new treatment options for a variety of mental disorders including substance use disorders. It seems only natural that the scientists of the soul use soul-revealing tools to treat their patients.

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