UNIVERSITY OF PADOVA

Department of General Psychology

Bachelor's Degree Course in Psychological Science

Final dissertation

The use of psychedelics in psychotherapy: A systematic review

Supervisor

Professor Agrillo Christian

Candidate: Styliani Karaiosifidou

Student ID number: 2014508

Academic Year 2022/2023

Table of contents

Abstract

In the recent years, the resurgence of interest in the therapeutic potential of psychedelic substances has initiated a profound transformation in the field of psychiatry. This thesis embarks on a comprehensive exploration into the role of psychedelics as powerful tools within psychotherapy, delving into their historical significance, their mechanisms on the brain and their contemporary relevance. The primary objective of this thesis is to conduct an in-depth exploration into the potential promise of psychedelic drugs within the field of psychiatry, specifically investigating their potential use as aids to psychotherapy.

A systematic literature review was conducted, to select the most relevant articles concerning the use of psychedelic drugs in psychotherapy. Of particular interest were clinical trials utilizing MDMA, Psilocybin, Ketamine, and LSD, given their extensive application in therapeutic settings.

Results showed that, that combining these psychedelic drugs with different kinds of therapy, could offer an effective and safe alternative in treating many disorders, including various substance use disorders, PTSD and comorbid conditions, Obsessive compulsive disorder (OCD), Major Depressive Disorder (MMD) as well as depression and anxiety in life threatening diseases.

In conclusion, this exploration highlights the therapeutic promise of psychedelic drugs in psychotherapy, showing their efficacy and safety in treating diverse mental health conditions. It is imperative to expand research in this area, to fully harness their possible potential as valuable aids in psychotherapeutic practices.

Introduction

1.1 Definition

Psychedelics are mind-altering substances that have a long history of therapeutic use, enabling individuals to experience altered states of consciousness and to perceive reality differently (Wheeler & Dyer, 2020). The term "classical psychedelics" refers to a wide range of substances that interact mainly with serotonin (5-HT2A) receptors in the brain (Gattuso et al., 2023).Interestingly, the word ‘psychedelic’ comes from the combination of two Greek words: 'psyche' (ψυχή), meaning 'mind' or 'soul,' and 'delein' (δηλοῦν), meaning 'to reveal,' 'to manifest,' or 'to become visible' (Carhart-Harris, 2018).

1.2 Categorization

Psychedelic drugs can be categorized into four groups, depending on their pharmacology and chemical structures: (1) classic psychedelics, which act like serotonin 2A (5-HT2A) receptors, (2) empathogens or entactogens, (as 3,4- methylenedioxy-methamphetamine; MDMA), which function as mixed serotonin and dopamine reuptake inhibitors and releasers. (3) dissociative anesthetic agents (as ketamine), which act as antagonists for the N-methyl-D-aspartate (NMDA) receptor; and (4) atypical hallucinogens, that have an impact on multiple systems of neurotransmitters (Reiff et al., 2020).

The first category, known as classic or serotonergic psychedelics, consists of lysergic acid diethylamide (LSD); psilocybin, a plant-derived indoleamine produced by many mushroom species; N,N- dimethyltryptamine (DMT) that is contained in the South American sacred beverage ayahuasca; mescaline; 2,5-dimethoxy-4-iodoamphetamine (DOI); 2,5-dimethoxy-4-bromoamphetamine (DOB), and others (Pearson et al., 2022).

Classic psychedelics can be further subdivided into tryptamines and phenethylamines. On the one hand, tryptamines encompass both synthetic compounds like LSD and naturally occurring indoleamines like psilocybin and DMT. On the other hand, phenethylamines consist of substances such as MDMA, which shares pharmacological similarities with amphetamine, methamphetamine and mescaline, the main psychoactive compound in the peyote, San and Peruvian torch cacti (Schenberg , 2018 and Reiff et al.,2020).

1.3 Effects

Psychedelics are commonly associated with the subjective phenomenon of ego dissolution, characterized by the dissolution of one's sense of self-identity, which in turn can lead to the modification of dysfunctional behavior patterns, thoughts, and emotions (Wheeler & Dyer, 2020). Most of the psychedelic compounds, induce perceptual effects like heightened perception, distortion, illusions, mental imagery, basic and complex hallucinations, while enhancements in the vividness of colors, textures, contours, light and sound intensities, and variations in timbre are amongst the commonly reported perceptual changes (Swanson, 2018).Interestingly, some of the effects unique to psychedelic substances are the so-called ''mystical experiences'' that are characterized by a feeling of deep connection between all individuals and things (Johnson et al., 2019). Apart from this, in settings with a supportive atmosphere, traditional psychedelics can foster emotions of compassion , bonding ,trust ,closeness, forgiveness, acceptance and a deep sense of unity with others (Swanson, 2018). This could be the reason why in clinical settings, the experiences brought about by psychedelics have been associated with significant and enduring transformations in one's personality (Pearson et al., 2022). For example, in a study conducted by Belser (Belser et al.,2017),all individuals involved in it, shared common themes including gaining insights into important relationships, experiencing emotional release and catharsis, attaining wisdom, and reevaluating life priorities as well as experiencing feelings of bliss and love, a heightened sense of embodiment, changes in personal identity, and a profound sense of interconnectedness (Wheeler & Dyer, 2020).

In fact, after a single controlled psychedelic experience, it has been observed a long term increase in the personality trait openness (Swanson, 2018). Last but not least, studies have indicated that the majority of psychedelic substances do not cause any physical addiction (Wheeler & Dyer, 2020).

1.4 Why is it Relevant

The field of psychiatry is facing an urgent need for innovative tools and approaches that can effectively assist in addressing the ongoing crisis and challenges posed by neuropsychiatric disorders. Neuropsychiatric conditions, such as mood and anxiety disorders, are among the primary contributors to disability on a global scale and impose a significant economic burden on society (Ly et al., 2018). A significant number of individuals with major depressive

disorder, do not respond adequately to conventional treatments such as selective serotonin reuptake inhibitors (SSRIs) or psychotherapy (Wheeler & Dyer, 2020).Even after undergoing multiple treatment attempts, this subgroup of patients, commonly referred to as "treatment-resistant," fails to meet the criteria for remission (Pearson et al., 2022).However, even the individuals who respond positive to treatment, typically need to undergo therapy for at least 2-4weeks before experiencing noticeable improvements (Ly et al., 2018). Nonetheless, many patients may discontinue medication prematurely or before its effectiveness can be fully realized, often due to the occurrence of side effects (Pearson et al., 2022).

2. History

Psychedelic compounds that produce psychedelic effects have been used since pre-historical times for healing purposes , in ceremonies, rituals and for enjoyment (Swanson, 2018). In the late 1800s, a new era of psychedelic research begins, which prompts the German pharmacologist Louis Lewin to scientifically examine the peyote cactus. This brings important advansment, when, in 1897, the German pharmacologist Arthur Carl Wilhelm Heffter extracts the active compound mescaline from the peyote cactus (Sessa, 2016).After the isolation of mescaline, scientists began to experiment with it, dosing themselves along with their colleagues and students and then sharing their findings in medical publications (Swanson, 2018). In 1912, the German pharmaceutical company Merck creates and obtains a patent for 3,4 Methylenedioxymethamphetamine (MDMA) that will not be used until the 1950s. In 1919, Ernst Späth, an Australian chemist, becomes the first to synthesize mescaline. Its synthetic form, is going to be used 8 years later, by a German chemist named Kurt Beringer in his experiments, where he links the psychedelic experience to psychosis (Sessa, 2016). Among the early pioneers who actually investigated scientifically the study of mental illness, was the German psychiatrist, Emil Kraepelin, who tried to understand the nature of mental disorders by using the method known as "experimentally induced psychoses" (Nichols & Walter, 2021). Later, also, Stockings, aimed at establishing a connection and similarity between the effects elicited by mescaline and the symptoms observed in naturally occurring psychoses, by reporting the outcomes of a series of self-experiments with mescaline and experiments on groups of people without mental illness. As he observed, there was not much difference between the mental alterations induced by mescaline and those seen in individuals

with psychoses. From his discoveries, Stockings highlighted the significance of mescaline in helping gaining insight about how mental illness works (Nichols & Walter, 2021).

The next, contemporary phase of psychedelic research begins with a discovery of a new compound: lysergic acid diethylamide (LSD). Even though it was found in 1938, the true potential of LSD to change mood and perception was not completely recognized until 1943, when its inventor, Albert Hofmann, conducted a personal experiment (Belouin & Henningfield, 2018). Hofmann, a chemist in a pharmaceutical company named Sandoz, took 250 micrograms of LSD and observed by his colleagues, he cycled back to his home from the laboratory, on a day that would later gain international recognition as Bicycle Day (Sessa, 2016).Due to the potent nature of LSD and its inexpensive synthesis process, Sandoz started distributing big amounts of the drug, to researchers interested in exploring its clinical potential. That led to the beginning of extended investigations of psychedelic drugs and their impact on consciousness and mental illnesses (Pearson et al., 2022). As mentioned before, during the 1940s, psychedelic drugs were classified as a psychotomimetic substances and they were associated with the neurophysiology of schizophrenia. Nevertheless, the following decade is marked with the increased recognition of LSD and related psychedelics in the area of psychotherapy (Sessa, 2016). In 1949, two American psychiatrists, Max Rinkel and Nick Bercel, obtained LSD from Sandoz and introduced it to the United States where they began experimenting with it (Johnson et al., 2019). In 1950, Busch and Johnson studied LSD's impact on 21 psychotic patients. Since eight of them showed significant progress, that led to the assumption that LSD might be promising for psychotherapy. This was the earliest mention of LSD used as psychotherapy support. After one year, Mayer-Gross publishes the earliest English paper comparing meschaline and LSD effects (Nichols & Walter, 2021). Meanwhile, in 1952, the british psychiatrist Ronald Sandison (1954), starts contributing LSD to patients who stopped making progress with traditional psychotherapy. Another important event took place in 1956 when the Czech physician, Milan Hausner manages the biggest LSD therapy program ever happened, near Prague, which provided treatment to more than 700 patients and included more than 6000 psychedelic sessions. It even continued secretly after LSD was prohibited in the Western world (Sessa, 2016). The following year, psilocybin mushrooms started to become famous in the public eye when the popular American magazine Life issued Wasson's experiences. Soon, psychedelics start to integrate into both the Western culture and the scientific and clinical practices (Johnson et al., 2019). Around that time, two separate psychotherapeutic methods of utilizing LSD prevailed: the ''psycholytic'' and the

‘’psychedelic’’. The Psycholytic approach, named by Sandison in 1960, was different from the psychedelic in that it entailed the administration of smaller doses of LSD, usually 50-200 μg, right before the psychotherapy session. With this amount of dosage, the patient was able to stay oriented and to communicate effectively with the therapist, as well as to understand the therapeutic nature of the experience. During the period from 1953 to 1968, over 7,000 patients received treatment using this method(Nichols & Walter, 2021). In the middle of the 60s, there was a clear progress in the research with psychedelic drugs, when it was discovered that also dissociative anesthetic compounds like ketamine and phencyclidine (PCP) can induce effects similar to psychedelics (Vollenweider & Kometer, 2010). The 1960s seem to be a thriving era for the psychedelic research. Between 1950 and 1966, more than 2000 clinical studies are published, highlighting the potential therapeutic benefits of LSD, psilocybin and ketamine and their overall safety when they are used in clinical settings. These studies, that involved more than 40,000 participants, showed that these substances have potential benefits in treating conditions such as anxiety and obsessive– compulsive disorder (OCD), depression, sexual dysfunction and alcohol addiction, as well as providing pain and anxiety relief in patients with terminal cancer (Sessa, 2016 and Vollenweider & Kometer, 2010). However, even though these findings were very promising, the gradually increased recreational use of LSD triggered a political and social negative reaction and a concern about its safety (Pearson et al., 2022). As a result, Sandoz Pharmaceuticals, ceased the administration of LSD in 1966. Its association with anti-war protesters and the counterculture ‘’hippies’’ movement, further contributed to the social agitation and indirectly initiated the ‘’drug war’’ by the Nixon administration in the United States. On top of this, the FDA (food and drug administration), placed stricter evaluation criteria in line with the Drug Amendments of 1962, which required demonstrating both the safety and effectiveness of a drug before approval. In contrast to many drugs, defining and measuring the effectiveness of LSD and other psychedelics is much more challenging and complicated (Nichols & Walter, 2021). As a consequence, around 1970, many Western countries classified LSD and similar drugs as Schedule I substances (Vollenweider & Kometer, 2010). Following this, lots of reports purpose that LSD leads to chromosomal damage, although subsequent studies challenged these findings. However, the damage was done and the stigma towards psychedelics became big and continued for multiple years (Sessa, 2016). Therefore, the 1970s and 1980s are the dark periods for psychedelic therapy. Research with human subjects becomes very limited, funding and legal LSD becomes impossible to find and the general enthusiasm for the therapeutic possibilities of psychedelics slowly fades away, leaving many areas of research uninvestigated and

multiple questions unsolved (Vollenweider & Kometer, 2010). Following the termination of the Spring Grove Hospital studies in 1976, a series of pioneering research investigations conducted in the mid-20th century in the USA, there was a cessation of clinical research involving psychedelics until 1994 (Nichols & Walter, 2021). At that period the psychedelic investigation continued mostly underground and with substances that were still legal. For example, in the beginning of the 1980s, MDMA, which was first known as ‘’Empathy’’, is starting to be used by psychotherapists in clinical settings. However, gradually MDMA, with its new name ‘’Ecstasy’’, becomes famous and spreads in the public. In response, the DEA classifies MDMA as Schedule *I* substance for a one-year period in May 1985, awaiting for more investigations. This inspired Doblin to establish the Multidisciplinary Association for Psychedelic Studies, known as MAPS (Sessa, 2016). Even though the study of psychedelics becomes very limited in that period, clinical research starts to bloom again from the 1990s. The new technology that emerges this period, gives a fresh outlook on psychedelic research and a resurgent enthusiasm. Hence, from the 1990s a new era of psychedelic interest begins with a noticeable acceleration of published studies, especially within the last ten years (Vollenweider &Kometer, 2010 and Pearson et al., 2022).

3. How Psychedelics Work

3.1 Mechanisms on brain

Psychedelics exert their effects predominantly through interactions as agonists or partial agonists on serotonin (5-HT) receptors, specifically the 5-HT2A subtype (Swanson, 2018). While most classical hallucinogens exhibit strong affinity for the 5-HT2 receptors, they also engage with different serotonin receptors (Vollenweider & Kometer, 2010). Importantly, the degree of the 5-HT2A activation determines the intensity of the perceptual alterations (Pearson et al., 2022). Apart from the primary influence of 5-HT2A receptor agonism, other receptor-related mechanisms also contribute to the classic psychedelic effects (Johnson et al., 2019). For example, MDMA functions by releasing monoamines, inhibiting the seretonin and norepinephrine transporter reuptake and by inhibiting the monoamine oxidase, it partially works as an agonism of serotonin receptors, while it also elevates oxytocin levels in blood. On the other hand, ketamine, as an NMDA (N-methyl D-aspartate) antagonist, leads to heightened activation of AMPA receptors and, consequently, indirectly boosts dopaminergic (D2) and serotonergic (5-HT2) activity (Reiff et.al., 2020).

One of the things that scientists have directed their attention to, is examining the equilibrium between AMPA (α-amino 3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA glutamate signaling in significant limbic regions, such as the hippocampus and medial prefrontal cortex (Pearson et al., 2022). During the 1990s, multiple preclinical studies highlighted the significance of the NMDA glutamate receptor in the mechanism of action of antidepressants. As a result of these discoveries, the hypothesis emerged that the NMDA-antagonist ketamine could hold promise as an antidepressant (Vollenweider & Kometer, 2010). There is growing evidence that, both dissociative anesthetics and classical hallucinogens influence glutamatergic neurotransmission in the prefrontal-limbic circuitry that is associated with mood disorder pathophysiology. (Reiff et al., 2020 and Vollenweider & Kometer, 2010). Indeed, research has shown that the shrinking of neurons in the prefrontal cortex (PFC) is a significant factor in the development of depression and related conditions (Ly et al., 2018). Furthermore, this change in glutaminergic neurotransmission in prefrontal-limbic circuities causes neuroplastic changes to occur, likely by enhancing the functioning of AMPA receptors. In other words, psychedelics promote neuroplasticity by boosting the movement of AMPA-type glutamate receptors and by elevating brain-derived neurotrophic factor (BDNF) levels (Vollenweider & Kometer, 2010).

Interestingly, an imaging study for brain function that was conducted by Roseman (2018), showed that subjects after psilocybin-assisted psychotherapy for TRD (treatment-resistant depression) , appeared to have heighted amygdala activity in response to images of fearful faces, with more intense responses linked to more favorable treatment results. This contrasts with the effects of SSRIs, where amygdala activity is reduced when viewing fearful faces, possibly reflecting reports from many participants that SSRIs dulled their emotions, while psychedelics allowed them to face and work through them (Wheeler & Dyer, 2020). Another interesting finding is that, psychedelics alter the network connectivity of the brain. To begin with, there is a notable decrease in functional connectivity between key central nodes, such as mPFC (medial prefrontal cortex) and PCC (posterior cingulate cortex). Additionally, under the influence of psychedelic substances, brain networks that typically exhibit opposing activity patterns start to show simultaneous activation. This phenomenon, known as enhanced between-network functional connectivity, has been observed during psilocybin administration, ayahuasca ingestion and notably LSD (Swanson, 2018). Finally, after consuming LSD, participants in a study, experienced visual perceptual alterations, which were linked to enhanced functional connectivity in the visual cortex. Similarly, changes in

their consciousness, including their sense of self, were found to be connected to reduced connectivity between the parahippocampus and retrosplenial cortex within the default mode network (Reiff et al., 2020).

3.2 DMN and the Entropic Brain Theory

The default mode network (DMN) is a prominent brain network, which becomes active during periods of daydreaming and deep contemplation, when the mind is at rest (Wheeler & Dyer, 2020). Specifically, the DMN is mainly composed of the posterior cingulate cortex (PCC), the medial prefrontal cortex (MPFC), and the lateral parietal cortex (LPC), and it is associated with the brain's mechanisms related to the subjective experience of self, making it a potential neural basis for the concept of the ego (Johnson et al., 2019 and Wheeler & Dyer, 2020). In fact, the DMN is commonly associated with self-referential thinking while, when individuals are engaged in external tasks, its activity tends to decrease (Rankaduwa & Owen, 2023). Each of the regions that form the DMN, play distinct roles in various cognitive processes. On the one hand, the PCC is linked to internally-focused cognitive processes, the MPFC is involved in rumination, autobiographical memory retrieval, self-related judgments, and theory of mind functions. On the other hand, the LPC is associated with empathy and the representation of self in spatial cognition (Johnson et al., 2019). From neuroimaging research, we now know that various psychedelics, such as psilocybin, LSD, ayahuasca, ketamine, and MDMA, have the capacity to influence the functional connectivity of the DMN (Wheeler & Dyer, 2020).

Consistent with this, classic psychedelic drugs are linked to hypofrontality, meaning reduced blood flow to the prefrontal cortex, as well as reduced connectivity and neural activity in crucial areas of the default mode network shortly after drug intake (Gattuso et al., 2023). Accordingly, Thomas et al. (2017), found that psychedelic substances, reduce connections within the DMN and enhance connections between different brain networks. This shift from separated to interconnected networks is unique to the psychedelic experience and is not observed with other substances such as, SSRIs (Gattuso et al., 2023). It is now known that, escalated within-DMN connectivity and lower between-network connectivity function is associated with the severity of various neuropsychiatric and neurodegenerative conditions, so this could be the reason why psychedelics show promise in treating depression and other disorders (Johnson et al., 2019 and Gattuso et al., 2023).

Perhaps one of the most important findings is that, reduced connections and oscillatory power (brain waves) of the DMN, is linked to what is referred to as: ‘’ego dissolution‘’ (Wheeler & Dyer, 2020). Ego dissolution (i.e., ego death or loss) involves a complete disintegration of the individual's identity and a merging of boundaries between oneself and the external world (Swanson, 2018). In other words, it happens when one feels connected to something greater than themselves, losing the sense of being a separate individual. Moreover, It is often metaphorically referred to as "dying before death’’ and it interrupts personal life stories and ingrained thought and behavior patterns, offering a fresh and objective view on oneself and the world. (Wheeler & Dyer, 2020). It is believed that, ego dissolution attributes its therapeutic potential by allowing individuals to observe their thoughts and emotions from a more detached and objective viewpoint (Gattuso et al., 2023). Individuals who underwent a profound sense of ego dissolution during psychedelic-assisted psychotherapy, showed a higher likelihood of achieving positive clinical results and experiencing long-term changes in life perspective and the personality trait of openness (Swanson, 2018). Thus, the experience of ego dissolution and its influence on the DMN appears to be a crucial mechanism responsible for the therapeutic effects of psychedelic drugs. (Wheeler & Dyer, 2020).

Apart from this, psychedelics activate 5-HT2A receptors in the cortex, which can lead to asynchronous glutamate release and desynchronized neuronal activity. As a consequence, the brain becomes less synchronized, causing a reduction in oscillatory power, which aligns with the brain entropy hypothesis (Gattuso et al., 2023).To begin with, the heightened brain entropy, reflecting increased randomness and uncertainty within the brain, has been suggested as a factor in inducing altered states of consciousness with mainly psilocybin and LSD (Johnson at al., 2019). In other words, entropy refers to a state of increased disorder, uncertainty and adaptability within the brain, which allows for a greater variety of dynamic brain activity patterns (Gattuso et al., 2023). Furthermore, when a system operates in a state between two distinct conditions, such as order and chaos, it is considered to be in a state of "criticality"(Rankaduwa & Owen, 2023). Indeed, psychedelics have the ability to bring the brain even closer to this critical state compared to regular waking consciousness as also recent fMRI studies with LSD suggest (Carhart-Harris, 2018).

Therefore, Entropic Brain Theory proposes that our mind has evolved to accurately represent the external world through secondary consciousness, which is supported by the ego, responsible for refining these representations. As normal secondary consciousness relies on connections between key regions of the DMN and medial prefrontal cortex, the hippocampal-

DMN disconnection caused by psychedelics, is seen as essential for transitioning to primary consciousness. Thus, higher entropy leads to increased criticality, moving the system closer to the potential shift from secondary to primary consciousness. (Rankaduwa & Owen, 2023). Last but not least, criticality brings functional benefits to a system as it optimizes information processing by enhancing adaptability and flexibility, while maintaining some level of order. As many disorders have been linked to sub-criticality and mainly depression, psychedelics seam to offer a therapeutic mechanism by shifting the brain closer to a more critical point (Carhart-Harris, 2018).

4. How Psychedelic Psychotherapy is Conducted

Contemporary academic research settings employ psychedelic-assisted psychotherapy, which includes administering a psychedelic substance within a structured series of therapy sessions, designed to guide and understand the psychedelic experience (Nielson & Guss, 2018). Psychedelic-assisted psychotherapy, that encompasses both psycholytic and psychedelic therapy, typically involves three session types: the preparatory, the medication (usually one to three sessions with moderate to high psychedelic doses), and the integration ones (Reiff et al., 2020). In the psychedelic approach, medium to higher psychedelic doses in 1 to 3 sessions, spaced several weeks apart, are administered. The goal is for the patient to have a profoundly intense autobiographical and/or mystical experience, which is subsequently explored during integration. In contrast, the psycholytic approach, utilizes a lower dose, administered at regular or varying intervals (Nielson & Guss, 2018). The rationale for this approach is that the psychedelic substance, relaxes the patient's defenses and brings forth unconscious emotions and memories, facilitating the procedure of psychotherapy (Reiff et al., 2020). In practice, these methods are occasionally combined. For example, therapists might promote introspection during the peak intensity of a psilocybin session but initiate discussions about the patient's experiences before the effects of the psychedelic have entirely subsided (Nielson & Guss, 2018).

The therapeutic benefit of the psychedelic psychotherapy, is thought to emerge from the interplay between the patient's mindset and external conditions, known as ''set'' and ''setting''. This combination is believed to reduce the likelihood of negative outcomes, even in the presence of difficult and distressing experiences, while addressing these challenges is

considered a vital aspect of therapy (Reiff et al., 2020). As it was mentioned before, usually psychedelic psychotherapy encompasses three sessions, with drug-free sessions occurring before and/or after the drug sessions, that are called preparatory and integrative respectively (Schenberg, 2018). These three components ready patients for the psychedelic sessions, foster the therapeutic alliance, provide guidance during the psychedelic experience, and aid in translating that experience into enduring, meaningful change (Nielson & Guss, 2018). First of all, in the preparatory sessions, the therapist or co-therapist team collaborates with the patient to delve into their life history, and to foster an understanding of symptoms and intentions, particularly emphasizing emotional and psychological growth possibilities. Additionally, they provide education regarding the forthcoming psychedelic session and endeavor to establish a strong therapeutic bond (Reiff et al., 2020).During the medication sessions, trained mental health professionals continuously supervise and assist patients in accordance with established guidelines (Schenberg, 2018). Moreover, usually there is a male-female co-therapy team, accompanying the patient, to ensure integrity and safety of the therapeutic relationship (Reiff et al., 2020). Typically, patients listen to instrumental music and are encouraged to remain introspective (often with eyeshades) ,as well as receptive to their emotions, thoughts and memories, while they are free to initiate psychotherapy discussions at any time they need (Schenberg, 2018). The setting is important, and for that the psychedelic substance is given in a cozy room featuring a reclining chair or bed, designed to create a comfortable and non-intimidating atmosphere, unlike the clinical and institutional setting of a medical office or laboratory. Following the drug session, in the integration sessions, therapists collaborate with the patient to translate the content of the psychedelic experience into lasting personal growth. This involves identifying insights and interpreting thoughts or ideas that emerged during the psychedelic session (Reiff et al., 2020).

One of the most important components of the psychedelic psychotherapy is music. Music plays a crucial and indispensable role in nearly all varieties of psychedelic-assisted psychotherapy, with the capacity to impact the mind on levels extending beyond conscious and verbal-cognitive dimensions (Oehen & Gasser, 2022). Furthermore, it is thought that music helps to create experiences with therapeutic significance. Research has indicated that psychedelics notably influence emotions triggered by music, mental imagery prompted by music, and the perceived personal significance of music (Kaelen et al, 2018).

Last but not least, for psychedelic psychotherapy to happen properly, licensed professionals with specialized training in the administration and monitoring of psychedelics, are needed

(Wheeler & Dyer, 2020). These psychedelic therapists must possess several key clinical attributes, including: maintaining self-awareness, a non-judgmental stance towards patients, appreciating experiences beyond conventional self-concepts (like ego dissolution and mystical states), embracing highly emotional and disordered thought states, being able to manage chaotic ego changes, and having a clear perspective on integrating these experiences into therapy. Moreover, therapists must have clinical training and psychotherapy experience. They get a detailed therapy manual and specific skills training, as they are guided on handling challenging emotional states, erratic behavior, and other tough reactions from participants (Nielson & Guss, 2018).

5. Research Studies on Psychedelic Psychotherapy

For the second part of this thesis a systematic literature review was conducted, to retrieve the main published articles concerning the topic of investigation, namely the use of psychedelic drugs in psychotherapy. Four primary psychedelic substances were chosen based on their widespread utilization on clinical settings: MDMA, Psilocybin, Ketamine and LSD.

Searches for the articles were conducted in American Psychologist Association (APA), ResearchGate, and Pubmed using mainly the following keywords: clinical trials with MDMA, clinical trials with psilocybin, clinical trials with Ketamine, research with psychedelic substances, and clinical trials with LSD.

Once articles were identified and considered significant for the present review, they were looked thoroughly at, to determine their degree of relevance with the present study. Four to five articles for each psychedelic drug were chosen on the basis of the following criteria: They had to be published in English and published in peer-review journals; journals with a higher impact factor were favored, in order to access the most relevant works of the scientific community, as well as more recent articles as possible. On the other side, the following exclusion criteria were applied: studies on healthy participants were not taken into consideration, as well as pilot studies were avoided, while main studies were preferred.

5.1 Research with MDMA

The amphetamine derivative known as MDMA (3,4-methylenedioxymethamphetamine), prompts the release of serotonin mainly by attaching to serotonin transporters located on presynaptic neurons of the brain. Research has demonstrated that MDMA can help erase fear memories, impact the reconsolidation of these memories, and improve social behaviors in animals. For this reason, it has exhibited significant promise, mainly in the treatment of PTSD (post-traumatic stress disorder) as well as the alleviation of social anxiety in autism spectrum disorder (ASD) (Nielson & Guss, 2018).

Danforth et al. (2018) conducted a study to investigate whether MDMA-assisted psychotherapy (MDMA-AT) is doable and safe, for the treatment of SAD (Social Anxiety Disorder) in autistic adults. This clinical trial, utilized a randomized, placebo-controlled, double-blind approach. Twelve participants with varying degrees of social anxiety were randomly assigned, with eight receiving MDMA and four receiving a placebo. After undergoing three preparatory psychotherapy sessions, participants were administered either MDMA or a placebo, during an interval of roughly one month. Three non-drug therapy sessions followed each experimental session, and after 6 months, those who initially had a placebo could choose two more MDMA treatment sessions. The results showed that the MDMA group experienced significantly greater improvements compared to the placebo group, both at the primary endpoint and the 6-month follow-up. Most individuals in the MDMA group either maintained or continued to slightly improve their social anxiety levels after completing the active treatment phase (Danforth et al., 2018).

In another phase 3 clinical study, conducted by Mitchell et al. (2021), the use of MDMA in psychotherapy was assessed for the safety and efficacy of treating patients with severe PTSD. Out of 345 individuals evaluated for eligibility, 91 ultimately confirmed for randomization: 46 received the MDMA and 44 the placebo. Initially, participants underwent 3 preparatory sessions, lasting 90 minutes each, followed by three 8-hour experimental sessions separated by approximately 4 weeks. During each experimental session, participants were administered a sole split dosage of 80-180mg of MDMA or placebo. Finally, following every experimental session, three 90-minute integration sessions occurred approximately one week apart. To assess outcomes, the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) interview, which examines trauma history, and the Sheehan Disability Scale (SDS), measuring

functional impairment, were administered at baseline and two months post-final session. The results indicated that, MDMA reduced significantly CAPS-5 scores and decreased SDS total scores compared to the placebo group. Moreover, MDMA did not lead to negative outcomes related to abuse risk, thoughts of suicide, or prolongation of QT intervals. Therefore, the data demonstrated high efficacy and safety of MDMA-AT in severe PTSD, even for those with additional medical conditions (Mitchell et al., 2021).

PTSD is more common in military personnel, veterans and first responders, than in the general population. A randomized, double-blind, phase 2 trial conducted by Mithoefer et al. (2018), investigated whether 26 participants with severe PTSD (22 veterans, 3 firefighters, and 1 police officer), could benefit from MDMA-AT, as well as if it is safe. Participants were assigned randomly to three different dose groups: 30, 75 and 125 mg. The trial contained 2 stages: the first consisted of three 90-minute preparatory sessions, followed by two double-blinded 8h experimental MDMA sessions that proceeded two non-drug integration sessions. For the assessment of the results, the PTSD Scale CAPS-IV was used: during the primary assessment, the 75 and 125 mg MDMA groups significantly reduced PTSD symptoms compared to the 30g groups. On the other hand, during the open-label MDMA sessions, the 30 mg group continued to improve, while the 75 mg did not show significant decreases. Finally, in the last assessment, all groups showed significant and sustained PTSD symptom reductions. Thus, the 75 mg and 125 mg MDMA doses, combined with psychotherapy, effectively reduced PTSD symptoms in veterans and first responders (Mithoefer at al., 2018).

PTSD has also shown to be closely linked to the simultaneous presence of alcohol and substance use disorders (ASUDs). A randomized, placebo-controlled, phase 3 trial by Nicholas et al. (2022), investigated the effects of MDMA-AT on alcohol and substance use for individuals with severe PTSD. Ninety adult participants with severe PTSD were randomly assigned to undergo three 3-8h blinded experimental sessions, with one group receiving MDMA-AT and the other receiving PLAC-AT (placebo-assisted therapy), preceded by three 90-minute preparatory sessions. After each experimental session, participants had three 90-minute therapy sessions spaced over 3–4 weeks. To measure the outcomes, two tests were used: the Alcohol Use Identification Test (AUDIT) and the Drug Use Identification Test (DUDIT), designed to indicate patterns of substance use and drug-related problems. Compared to PLAC-AT, MDMA-AT significantly reduced AUDIT scores, but had no significant impact on DUDIT scores. Therefore, these data provided evidence that MDMA-

AT for severe PTSD might also result in enhancements in alcohol consumption while it does not seem to raise the likelihood of engaging in illegal drug use (Nicholas et al., 2022).

Another highly comorbid disorder with PTSD, are eating disorders (EDs). In a double-blind randomized phase 3 trial conducted by Brewerton et al. (2022), the changes in Eating Attitudes Test 26 (EAT-26) were examined in individuals with severe PTSD, using MDMA-AT or PLAC-AT. In addition to this, CAPS-5 scale was used to measure change in PTSD symptoms at baseline and at study termination. Altogether, the sessions comprised three 8-h experimental ones (4 weeks apart) of either MDMA-AT or PLAC-AT, followed by three 90-minutes integration sessions (1 week apart). For those who completed the study (n=82), there was a significant decrease in EAT-26 scores after MDMA-AT compared to the placebo, while especially women with high EAT-26 scores also saw significant reductions in scores after MDMA-AT compared to the placebo. In conclusion, psychotherapy with MDMA proved to be efficient for the reduction of eating disorder symptoms in comparison with placebo and therapy, in individuals with severe PTSD (Brewerton et al., 2022).

5.2 Research with Psilocybin

The potential of psilocybin-assisted therapy as a novel antidepressant, is attributed to the serotonergic and glutamatergic action of psilocybin. A randomized, waiting-list clinical trial by Davis et al. (2021), investigated the effects of psilocybin therapy in 27 patients with MMD (Major Depressive Disorder). A total of 15 participants, were randomized to an immediate treatment condition group while the other 12, began the treatment with an 8-week delay. The sessions comprised of two with administration of psilocybin (20-30mg/70kg), preceeded by two 4h preparatory meetings and followed by the final integration ones. For the assessment of the results, the GRID-Hamilton Depression Rating Scale (GRID-HAMD) for depression severity, and the Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR) test were used, at baseline and at the first and the fourth week after enrollment, for the immediate treatment group, corresponding to weeks 5 and 8 for the delayed treatment group. The data showed a significantly lower mean of GRID-HAMD scores at weeks 1 and 4 in the immediate group in comparison to the corresponding weeks for the delayed group, while the QIDS-SR scores showed a quick drop in the average (SD) depression score from the starting point to day 1 after the first session and this reduction remained statistically significant up to the week

4 follow-up. In conclusion, psilocybin alongside with therapy showed to be effective for treating MDD (Davis et al., 2021).

In another double-blind, cross-over study conducted by Griffiths et al. (2016), 51 cancer patients with life-threatening depression and anxiety, were randomized to receive either a very low dose of psilocybin (1-3mg/70kg) and in the second session a higher one (22-30mg/70kg), or the opposite. The duration of each patient's participation was for about 9 months, with 2 psilocybin sessions, preceded by 2 preparation meetings. Apart from primary outcome measures for depression and anxiety (as the GRID-HAM-D-17), fifteen secondary measures concentrated on psychiatric symptoms, emotions, and mindset, at baseline, 5 weeks after the last session and at a 6-month follow-up. The results indicated that high-dose psilocybin reduced depression and anxiety, improving quality of life, optimism, and purpose while reducing fear of death even after 6 months. Interestingly, the mystical-type experiences of some participants that were assessed at the end of the study (with the MEQ30 test), seem to be associated with enduring positive transformations in attitudes, emotions, behaviors and spirituality (Griffiths et al., 2016)

Alcohol use disorder (AUD) is another significantly promising area of research with psilocybin. A single-group proof-of –concept study by Bogenschutz et al. (2015) assessed the outcome and safety of psilocybin assisted psychotherapy in 10 participants with DSM-IV alcohol dependence. Overall, participants underwent two psilocybin sessions (one after 4 weeks of treatment and another after 8 weeks), and twelve sessions which consisted of: 7 of Motivational Enhancement Therapy, 3 preparation and 2 integration ones. Many assessments were used to measure mainly the alcohol withdrawal, the drinking behavior and the intensity of the psilocybin experience. During the initial 4 weeks, abstinence levels didn't notably rise. However, they significantly increased after administering psilocybin, and were largely sustained after 36 weeks, showing that when administered with suitable psychosocial interventions, psilocybin may offer long-term advantages in treating alcohol use disorder. Moreover, the intensity of the first psilocybin session strongly correlated with changes in drinking behavior, while it predicted reductions in cravings and boosts in self-efficacy for maintaining abstinence (Bogenschutz et al., 2015).

In another double-blind randomized clinical trial conducted by Bogenschutz (2022), it was examined whether Psilocybin-AT could reduce the percentage of heavy drinking days in 95 patients with AUD. Specifically, participants were randomized to receive either psilocybin

(25-40mg/70kg) or diphenhydramine (50-100 mg) in two 8h sessions at the 4th and 8th weeks. Moreover, a total of 12 psychotherapy sessions that included motivational enhancement therapy and cognitive behavioral therapy, were offered: 4 prior to the first experimental session, 4 between the first and the second one and 4 during the month following the second. For the assessment of results, a primary measure of drinking behavior, the percentage of heavy drinking days (PHDD), was used, while the secondary measures consisted of the percentage of drinking days (PDD) and mean drinks per day (DPD). The results indicated that both the percentage of heavy drinking days and the mean daily alcohol consumption was significantly lower in the psilocybin group compared to the diphenhydramine, with no severe adverse events occurring during psilocybin administration (Bogenschutz et al., 2022).

Recently, psilocybin has also been examined for smoking cessation, as many other treatments have failed to provide long term abstinence. Johnson et al. (2017), conducted an open-label pilot-study, in 15 heavy smoker participants that underwent a total of 15 weeks of treatment, including four preparatory meetings with mindfulness techniques, CBT (cognitive behavioral therapy) and guided imagery. Furthermore, in the fifth week, participants were administered a moderate dose of psilocybin (20mg/70kg) as well as a high one (30mg/70kg), 2 weeks after, while they were given the choice to take part in a third, optional session. Many measurements were used to assess results as the Timeline Follow-back (TLFB) for the daily cigarette consumption and various smoking biomarkers (as urine samples) to assess participant's smoking status. All participants completed a 12-month follow-up, with 10 confirmed non-smokers. Additionally, 12 participants returned for a long-term (≥16 months) follow-up, and 9 remained smoke-free. Last but not least, at the 12-month follow-up, 13 participants considered their psilocybin experiences one of their top 5 personally meaningful and spiritually significant life events (Johnson et al, 2017).

5.3 Research with Ketamine

Ketamine, a glutamatergic modulator, has garnered research interest due to its fast-acting antidepressant effects observed within hours when administered at doses below those typically used for anesthesia. A randomized, cross-over, single-dose clinical trial by Dwyer et al. (2021), examined whether 17 adolescents with treatment resistant depression (who have failed at least one prior 8-week trial of a standard antidepressant), could benefit from ketamine therapy. Specifically, participants were randomized to receive a single infusion of

either ketamine hydrochloride (0.5 mg/kg) or midazolam (0.045 mg/kg) on the first day, and the other substance two weeks later. The key assessment was depression symptom severity, evaluated using the Montgomery-Åsberg Depression Rating Scale (MADRS) 24 hours post-infusion. The findings demonstrated that a single ketamine infusion effectively alleviated depressive symptoms for up to 14 days following administration in comparison to midazolam, all while being well-tolerated with no severe side effects reported by participants (Dwyer et al., 2021).

Suicidal ideation represents a critical and adverse symptomatology within individuals diagnosed with Major Depressive Disorder (MDD), necessitating immediate clinical attention and intervention. In a randomized clinical trial by Grunebaum et al. (2018), 80 participants with MDD, and a score ≥ 4 on the Scale for Suicidal Ideation (SSI), randomized to receive either intravenous racemic ketamine hydrochloride (0.5 mg/kg) or midazolam (0.02 mg/kg) at a 40 minute session. SSI scores were assessed before and after infusion, and for 6 weeks of follow-up, as well as other measures were used as the Hamilton Depression Rating Scale HAM-D, the Beck Depression Inventory (BDI), and the Profile of Mood States (POMS) to assess depressive symptoms. Results indicated an average of SSI score at the first day of 4.96 point lower for the ketamine group compared with the midazolam one, while the ketamine group also showed a more significant improvement in the depression subscale of the POMS on the first day, compared to the midazolam group. Moreover, suicidal ideation improvement largely continued throughout a six-week period of an uncontrolled observation (Grunebaum et al., 2018).

Preliminary findings suggest ketamine's potential for sustaining alcohol abstinence, possibly by promoting synaptic and neuronal growth, which is disrupted in addiction. In a double-blind-controlled phase 2 clinical trial by Grabski et al. (2022), 96 participants with severe AUD, were randomly divided into four groups to receive: 1) three ketamine infusions administered weekly at a rate of 0.8mg/kg over 40 minutes, coupled with psychological therapy, 2) three saline infusions combined with psychological therapy, 3) three ketamine infusions combined with alcohol education, 4) three saline infusions paired with alcohol education. The therapy and alcohol education sessions were consistently scheduled prior to the infusion session and approximately 24 hours subsequent to it. The aim of the seven mindfulness-based therapy sessions was alcohol-free living, while education sessions focused on addiction triggers, alcohol's effects, and healthy living. The primary outcome measures were abstinence percentage days and confirmed relapse from alcohol at 6 months after the

initial infusion, assessed with the Alcohol Timeline Followback questionnaire. Some secondary outcomes for depressive symptoms, included the BDI and the HAM-D. At the 6-month follow-up, the ketamine group showed more alcohol abstinence days than the placebo group, with the ketamine plus therapy group showing the most significant improvement compared to the saline plus education one. Moreover, the relapse rate was not significantly different between the ketamine and placebo groups and overall, ketamine was well tolerated by patients (Grabski at al., 2022).

Studies propose that subanesthetic ketamine doses may also enhance susceptibility to cocaine-related issues and aid in behavioral changes. A randomized, placebo-controlled clinical trial by Dakwar et al. (2019), investigated whether one ketamine infusion enhanced treatment outcomes for adults with cocaine dependence participating in mindfulness-based relapse prevention (MBRP). Fifty-five participants were randomly administered either an intravenous infusion of ketamine (0.5mg/kg) in a 40 minute session, or midazolam (0.025 mg/kg). The 5-week trial involved a 5-day hospitalization where patients received MBRP and an infusion on day 2, followed by sessions and monitoring for 4 weeks. Cocaine usage was evaluated using self-reported information and urine toxicology, while the primary outcome measures were study completion without cocaine use and time to relapse (defined as first use or dropout). Results indicated that the ketamine group had higher abstinence (48.2%) compared with the midazolam (10.7%), with a 53% lower relapse risk and 58.1% lower cravings, throughout the study. Thus, a single ketamine infusion showed significant clinical improvement in cocaine-dependent patients involved in MBRP, with no severe adverse events taking place in the study (Dakwar et al., 2019).

In another, double-blinded, placebo-controlled clinical trial by Krupitsky et al. (2002), seventy detoxified heroin-addicted participants were randomized to receive either a high, hallucinogenic dose of ketamine (0.2mg/kg) and psychotherapy, or a low sub-psychedelic dose of ketamine (0.2 mg/kg) plus psychotherapy. Overall, subjects received ten hours of preparatory therapy before the ketamine session (1.5-2 hours) as well as, five hours after it. Some of the primary assessment measures of the abstinence and relapse of the patients after a two-year follow-up, included data about the subject's drug usage, inspection for any signs of injection on their veins, input from the subject's family or associates regarding their drug use, as well as urine drug screening. Results indicated that, a high dose of KPT (Ketamine Psychotherapy) led to higher rates of abstinence among heroin addicts during the initial two years of follow-up, as well as a more substantial and enduring reduction in heroin cravings

and more pronounced positive shifts in nonverbal unconscious emotional attitudes compared to a low dose of KPT (Krupitsky et al., 2002).

5.4 research with LSD

Lysergic acid diethylamide (LSD), a renowned classic psychedelic compound, has been employed in therapeutic contexts for addressing conditions such as anxiety, depression, psychosomatic illnesses, and addiction (Gasser et al., 2014).

A randomized, double-blind, placebo-controlled phase 2 study by Holze et al. (2022), aimed to explore the effectiveness and safety of LSD-AT (assisted psychotherapy) for patients dealing with anxiety, whether related to a life-threatening illness or not. Overall, the trial lasted 24-weeks and consisted of 2 treatment sessions, separated by 6 weeks, as well as 5 study sessions, including psychotherapy and assessment of adverse effects occurring throughout the study. Participants were randomized and crossed over to receive either LSD (200µg) or placebo in 2 different sessions. A total of 42 participants, were primary assessed for anxiety symptoms, with STAI-Global (STAI-G) score, 16 weeks after the last LSD session. Secondary outcome measures, included assessments of depressive symptoms using the BDI and the HAM-D, as well as evaluations of acute subjective drug effects. LSD-AT led to notable decreases in STAI-Global scores that persisted for up to 16 weeks post-treatment, while comparable results were noted in assessments of concurrent depression, with no serious adverse events taking place (Holze et al., 2023).

Another double-blind, randomized, active placebo-controlled pilot study by Gasser et al. (2014) also examined how safe and efficient LSD-AT could be in 12 patients with anxiety associated with life-threatening diseases. Firstly, participants were randomized to receive 2 blinded experimental sessions with either a high dose of LSD (200µg), or an active placebo (20µg), which was followed by an open-label cross-over to 200µg of LSD after revealing the blinded of the treatment (after 2 months). Following each experimental session, there were three integrative, psychotherapy sessions lasting 60 to 90 minutes. The primary assessment measure was the STAI, evaluating state and trait anxiety, while the overall outcomes were assessed at baseline, 1 week after the experimental sessions, and at a 2 month follow-up. The experimental dose consistently lowered anxiety levels, in both the blinded treatment phase and the open-label cross-over treatment phase for participants who initially received the active

placebo. Results indicated a reduction in STAI scores that was more prominent after the second LSD session, showing that a minimum of two LSD sessions is required to reveal these effects (Gasser et al., 2014).

A follow-up qualitative study by Gasser et al. (2015), conducted 12 months after the previously mentioned clinical trial, examined whether the outcomes of LSD-AT, remained steady over time. Ten out of the twelve participants that completed the original clinical trial, enrolled in the long term follow-up (LTFU). The assessment measures that were used in this study were: the analysis of changes in the STAI scores over time, as well as, qualitative semi-structured interviews, to obtain a more comprehensive understanding from a client-centered viewpoint. All interviews were recorder and assessed by using the Qualitative Content Analysis (QCA) summary approach, while they were centered on personal experiences, alterations in daily life, quality of life, anxiety, and perspectives concerning LSD-AT. The interviews showed consistent benefits from LSD-AT. Data from the interviews aligned with the STAI results, with 77.8% reporting lasting anxiety reduction, 77.8% reduced fear of death, and 66.7% an improved quality of life. Most participants noted positive personality changes like increased openness and heightened awareness. Overall, participants felt more relaxed and patient, supporting the sustained STAI improvements observed from the study's end to the LTFU. Therefore, LSD, within medically supervised psychotherapeutic context, proves to be both safe and capable of yielding enduring advantages for individuals facing life-threatening illnesses (Gasser et al., 2015).

A different therapeutic approach was adopted by Oehen and Gasser (2022), who devised a group therapy approach, incorporating MDMA and LSD for psychedelic-assisted treatment. Overall, 50 participants were treated with this method, with various disorders. In this approach, MDMA primarily served in the initial phase to boost motivation for change and make the therapeutic connection stronger. Once emotional self-regulation improved and trauma exposure became more manageable, LSD was introduced, to enhance and deepen the therapeutic journey. Based on diagnosis, patients were either placed directly into group sessions or underwent a series of individual substance-assisted sessions before joining the group. The group sessions, occurred 4 times a year, and consisted of 12 participants, who were observed by 3 therapists. Prior to group sessions, participants engaged in a 3-hour preparatory session that encompassed exercises focused on breath and bodily awareness. Following group sessions, 4-hour integration sessions involving verbal discussions were conducted. Participants had to write detailed reports, complete the 5D-ASC (5 Dimensions

Altered States of Consciousness) and MEQ (Mystical Experience) questionnaires, and discuss their reports during integrative psychotherapy sessions. Results were assessed based on clinical judgment and showed that: among patients with trauma-related disorders, 4 achieved remission, 13 improved and 3 did not; in the anxiety disorder group, 2 achieved remission, 5 improved and 3 did not; for patients with OCD, 1 achieved remission, and 1 did not improve; in cluster headache, 1 improved, 3 did not and 1 deteriorated; while in patients with ASD (Autistic Spectrum Disorder), 1 improved and 1 did not. Overall, the clinical outcomes for participants with trauma-related disorders were more positive than in the other subgroups (Oehen & Gasser, 2022).

6. Discussion

In the previous section, we delved into a comprehensive exploration of recent research, which illuminated the therapeutic potential of four prominent psychedelic substances: MDMA, psilocybin, ketamine and LSD. Building upon these insights, this discussion will synthesize the findings from these studies, drawing connections, and indicating implications for the broader field of psychedelic-assisted psychotherapy.

Review of the findings of research with MDMA

The studies on MDMA have demonstrated its promising efficacy in the treatment of SAD in autistic adults, severe PTSD, and comorbid disorders such as alcohol and substance use disorders as well as eating disorders. Remarkably, none of these studies reported any serious adverse events. Apart from the two phase 3 clinical trials by Mitchell et al.(2011) and Nicholas et al. (2022), that utilized a larger sample size, the other three studies showed a limited number of participants, reducing thus the generalizability of results. Another limitation, that is evident in most of the studies with psychedelic substances, is the blinding of the study. For example, in the study by Mitchell et al. (2011), it is mentioned that the therapists guessed the dose wrong for about 42% of the blind sessions, while participants guessed wrong about 53% of the time, suggesting that the blind of the study was only partially effective (Mitchell et al., 2021). In conclusion, MDMA shows promise in treating various disorders with no serious adverse events reported. However, limited sample sizes and blinding challenges highlight the need for further research.

Review of the findings of research with Psilocybin

The studies with psilocybin has shown efficiency and overall safety (with no severe adverse effects in all the studies mentioned before), for the treatment of MDD, life-threatening depression and anxiety in patients with cancer and various substance use disorders like AUD and smoking. Overall, results indicated lasting effects of the treatment, in all five studies, up to even 6 months. However, in three studies a prominent limitation seems to be the small and not diverse sample size that reduced generalizability, indicated by the studies conducted by Davis et al. (2020), Bogenschutz et al. (2015) and Johnson et al. (2017). Besides that, in the

studies conducted by Bogenschutz et al. (2015) and Johnson et al. (2017), there was a lack of control condition, needed to draw meaningful conclusions about the efficiency of the drug and reduce bias. Last but not least, as it is mentioned in the study of Bogenschutz et al. (2022), the placebo was ineffective in maintaining the blind of the study, something that remains a general problem with psilocybin psychotherapy (Bogenschutz et al., 2022). In summary, psilocybin shows promise in treating various mental health conditions, but limitations such as small sample size and blinding challenges should be addressed in future research.

Review of the findings of research with Ketamine

The studies with Ketamine, indicated a promise in treating various conditions as treatment-resistant depression, reduction of suicidal thoughts in MDD, AUD, as well as cocaine and heroin addiction, while overall it was well-tolerated and safe. In most of the studies, a single dose of ketamine was enough to show statistically significant outcomes, showing that ketamine is short acting and possibly easier applicable for a clinical design. Nonetheless, in the investigations by Dwyer et al.(2022), Grunebaum et al.(2018) and Dakwar et al. (2019), the sample size was small and not diverse, limiting thus the generalibility of the findings. Additionally, apart from two studies, in all the rest, midazolam, that produces a mild change in consciousness, was used as the active control. (Dakwar et al., 2019).While midazolam is superior to saline infusions, as a placebo, the issue of blinding in studies involving ketamine and other psychedelics still persists. Lastly, ketamine has shown significant clinical improvement in cocaine and heroin addicted patients, for whom treatment methods are limited. Notably, in the study of Krupitsky et al. (2002), is it mentioned that the rate of abstinence in the high dose group exceeded the usual abstinence rate found in standard heroin addiction treatment programs in Russia, where the study was conducted (Krupitsky et al., 2002). In conclusion, ketamine exhibits promise in treating various disorders, with good tolerability, yet challenges in study design and blinding methods persist, warranting further research to unlock its full therapeutic potential.

Review of the findings of research with LSD

Lysergic acid diethylamide, (LSD), is the least used psychedelic substance in clinical trials of the four described, possibly because of its more complex history and stigmatation as well as

longer-lasting acute effects than psilocybin (Holze et al., 2023). The studies, demonstrated that LSD could be an aid in psychiatry for the effective treatment of various conditions such as anxiety, OCD and trauma related disorders, while it did not cause any serious adverse events in any of the trials. From these studies, the one conducted by Gasser et al. (2014), was a pilot study, with limited sample size and thus reduced precision in results. Nonetheless, the blinding of the study still remains a problem also with LSD-AT. Holze et al. (2023) noted that using an inactive placebo was a limitation in their study. They stress the fact that even with an active placebo (lower dose of LSD), the study's blinding would remain imperfect, as in other studies with active placebos (Holze et al., 2023). Finally, Ohen and Gasser (2022) introduced group therapy as a novel approach to psychedelic psychotherapy. The group therapy model was overall feasible and safe, while it allowed researchers to work with more patients at the same time. Additionally, the group psychedelic experiences, enhanced and enriched individual therapeutic journeys, resulting in improved therapeutic effectiveness compared to individual sessions (Oehen & Gasser, 2022). In summary, LSD shows promise in psychiatric treatment but faces challenges like blinding issues and limited sample sizes, while group therapy could be a valuable avenue for further research.

7. Conclusions and Future Directions

Overall, studies with MDMA, Psilocybin, Ketamine and LSD, indicate that combining a psychedelic with different kinds of therapy, could offer an effective and safe alternative in treating many disorders. As it was mentioned before, these 4 most commonly used psychedelic substances in clinical trials, have shown promise in the treatment of many disorders such as various substance use disorders, PTSD and comorbid conditions, MDD, as well as depression and anxiety in life threatening diseases. Interestingly, most of the positive clinical improvements persisted for a long period of time, even after 6- 12 month follow-ups, as it is evident in most of the studies with psilocybin and LSD. On the other hand, a notable limitation of the ketamine studies was the relatively short follow-up period, typically not extending beyond 14 weeks. Future studies involving ketamine should aim to address this limitation by extending their follow-up assessments to longer durations, allowing for a more comprehensive understanding of its lasting effects in psychotherapeutic contexts. Additionally, compared to psilocybin and LSD, most experimental sessions with Ketamine used only a single infusion to show promising therapeutic outcomes, suggesting it might be

more practical for clinical use. As it is evident from all the studies mentioned, all psychedelic substances show promising therapeutic outcomes. However, the long and turbulent history of psychedelics, marked by a nearly two-decade cessation of research due to socio-political factors, imposes limitations on the extent to which these substances are allowed to be used in clinical trials. The majority of clinical trials involving psychedelics are currently in phase 2, with phase 3 clinical trials conducted only with MDMA. Nevertheless, a need for the field of psychedelic research is the expansion into phase 3 trials. The rationale behind this call for progression is rooted in the necessity to provide researchers with the opportunity to conduct investigations on a more extensive scale, allowing for the inclusion of larger and more diverse sample sizes, ultimately enhancing the robustness and generalizability of findings in the realm of psychedelic psychotherapy. Furthermore, a significant concern within psychedelic psychotherapy research is the challenge of maintaining effective blinding protocols, primarily due to the distinctive and often unmistakable subjective effects induced by these substances, necessitating further investigation into innovative blinding methodologies. Additionally, another issue that needs further exploration in future research is the type of psychotherapy that should be used in combination with every different psychedelic (Davis et al., 2021). Further research is also imperative to develop comprehensive educational programs and certifications, equipping mental health professionals with the essential skills and knowledge required for the safe and effective utilization of psychedelic therapies. In conclusion, the studies conducted on MDMA, Psilocybin, Ketamine and LSD have illuminated potential of psychedelic-assisted therapies as effective and safe treatments for a wide array of disorders. The enduring positive clinical outcomes observed, particularly in psilocybin and LSD studies, highlight their potential in the field of psychotherapy. However, as the research continues to evolve, addressing issues such as extended follow-up periods, blinding protocols, and therapist characteristics will be essential to advancing our understanding and utilization of these powerful substances in therapeutic contexts.

Bibliography

Belouin, S. J., & Henningfield, J. E. (2018). Psychedelics: Where we are now, why we got here, what we must do. Neuropharmacology, 142, 7–19. https://doi.org/10.1016/j.neuropharm.2018.02.018

Bogenschutz, M. P., Forcehimes, A. A., Pommy, J. A., Wilcox, C. E., Barbosa, P., & Strassman, R. J. (2015). Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. Journal of Psychopharmacology, 29(3), 289–299. https://doi.org/10.1177/0269881114565144

Bogenschutz, M. P., Ross, S., Bhatt, S., Baron, T., Forcehimes, A. A., Laska, E., Mennenga, S. E., O'Donnell, K., Owens, L. T., Podrebarac, S., Rotrosen, J., Tonigan, J. S., & Worth, L. (2022). Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial. JAMA Psychiatry, 79(10), 953. https://doi.org/10.1001/jamapsychiatry.2022.2096

Brewerton, T. D., Wang, J. B., Lafrance, A., Pamplin, C., Mithoefer, M., Yazar-Klosinki, B., Emerson, A., & Doblin, R. (2022). MDMA-assisted therapy significantly reduces eating disorder symptoms in a randomized placebo-controlled trial of adults with severe PTSD. Journal of Psychiatric Research, 149, 128–135. https://doi.org/10.1016/j.jpsychires.2022.03.008

Carhart-Harris, R. L. (2018). The entropic brain—Revisited. Neuropharmacology, 142, 167–178. https://doi.org/10.1016/j.neuropharm.2018.03.010

Dakwar, E., Nunes, E. V., Hart, C. L., Foltin, R. W., Mathew, S. J., Carpenter, K. M., Choi, C. J. "Jean", Basaraba, C. N., Pavlicova, M., & Levin, F. R. (2019). A Single Ketamine Infusion Combined With Mindfulness-Based Behavioral Modification to Treat Cocaine Dependence: A Randomized Clinical Trial. American Journal of Psychiatry, 176(11), 923–930. https://doi.org/10.1176/appi.ajp.2019.18101123

Danforth, A. L., Grob, C. S., Struble, C., Feduccia, A. A., Walker, N., Jerome, L., Yazar-Klosinski, B., & Emerson, A. (2018). Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: A randomized, double-blind, placebo-controlled pilot study. Psychopharmacology, 235(11), 3137–3148. https://doi.org/10.1007/s00213-018-5010-9

Davis, A. K., Barrett, F. S., May, D. G., Cosimano, M. P., Sepeda, N. D., Johnson, M. W., Finan, P. H., & Griffiths, R. R. (2021). Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry, 78(5), 481. https://doi.org/10.1001/jamapsychiatry.2020.3285

Dwyer, J. B., Landeros-Weisenberger, A., Johnson, J. A., Londono Tobon, A., Flores, J. M., Nasir, M., Couloures, K., Sanacora, G., & Bloch, M. H. (2021). Efficacy of Intravenous Ketamine in Adolescent Treatment-Resistant Depression: A Randomized Midazolam-Controlled Trial. American Journal of Psychiatry, 178(4), 352–362. https://doi.org/10.1176/appi.ajp.2020.20010018

Gasser, P., Holstein, D., Michel, Y., Doblin, R., Yazar-Klosinski, B., Passie, T., & Brenneisen, R. (2014). Safety and Efficacy of Lysergic Acid Diethylamide-Assisted Psychotherapy for Anxiety Associated With Life-threatening Diseases. Journal of Nervous & Mental Disease, 202(7), 513–520. https://doi.org/10.1097/NMD.0000000000000113

Gasser, P., Kirchner, K., & Passie, T. (2015). LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: A qualitative study of acute and sustained subjective effects. Journal of Psychopharmacology, 29(1), 57–68. https://doi.org/10.1177/0269881114555249

Gattuso, J. J., Perkins, D., Ruffell, S., Lawrence, A. J., Hoyer, D., Jacobson, L. H., Timmermann, C., Castle, D., Rossell, S. L., Downey, L. A., Pagni, B. A., Galvão-Coelho, N. L., Nutt, D., & Sarris, J. (2023). Default Mode Network Modulation by Psychedelics: A Systematic Review. International Journal of Neuropsychopharmacology, 26(3), 155–188. https://doi.org/10.1093/ijnp/pyac074

Grabski, M., McAndrew, A., Lawn, W., Marsh, B., Raymen, L., Stevens, T., Hardy, L., Warren, F., Bloomfield, M., Borissova, A., Maschauer, E., Broomby, R., Price, R., Coathup, R., Gilhooly, D., Palmer, E., Gordon-Williams, R., Hill, R., Harris, J., … Morgan, C. J. A. (2022). Adjunctive Ketamine With Relapse Prevention–Based Psychological Therapy in the Treatment of Alcohol Use Disorder. American Journal of Psychiatry, 179(2), 152–162. https://doi.org/10.1176/appi.ajp.2021.21030277

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A

randomized double-blind trial. Journal of Psychopharmacology, 30(12), 1181–1197. https://doi.org/10.1177/0269881116675513

Grunebaum, M. F., Galfalvy, H. C., Choo, T.-H., Keilp, J. G., Moitra, V. K., Parris, M. S., Marver, J. E., Burke, A. K., Milak, M. S., Sublette, M. E., Oquendo, M. A., & Mann, J. J. (2018). Ketamine for Rapid Reduction of Suicidal Thoughts in Major Depression: A Midazolam-Controlled Randomized Clinical Trial. American Journal of Psychiatry, 175(4), 327–335. https://doi.org/10.1176/appi.ajp.2017.17060647

Holze, F., Gasser, P., Müller, F., Dolder, P. C., & Liechti, M. E. (2023). Lysergic Acid Diethylamide–Assisted Therapy in Patients With Anxiety With and Without a Life-Threatening Illness: A Randomized, Double-Blind, Placebo-Controlled Phase II Study. Biological Psychiatry, 93(3), 215–223. https://doi.org/10.1016/j.biopsych.2022.08.025

Johnson, M. W., Garcia-Romeu, A., & Griffiths, R. R. (2017). Long-term follow-up of psilocybin-facilitated smoking cessation. The American Journal of Drug and Alcohol Abuse, 43(1), 55–60. https://doi.org/10.3109/00952990.2016.1170135

Johnson, M. W., Hendricks, P. S., Barrett, F. S., & Griffiths, R. R. (2019). Classic psychedelics: An integrative review of epidemiology, therapeutics, mystical experience, and brain network function. Pharmacology & Therapeutics, 197, 83–102. https://doi.org/10.1016/j.pharmthera.2018.11.010

Kaelen, M., Giribaldi, B., Raine, J., Evans, L., Timmerman, C., Rodriguez, N., Roseman, L., Feilding, A., Nutt, D., & Carhart-Harris, R. (2018). The hidden therapist: Evidence for a central role of music in psychedelic therapy. Psychopharmacology, 235(2), 505–519. https://doi.org/10.1007/s00213-017-4820-5

Krupitsky, E., Burakov, A., Romanova, T., Dunaevsky, I., Strassman, R., & Grinenko, A. (2002). Ketamine psychotherapy for heroin addiction: Immediate effects and two-year follow-up. Journal of Substance Abuse Treatment, 23(4), 273–283. https://doi.org/10.1016/S0740-5472(02)00275-1

Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., Burbach, K. F., Soltanzadeh Zarandi, S., Sood, A., Paddy, M. R., Duim, W. C., Dennis, M. Y., McAllister, A. K., Ori-McKenney, K. M., Gray, J. A., & Olson, D. E. (2018). Psychedelics Promote

Structural and Functional Neural Plasticity. Cell Reports, 23(11), 3170–3182. https://doi.org/10.1016/j.celrep.2018.05.022

Mitchell, J. M., Bogenschutz, M., Lilienstein, A., Harrison, C., Kleiman, S., Parker-Guilbert, K., Ot'alora G., M., Garas, W., Paleos, C., Gorman, I., Nicholas, C., Mithoefer, M., Carlin, S., Poulter, B., Mithoefer, A., Quevedo, S., Wells, G., Klaire, S. S., Van Der Kolk, B., … Doblin, R. (2021). MDMA-assisted therapy for severe PTSD: A randomized, double-blind, placebo-controlled phase 3 study. Nature Medicine, 27(6), 1025–1033. https://doi.org/10.1038/s41591-021-01336-3

Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., Holland, J., Hamilton, S., Yazar-Klosinski, B., Emerson, A., & Doblin, R. (2018). 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: A randomised, double-blind, dose-response, phase 2 clinical trial. The Lancet Psychiatry, 5(6), 486–497. https://doi.org/10.1016/S2215-0366(18)30135-4

Nicholas, C. R., Wang, J. B., Coker, A., Mitchell, J. M., Klaire, S. S., Yazar-Klosinski, B., Emerson, A., Brown, R. T., & Doblin, R. (2022). The effects of MDMA-assisted therapy on alcohol and substance use in a phase 3 trial for treatment of severe PTSD. Drug and Alcohol Dependence, 233, 109356. https://doi.org/10.1016/j.drugalcdep.2022.109356

Nichols, D. E., & Walter, H. (2021). The History of Psychedelics in Psychiatry. Pharmacopsychiatry, 54(04), 151–166. https://doi.org/10.1055/a-1310-3990

Nielson, E. M., & Guss, J. (2018). The influence of therapists' first-hand experience with psychedelics on psychedelic-assisted psychotherapy research and therapist training. Journal of Psychedelic Studies, 2(2), 64–73. https://doi.org/10.1556/2054.2018.009

Oehen, P., & Gasser, P. (2022). Using a MDMA- and LSD-Group Therapy Model in Clinical Practice in Switzerland and Highlighting the Treatment of Trauma-Related Disorders. Frontiers in Psychiatry, 13, 863552. https://doi.org/10.3389/fpsyt.2022.863552

Pearson, C., Siegel, J., & Gold, J. A. (2022). Psilocybin-assisted psychotherapy for depression: Emerging research on a psychedelic compound with a rich history. Journal of the Neurological Sciences, 434, 120096. https://doi.org/10.1016/j.jns.2021.120096

Rankaduwa, S., & Owen, A. M. (2023). Psychedelics, entropic brain theory, and the taxonomy of conscious states: A summary of debates and perspectives. Neuroscience of Consciousness, 2023(1), niad001. https://doi.org/10.1093/nc/niad001

Reiff, C. M., Richman, E. E., Nemeroff, C. B., Carpenter, L. L., Widge, A. S., Rodriguez, C. I., Kalin, N. H., McDonald, W. M., & and the Work Group on Biomarkers and Novel Treatments, a Division of the American Psychiatric Association Council of Research. (2020). Psychedelics and Psychedelic-Assisted Psychotherapy. American Journal of Psychiatry, 177(5), 391–410. https://doi.org/10.1176/appi.ajp.2019.19010035

Schenberg, E. E. (2018). Psychedelic-Assisted Psychotherapy: A Paradigm Shift in Psychiatric Research and Development. Frontiers in Pharmacology, 9, 733. https://doi.org/10.3389/fphar.2018.00733

Sessa, B. (2016). The History of Psychedelics in Medicine. Στο M. Von Heyden, H. Jungaberle, & T. Majić (Επιμ.), Handbuch Psychoaktive Substanzen (σσ. 1–26). Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-55214-4_96-1

Swanson, L. R. (2018). Unifying Theories of Psychedelic Drug Effects. Frontiers in Pharmacology, 9, 172. https://doi.org/10.3389/fphar.2018.00172

Vollenweider, F. X., & Kometer, M. (2010). The neurobiology of psychedelic drugs: Implications for the treatment of mood disorders. Nature Reviews Neuroscience, 11(9), 642–651. https://doi.org/10.1038/nrn2884

Wheeler, S. W., & Dyer, N. L. (2020). A systematic review of psychedelic-assisted psychotherapy for mental health: An evaluation of the current wave of research and suggestions for the future. Psychology of Consciousness: Theory, Research, and Practice, 7(3), 279–315. https://doi.org/10.1037/cns0000237