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The Therapeutic Potential of Psilocybin and 3,4-Methylenedioxymethamphetamine in the Treatment of Depression and Post-Traumatic Stress Disorder

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Abstract

The psychedelic psilocybin and the entactogen 3,4-methylenedioxymethamphetamine (MDMA) are being scientifically studied again after a long hiatus, and especially for their potential in the treatment of psychiatric disorders. Their profound effect on cognitive, perceptual, and affective processes have led to several clinical studies during the last decade that have forced the reconsideration of the utility of these substances. The research includes clinical trials with psilocybin-assisted psychotherapy for depressive and anxiety symptoms, and MDMA-assisted psychotherapy for the treatment of post-traumatic stress disorder (PTSD). The results have shown a significant reduction in depressive and anxiety symptoms in psilocybin-assisted psychotherapy, and in PTSD symptoms in MDMA-assisted psychotherapy, with acceptable adverse effects. Moreover, the reductions in symptoms have been shown to be sustained several years later. Given the results indicate short- and long-term safety and efficacy, even for treatment resistant conditions, this suggest that these substances administered with psychotherapy are promising and deserve to be taken seriously as a therapeutic tool. The present thesis provides an overview of the latest clinical studies on the treatment of depression, anxiety, and PTSD with psilocybin and MDMA, respectively, as well as reviews the history, mechanisms of action, the therapeutic process used with psilocybin and MDMA, and any adverse physiological and psychological effects of both substances.

Keywords: 3,4-methylenedioxymethamphetamine, MDMA, psilocybin, entactogen, psychedelic, psilocybin-assisted psychotherapy, MDMA-assisted psychotherapy, depression, anxiety, post-traumatic stress disorder, treatment-resistant depression

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Introduction

"*Your assumptions are your windows on the world. Scrub them off every once in a while, or the light won't come in.*"

– Alan Alda, 1980 (Connecticut College, Speech)

The scientific study of psilocybin and 3,4-methylenedioxymethamphetamine (MDMA) has a long and complicated history with many setbacks. Our current conceptions of these substances have been shaped by popular cultural movements, national and international politics, and laws making research on these substances highly challenging. Nevertheless, over the past decades several studies and clinical trials have been conducted. For example, the first brain imaging study on psilocybin was published in 1997. This study utilized positron emission tomography (PET) to investigate how the ingestion of psilocybin affects brain activity (Vollenweider et al., 1997). This led to a number of brain imaging studies on subsequent years, and for example, to the first functional magnetic resonance imaging (fMRI) study on psilocybin in 2012 (Carhart-Harris et al., 2012), and the first fMRI study with MDMA in 2015 (Carhart-Harris et al., 2015).

Psilocybin, classified as "classical hallucinogen" or "psychedelic" profoundly alters human perception, mood, and cognition (Miller, 2017). Psilocybin has a way of shifting perspective, enhancing introspection, and reframing experiences and relationships making it a good candidate for the treatment of depressive symptoms. MDMA, classified as an "entactogen", is a synthetic drug that produces prosocial and interpersonal behavioral states (Miller, 2017) that shares properties of both mescaline (a classical hallucinogen) and methamphetamine (Hysek et al., 2012). MDMA has a tendency to enhance empathy, openness, and interpersonal warmth, which is why it might work well with post-traumatic stress disorder (PTSD) patients (Wagner et al., 2017).

While their pharmacology is diverse, psilocybin and MDMA share a fascinating effect of an immediate and lasting improvement in symptoms of depression/anxiety (psilocybin) and PTSD (MDMA) from a single exposure in a therapeutic setting, an effect that persists long after the substance is metabolized and gone from the body. Based on the published clinical studies thus far, both substances have shown promise as a potential tool administered with psychotherapy. The combination of low safety concerns and high potential for the reduction of psychological symptoms makes psilocybin- and MDMA-assisted psychotherapy a potential treatment option for people with depression/anxiety symptoms and PTSD. This represents a completely new way to treat patients. However, psilocybin and MDMA research is sill in its infancy.

This literature review will present the latest clinical studies with the aim to answer whether psilocybin-assisted psychotherapy has the potential to safely and efficaciously reduce depressive and anxiety symptoms, and whether MDMA-assisted psychotherapy has the potential to safely and efficaciously reduce PTSD symptoms. Articles have been attained through a literature search on the databases Scopus, Web of Science, and Google Scholar by using the keywords "MDMA", "3,4-methylenedioxymethamphetamine", "psilocybin", "depression", "anxiety", "PTSD", "post-traumatic stress disorder", "treatment", and

"psychotherapy". This limitation to two substances and two mental disorders has been a question of prioritization and based on the amount of published clinical studies. To present a clear and concise view of the topic, I will discuss the history of psilocybin and MDMA, their mechanisms of action, what depression and PTSD are, the therapeutic process used in this treatment, and also address safety issues, i.e., discuss any adverse physiological and psychological effects of the substances.

History of Psychedelic and Entactogen Research

Naturally occurring psychedelic substances have been used by indigenous cultures in spiritual and religious ceremonies for thousands of years, for example, to enter a trance state and achieve greater enlightenment and open-mindedness (Carod-Artal, 2015). Scientific research on psychedelics begun in the early 1900s, and one of the key historical events involved the synthesis of lysergic acid diethylamide (LSD) in 1938 by the Swiss scientist Albert Hofmann. However, it was not until the famous "Bicycle Day" in 1943 when he accidentally absorbed a small dose through his fingertips that he realized LSD's psychoactive effects (Belouin & Henningfield, 2018). The interest for LSD (among other psychedelics) as a psychotherapeutic tool started in 1950, when the first English publication about LSD appeared (Busch & Johnson, 1950).

Psilocybin was isolated in 1958 as the active ingredient of the mushroom *psilocybe mexicana* by Hofmann (around 180 species of mushrooms have been found to contain psilocybin) (Hofmann, 1980). A year later Hofmann had developed a way to produce a synthetic version of the psychedelic compound which was marketed by Sandoz under the name Indocybin for basic psychopharmacological and therapeutic clinical research (Hofmann, 1980; Passie, Seifert, Schneider, & Emrich, 2002). However, psilocybin got caught up in the political backlash against LSD.

LSD had gained popularity in the "counterculture movement", a movement of young people whose views were opposed to the Vietnam war and other social issues (Pollan, 2018). Simultaneously, the MK-Ultra project by the Central Intelligence Agency (CIA) studied LSD in a military sense. Their goal to *"investigate whether and how it was possible to modify an individual's behavior by covert means"* came to light during a congressional investigation into widespread illegal CIA activities within the United States and around the world (Pollan, 2018, pp. 172). The political climate eventually led to the stigmatization of psychedelics and adverse political repercussions, and President Nixon signed the Controlled Substance Act (CSA) in 1970 in which LSD and psilocybin were listed as Schedule 1 drugs. Schedule 1 substances are defined in the CSA by three factors: *(I) The drug or other substance has a high potential for abuse; (II) The drug or other substance has no currently accepted medical use in treatment in the United States; (III) There is a lack of accepted safety for use of the drug or other substance under medical supervision* (Drug Enforcement Administration, 2017). The CSA effectively ended all government-sanctioned psychedelic research. This does not mean that the law outright banned research on Schedule 1 substances, but it includes restrictions, significant barriers, and requirements that discourage scientists from attempting to conduct research on these substances or even applying for funding for such research.

Although Hofmann's discovery started the first wave of psychedelic research, MDMA was actually synthesized already in 1912 by the company Merck (Dunlap, Andrews, & Olson, 2018). MDMA was patented by Merck but was not tested on animals until 15 years later (unfortunately, the results of these tests could not be found in the Merck archive). While some preliminary human and animal data was produced during the first half of the 20th century, MDMA did not rise from scientific and cultural obscurity until the second half of the 20th century with the first peer-reviewed paper on the synthesis of MDMA being published in 1960 (Biniecki & Krajewski, 1960).

MDMA had remained relatively unexplored since its discovery until Alexander Shulgin learned of the drug and tested it on himself in 1976. He then began to synthesize MDMA and distributed it to his friend, Dr. Leo Zeff who began using the drug in psychotherapy sessions (Benzenhöfer & Passie, 2010). When Zeff realized its potential, he shared his findings with other therapists who also started to use MDMA in their practice. In 1978, the first MDMA study on humans was reported (Shulgin & Nichols, 1978). It seemed like the drug had some promise in a clinical setting but that changed when MDMA started to gain popularity in recreational use, and in 1981 acquired its street name "ecstasy" (Garcia-Romeu, Kersgaard, & Addy, 2016). Because of the limited studies on the safety of MDMA, the Drug Enforcement Administration (DEA) decided to place MDMA on the Schedule 1 list in 1985, despite many protests from scientists and therapists (Dunlap et al., 2018).

Not many clinical studies have been conducted with psilocybin and MDMA. This can partly be attributed to the legal restrictions of Schedule 1 substances and their non-profit potential. Both psilocybin and MDMA cannot be patented (psilocybin because it is naturally occurring, and MDMA because the patent by Merck has expired). This hinders for-profit pharmaceutical companies to invest in psilocybin or MDMA research, leaving the funding to private donors and non-profit foundations. This funding issue along with the legal restrictions have contributed greatly to the limited number of clinical studies (Multidisciplinary Association for Psychedelic Studies, 2016). Thus far, the non-profit organisation Multidisciplinary Association for Psychedelic Studies (MAPS) is the only organisation that has funded the MDMA-assisted psychotherapy studies included in this review. Similarly, the Heffter Research Institute (also non-profit) funded three out of the four psilocybin-assisted psychotherapy studies. This can be viewed as a source of potential bias, but ultimately, researchers are bound by ethical guidelines that aim to assure publication of unbiased results.

The organisation MAPS has been pioneering research into the psychotherapeutic potential of MDMA and made great strides in the past decade. Their study in 2010 was the first clinical trial that evaluated the potential of MDMA-assisted psychotherapy for alleviating treatment-resistant PTSD (Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2010). The results were positive, and this eventually led MAPS to being granted clearance by the Food and Drug Administration (FDA) in 2016 for large-scale Phase III trials for investigating the potential of MDMA as a treatment for PTSD (a Phase III trial means that the drug is presumed to have some effect, and the testing is to determine effectiveness, safety, and the drug's therapeutic effect in patient groups). This led the FDA to designate MDMA as a 'Breakthrough Therapy' for PTSD in 2017, and in 2019 MAPS started their studies in 15 locations across the US, Canada, and Israel. The Phase III trials are expected to be completed in 2021, meaning that the FDA could approve the treatment as early as 2022. MAPS is also

initiating Phase II trials in Europe and they have hopes for Phase III trials in 2020 (Doblin, Christiansen, Jerome, & Burge, 2019).

In 2018, the UK based company Compass Pathways received FDA 'Breakthrough Therapy' designation for psilocybin-assisted psychotherapy for treatment-resistant depression (TRD) (Compass Pathways, 2018), also approved by the European Medicines Agency (EMA). The study started at the beginning of 2019 and should report results in December 2020. In 2019, the FDA granted another 'Breakthrough Therapy' status to the Usona Institute for major depressive disorder (MDD) (Business Wire, 2019). The Phase II trial is expected to be completed by early 2021, and with the help of this status, Usona expects to quickly move into a larger Phase III trial. The most important landmarks of the 20th century in research of psychedelics and entactogens are summarized in Table 1.

Table 1. Notable landmarks of the 20th century in research of psychedelics and entactogens.

Year	Substance	Landmark	Reference
1912	MDMA	Synthesized by Merck	Dunlap et al., 2018
1938	LSD	Synthesized by Hofmann	Belouin & Henningfield, 2018
1943	LSD	"Bicycle Day", psychoactive effects discovered by Hofmann	Belouin & Henningfield, 2018
1950	LSD	First English publication, started the interest for psychotherapy with psychedelics	Busch & Johnson, 1950
1958	Psilocybin	Isolated by Hofmann	Hofmann, 2005
1970	Psilocybin	Controlled Substance Act, classified as Schedule 1	Pollan, 2018
1976	MDMA	Shulgin tested MDMA on himself and distributed to therapists	Benzenhöfer & Passie, 2010
1978	MDMA	First reported study on humans	Shulgin & Nichols, 1978
1985	MDMA	Classified as Schedule 1	Dunlap et al., 2018
2016	MDMA	MAPS was granted FDA clearance for Phase III trials for PTSD	Doblin et al., 2019
2017	MDMA	FDA designated MAPS use of MDMA as 'Breakthrough Therapy' for PTSD	Doblin et al., 2019
2018	Psilocybin	FDA designated Compass Pathways use of psilocybin as 'Breakthrough Therapy' for TRD approved by the EMA	Compass Pathways, 2018
2019	MDMA	Beginning of MAPS's FDA regulated Phase III trials for PTSD	Doblin et al., 2019
2019	Psilocybin	FDA designated Usona Institute use of psilocybin as 'Breakthrough Therapy' for major depressive disorder	Business Wire, 2019

Note. MAPS: Multidisciplinary Association for Psychedelic Studies; FDA: Food and Drug Administration; TRD: treatment-resistant depression; EMA: European Medicines Agency.

Action Mechanisms of Psychedelics and Entactogens

Psychedelics (also called classical hallucinogens or serotonergic psychedelics) are a class of drugs which induce profound altered states of consciousness, involving alterations in perception and cognition, amplified emotional states, an altered sense of time, spiritual

experiences, and, depending on dose, synesthesia (a mixing of the senses) (Miller, 2017). Psychedelics include lysergic acid diethylamide (LSD), 4-phosphoryloxy-N,N-DMT (psilocybin) (see Figure 1a), dimethyltryptamine (DMT), and mescaline (Garcia-Romeu et al., 2016).

Entactogens are a class of synthetic drugs that reliably produce prosocial and interpersonal behavioral states, a sense of euphoria, increased empathy, personal insight, and heightened sensations (including sexual sensations) (Miller, 2017). This unique profile comes from the combination of the catecholaminergic effects of methamphetamine and the serotonergic effects which resemble psychedelics. Within this category are 3,4-methylenedioxymethamphetamine (MDMA) (see Figure 1b), 3,4-methylenedioxyamphetamine (MDA), and 3,4-methylenedioxyethylamphetamine (MDE) (Garcia-Romeu et al., 2016). Next, the receptor mechanisms of these agents and their effects on brain activity are discussed.

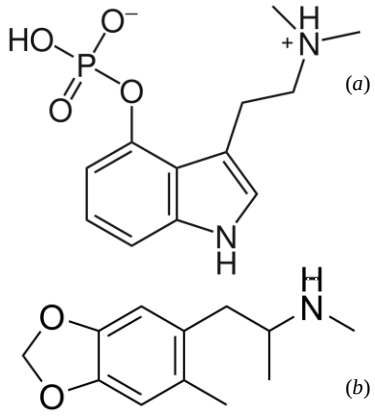

Figure 1. (*a*) Psilocybin's molecular structure (Wikimedia Commons, 2008b). (*b*) MDMA's molecular structure (Wikimedia Commons, 2008a).

The Effects of Psilocybin on the Brain. Psychedelics share a common mechanism of action, the activation of serotonin receptors (Guimarães dos Santos & Hallak, 2020). Psilocybin's active dephosphorylated form is called psilocin (4-hydroxy-dimethyltryptamine), and it is the primary psychoactive compound in several species of hallucinogenic mushrooms found throughout the world (Grinspoon & Bakalar, 1979). In 1988, pharmacological tools such as the selective 5-hydroxytryptamine receptor 2 (5-HT_2) agonist 2,5-dimethoxy-4-iodoamphetamine (DOI), and the antagonist ketanserin, became available. This allowed the 5-HT_2 receptor to be identified as the target for psychedelics (Kyzar, Nichols, Gainetdinov, Nichols, & Kalueff, 2017). In the body, psilocybin transforms into psilocin and, as an agonist or partial agonist, it activates several serotonin receptors (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}) (Ruban & Kołodziej, 2018). However, it is the activation of the 5-HT_{2A} receptor that plays a major role in producing the altered state of consciousness commonly associated with psilocybin (Ruban & Kołodziej, 2018).

The 5-HT_2 receptors are widely expressed throughout the brain in areas such as the claustrum, Layer 5 in the medial prefrontal cortex (PFC), the reticular nucleus of the thalamus, ventral tegmental area, the locus coeruleus, and the amygdala (Nichols, Johnson, & Nichols, 2017). The decreased functional connectivity between the ventral medial PFC and amygdala post-psilocybin treatment is significantly associated with decreased rumination (Mertens et al., 2020). Psilocybin administration has also been shown to lead to decreased amygdala activity and reduced reactivity to threats (Kraehenmann et al., 2016), and in decreased connectivity between amygdala and the striatum during angry face discrimination (Grimm, Kraehenmann, Preller, Seifritz, & Vollenweider, 2018). Enhanced neuroplasticity, both structurally and functionally, in neurites and dendritic spines in prefrontal cortical neurons has been seen following psilocybin administration (Ly et al., 2018). Ly et al. suggest

that the antidepressant and anxiolytic effects might come from psilocybin's ability to enhance neuroplasticity.

The claustrum, with a high expression of 5-HT_2 receptors, is ideally positioned as a modulator that could desynchronize or terminate activation of the areas related to the default mode network (DMN) (Reser et al., 2014). The DMN is a specific, anatomically defined brain network, composed of the posterior cingulate cortex (PCC), medial PFC, medial, lateral and inferior parietal cortex, as well as portions of the medial temporal lobe (MTL) (Raichle et al., 2001). The DMN seems to deactivate during the initiation of task-related activity (Buckner, Andrews-Hanna, & Schacter, 2008) and is active when we daydream, engage in mental time-travel, and reflect on ourselves (Pollan, 2018). Psilocybin's ability to regulate the DMN was first tested in a study by Carhart-Harris et al. (2012). They observed decreased connectivity of the DMN in conjunction with psilocybin with a decreased activity in the PCC, one of the key regions of the DMN which normally has high resting state metabolic activity. They also found that psilocybin caused decreased activity in the medial PFC, which is a region of the DMN where high activity can be seen in individuals with MDD (Greicius et al., 2007). These results were later replicated by Muthukumaraswamy et al. (2013) who found a decreased blood-oxygen-level-dependent imaging (BOLD) signal in cortical nodes of the DMN, with some of the largest decreases in oscillatory power in areas of the DMN. Decreased DMN connectivity was also found in studies using LSD whose mechanism of action is similar to psilocybin's (Carhart-Harris, Muthukumaraswamy et al., 2016; Müller, Dolder, Schmidt, Liechti, & Borgwardt, 2018). However, in a recent study *increased* resting state functional connectivity (RSFC) within the DMN one day post-psilocybin-treatment was observed (Carhart-Harris et al., 2017) leaving the field open for more studies to clarify the results.

In a study mapping the brain of healthy individuals on psilocybin (Petri et al., 2014), more connections between brain areas could be seen relative to the placebo group. Petri et al. found that the RSFC analysis of the psilocybin imaging data were characterized by the emergence of both short-lived and persisting connectivity networks between brain regions that normally do not show significant functional association. In sum, Petri et al. discovered that the brains of the participants who were administered psilocybin were less constrained and more intercommunicative, and their brain networks appeared to become less specialized and more globally interconnected.

The Effects of MDMA on the Brain. Pharmacologically, MDMA possesses properties of both methamphetamine and mescaline. However, MDMA is not as hallucinogenic as mescaline and not as stimulating as methamphetamine (Holland, 2001). MDMA is a potent releaser of pre-synaptic serotonin (regulated by the 5-HT_2 receptors), which is the major mechanism of action underlying the distinct mental effects of MDMA (Liechti & Vollenweider, 2000). MDMA is also similar to dopamine, which makes MDMA a potent releaser of catecholamine neurotransmitters like epinephrine, norepinephrine, and dopamine (Garcia-Romeu et al., 2016). Because MDMA binds to and inhibits serotonin, dopamine, and norepinephrine transporters, it thus inhibits monoamine reuptake and leads to increased extracellular levels of these amines (Hysek et al., 2012). In addition to this, MDMA also inhibits the transportation of monoamines into vesicles (Dunlap et al., 2018). The

increase of noradrenaline is mainly responsible for the physical effects that MDMA shares with methamphetamine (Kalant, 2001).

PET and fMRI studies have found MDMA to lead to decreased cerebral blood flow (CBF) in the amygdala (Carhart-Harris et al., 2015; Gamma, Buck, Berthold, Hell, & Vollenweider, 2000), hippocampus (Carhart-Harris et al., 2015), insula (Gamma et al., 2000; Walpola et al., 2017), posterior and anterior cingulate, and MTL in healthy subjects (Gamma et al., 2000). Also an increased RSFC between the amygdala and hippocampus, a decreased RSFC between the PFC and hippocampus (Carhart-Harris et al., 2015), and increased CBF in the prefrontal, inferior temporal, and cerebellar cortex (Gamma et al., 2000) have been observed. These changes were interpreted as causing mood enhancements, increased extraversion, decreased anxiety, and a mild intensification of sensory perception (Gamma et al., 2000). MDMA has also been seen to attenuate amygdala reactivity to angry faces, while enhancing central striatum's response to happy faces, and increasing sociability (Bedi, Phan, Angstadt, & de Wit, 2009).

Additionally, MDMA leads to changes in hormone secretion, namely in an increase in plasma levels of cortisol, prolactin, dehydroepiandrosterone, vasopressin, and oxytocin (Harris, Baggott, Mendelson, Mendelson, & Jones, 2002). These hormonal changes are likely responsible for some of the most commonly associated effects of MDMA. For instance, the rise of plasma dehydroepiandrosterone levels is correlated with feelings of euphoria (Harris et al., 2002), and the increase of oxytocin levels can explain the prosocial effects of MDMA (Dumont et al., 2009).

Depression and Post-Traumatic Stress Disorder

Major depressive disorder (MDD) is one of the most common psychiatric disorders affecting more than 264 million people worldwide (World Health Organization, 2020). Depression is characterized by persistent sadness, lack of interest or pleasure, disturbed sleep and appetite, tiredness, and poor concentration. The World Health Organization (WHO) has ranked MDD as the fourth leading contributor to the global burden of disease, and it is on the rise globally (World Health Organization, 2020).

There is no universally accepted criteria for defining treatment-resistant depression (TRD), but the general consensus is a lack of response to an adequate trial of antidepressant treatment. The exact number of treatment/medication attempts that need to fail before someone is labeled with TRD varies. TRD is the form of depression that is considered to cause the most burden, both for the individual and society, because of its chronic nature (Trevino, McClintock, Fischer, Vora, & Husain, 2014). Psilocybin in conjunction with psychotherapy has shown great promise in alleviating TRD and could be a useful treatment option, especially since currently available antidepressants do not seem to work for people with TRD.

MDD is present in about one in four people with cancer, and people who have had depression at some point in their lives prior to cancer are more likely to develop depression after their cancer diagnosis (American Cancer Society, 2020). Millions of new cancer cases are diagnosed yearly, with cancer being the second leading cause of death globally with an

estimated 9.6 million deaths in 2018 (World Health Organization, 2018). Although an exact estimate could not be found, millions of cancer patients are likely to suffer from depression and anxiety, symptoms that psilocybin has shown promise in alleviating.

PTSD is a trauma- and stress-related disorder with a lifetime prevalence of around 3.9% worldwide, according to the WHO (Koenen et al., 2017). PTSD is caused by personal exposure, being witness to, or having close friends and family being affected by traumatic events (Garcia-Romeu & Richards, 2018). It is characterized by overwhelming negative emotions, psychological distress, negative alterations in cognition, intrusive re-experiencing of traumatic events (recurring dreams and flashbacks), avoidance, and hyper-arousal symptoms that are prevalent for at least one month (American Psychiatric Association, 2013; Ot'alora et al., 2018). Most, but not all, traumatized people experience these symptoms short-term, however, the majority do not develop chronic PTSD (Garcia-Romeu & Richards, 2018). Chronic PTSD is resistant to treatment, but MDMA administered concomitantly with psychotherapy has shown good promise in alleviating PTSD symptoms.

The Therapeutic Process: Preparation, Support, and Integration

Psilocybin- and MDMA-assisted psychotherapy is usually comprised of three parts: preparation before the dosing session, support during the dosing session, and integration sessions afterwards. It is not unusual that two therapists (one female and one male) are present at all stages. These three stages are used for most clinical trials of psilocybin- and MDMA-assisted psychotherapy, but the preparation and integration stages have varied depending on the condition being treated and therapeutic orientation of the therapists and researchers (Sloshower et al., 2020).

The preparatory sessions provide the participants with information about the drug session, such as what will likely happen during the session, what the patient might feel and experience, and to discuss the therapeutic approach used (Sloshower et al., 2020). Psychedelic substances typically enhance a person's current state of mind. Therefore, entering the session with a relaxed mindset could help guide the experience towards a positive direction, something that the preparatory sessions will help the participants with.

Support during the drug session is largely nondirective, and patients are encouraged to have an inward directed experience. The therapists are there to provide support and deal with any difficult thoughts or memories that might arise. However, they can guide the patient into discussions related to their condition or trauma if deemed beneficial. They also help the patients with any needs they might have and ensure their safety (Garcia-Romeu & Richards, 2018). The setting where the drug session takes place is extremely important and can partially determine the outcome of the drug session. Therefore, the drug session is conducted in a comfortable setting that feels safe, warm, and inviting, in a private area where only the patient and the therapist(s) are present. Patients are usually encouraged to lie on a sofa with eyeshades on and headphones playing pre-selected music. This is meant to help the patient experience a mostly uninterrupted 'inner journey' where they can focus on their thoughts and emotions (Garcia-Romeu & Richards, 2018; Sloshower et al., 2020).

Integration usually begins the day after the drug session and the purpose is to thoroughly review and reflect on the patient's experience during the drug session. Integration can be described as the continuation of the therapeutic process that began during the preparation sessions (Sloshower et al., 2020). There has not been a validated quantity or frequency of integration sessions that are most effective, but weekly sessions lasting one to three months are common (Garcia-Romeu & Richards, 2018).

The Therapeutic Potential of Psilocybin

Thus far only four studies have been conducted in the last two decades in regards to psilocybin and depression. One has been directly with patients who have TRD (Carhart-Harris et al., 2018), and the other three have been with cancer patients who have depressive and anxiety symptoms (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016).

Psilocybin for Treatment-Resistant Depression. The Carhart-Harris et al. (2018) study was an open-label feasibility study (with no control group) assessing the efficacy and safety of psilocybin in patients with TRD (defined as no improvement despite two adequate courses of antidepressants, each course at six weeks minimum) (see Table 2). The participants (N = 19; 13 males) were asked to be antidepressant-free for at least two weeks before the study. Prior to the first dose, an initial four-hour preparatory psychotherapy session was completed. Two doses were given to the participants, one initial safety dose of 10 mg and a subsequent treatment dose of 25 mg. This was done seven days apart and with psychological support before, during, and after each session. After the treatment dose, follow-up assessments were conducted at one week, two weeks, three weeks, five weeks, three months, and six months. The participants' depressive scores, measured with the Quick Inventory of Depressive Symptoms (QIDS), significantly improved from baseline to six months post-treatment. At baseline the mean depressive severity was measured at 'severe depression', and at six months the mean score was statistically significantly reduced to 'mild depression' (see Table 2). Anhedonia scores, measured with the Snaith-Hamilton Pleasure Scale (SHAPS), improved significantly from baseline to three months. In addition, anxiety symptoms, measured with State Trait Anxiety Inventory (STAI), significantly improved from baseline to six months post-treatment (see Table 2).

Six months after their dose, the patients were invited to a follow-up interview where they could share their opinions of the experience (Watts, Day, Krzanowski, Nutt, & Carhart-Harris, 2017). All 19 participants took part, and all reported preferring psilocybin to conventional treatments and expressed interest in further psilocybin-assisted psychotherapy.

Psilocybin for Cancer Patients. The first cancer patient study was conducted by Grob et al. (2011) who investigated the effects of psilocybin on depression, state-trait anxiety, and mood states in advanced-stage cancer patients in a within-subject, double-blind, placebo-controlled study (see Table 2). The patients were asked to refrain from taking any medications the day of and the day after the experimental treatment session (except for prescriptions or pain medications). Twelve patients (11 females) participated in the study that consisted of two

experimental sessions. Each subject acted as their own control where they received a moderate dose of psilocybin (0.2 mg/kg of body weight) on one session, and an active placebo of niacin (250 mg), which induces a mild physiological reaction such as flushing, on the other session. These sessions were several weeks apart. Follow-up assessments were scheduled monthly for six months after treatment. A significant drop in Beck Depression Inventory (BDI) scores was seen from the first session to one month after the second treatment session. This drop was sustained and further declined at the six months follow-up (see Table 2). A reduction in trait anxiety measured by STAI was observed and reached significance at the one-month follow-up, and was sustained for the entire six months (see Table 2).

Griffiths et al. (2016) conducted the, thus far, largest rigorous psilocybin study on cancer patients (N = 51; 26 males) (see Table 2). It was a double-blind, randomised, placebo-controlled, crossover trial assessing the effects of psilocybin on symptoms of depression and anxiety in patients with life-threatening cancer. Two psilocybin doses were administered five weeks apart. The low dose (considered the placebo) was 1 or 3 mg/70 kg, and the high dose (treatment dose) was 22 or 30 mg/70 kg. When designing the study, they had little experience with what the most optimal dosing would be. They decreased the high dose from 30 to 22 mg/70 kg and the placebo from 3 to 1 mg/70 kg after realizing that both doses were too high (i.e., the change was made after the study had already started). Follow-up assessments were the day after each session, plus two or more between the two psilocybin sessions, and two or more between the second session and the six-month follow-up. At six months, they found that psilocybin produced large and significant decreases in clinician-rated and self-rated measures of depression and anxiety, measured with the Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) (see Table 2). Also increases in measures of quality of life, life meaning, death acceptance, and optimism endured at six months. However, a similar (but not as significant) response was seen for the low dose of psilocybin on all measures, even though it was considered as placebo.

The third cancer study investigating the efficacy of psilocybin was a randomised, double-blind, placebo-controlled, crossover study conducted by Ross et al. (2016) (see Table 2). Twenty-nine (18 females) patients with life-threatening cancer and clinically significant anxiety and depression participated in the study. They were assigned to receive treatment with a single-dose psilocybin (0.3 mg/kg) and niacin (250 mg) in random order, both in conjunction with psychotherapy. Before the crossover at seven weeks post-dose one, there were significant differences between the experimental and control group for both anxiety and depressive scores (measured by the Hospital Anxiety and Depression Scale (HADS), BDI, STAI) (high effect size for all measures). For example, seven weeks after dose one, 83% of participants in the group that received psilocybin first met the criteria for antidepressant response (BDI) and 58% for anxiolytic response (HADS), compared to 14% in the group that received niacin first. These effects were immediate and sustained (for the group that received the psilocybin dose first) at each time point, including the final point at 6.5 months post dose two. The BDI and HADS response rates were approximately 60-80% improved at the 6.5-month follow-up (when both groups had received psilocybin). Prior to the crossover, there was no significant within-group reduction in symptoms in the group that received niacin first. However, after receiving psilocybin (dose two), there were significant within-group

reductions in anxiety and depression, and these improvements persisted until the end of the study (6.5 months post-psilocybin). Notably, these improvements were not as significant as in the group that received psilocybin as the first dose.

The first long-term follow-up (LTFU) study (Agin-Liebes et al., 2020) was conducted with 14 of the 29 participants from the Ross et al. (2016) study (14 had died and one did not agree to participate) approximately 3.2 and 4.5 years following the psilocybin dosing date. Statistically significant reductions relative to baseline on measures of anxiety and depression were observed at both the first and second LTFU points (high effect size on both measures). At the second LTFU point, the majority of participants showed a clinically significant anxiolytic response and depression symptom remission rate (see Table 2).

Table 2. Summary of completed psilocybin clinical trials.

Study	(*N*)	Dosage	Diagnosis	Sessions	Outcome
Carhart-Harris et al., 2018	19	10 mg and 25 mg psilocybin	TRD	1 introductory + 2 experimental + 6 follow-up sessions (during 6 months)	QIDS score improved after 6 months (p = .0035); SHAPS improved from 6.6/14 to 3.3/14 after 3 months; STAI scores improved from 68.6/80 to 53.8/80 after 6 months
Griffiths et al., 2016	51	1 or 3 mg/70 kg and 22 or 30 mg/70 kg psilocybin	Cancer	2 introductory + 2 experimental + 6 or more follow-up sessions (during 6 months)	78% of patients had a positive clinical response to depressive states measured with HAM-D; 83% had a positive clinical response to anxiety measures with HAM-A; 80% of patients reported increased well-being or life satisfaction
Grob et al., 2011	12	0.2 mg/kg psilocybin and 250 mg niacin	Cancer	1 introductory + 2 experimental + 6 months monthly follow-up sessions	BDI scores decreased 30% from baseline and reached highest significance at 6 months (p = .03); STAI reduction reached significance at 1 month (p = .001) and was maintained at 6 months
Ross et al., 2016 + Agin-Liebes et al., 2020 (LTFU)	29	0.3 mg/kg psilocybin or 250 mg niacin	Cancer	3 introductory + 2 experimental + 9 follow-up session (during 8 months)	At LTFU, 57% showed anxiolytic response and 50-79% antidepressive response on HADS; HADS scores decreased from 16.45 at baseline to 7.32 at the second LTFU

Note. TRD: treatment-resistant depression; BDI: Beck Depression Inventory; STAI: State Trait Anxiety Inventory; HAM-D: Hamilton Depression Rating Scale; HAM-A: Hamilton Anxiety Rating Scale; HADS: Hospital Anxiety and Depression Scale; QIDS: Quick Inventory of Depressive Symptoms; SHAPS: Snaith-Hamilton Pleasure Scale.

Limitations. These studies showed significant improvements in depressive and anxiolytic symptoms after administration of psilocybin, however, they share some methodological limitations that need to be taken into consideration when interpreting the results. For instance, there are issues with patient selection and sample size, different dosing schemes, limited blinding, lack of strict therapeutic model, and lack of control group. Without a control group, it will be difficult to distinguish the effects of the drug from those of the psychological treatment. Notably, in studies where the participants received placebo first (niacin or low dose of psilocybin), they improved less than those who received the therapeutic dose first. This may speak of another limitation, i.e., the potential expectancy bias that the

patients might have had. Psychedelics are known to promote suggestibility (Carhart-Harris, Kaelen et al., 2014) which might have enhanced positive outcomes. Future double-blind randomised controlled trials could address the role of expectancy and suggestibility by measuring and controlling these variables (Carhart-Harris, Bolstridge et al., 2016).

Adverse Physiological and Psychological Effects of Psilocybin. Psilocybin used in a responsible clinical or research setting is generally well tolerated (Studerus, Kometer, Hasler, & Vollenweider, 2011) since classical hallucinogens possess low physiological toxicity and have not been shown to result in organ damage or neuropsychological deficits (Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004). Approximately 2000 doses of psilocybin have been safely administered to humans in a carefully controlled scientific settings in the US and Europe since the early 90s. No medical or psychiatric serious long-term adverse events, including cases of hallucinogen persisting perception disorder (HPPD), have been reported (Ross et al., 2016). This data is consistent with the 2001-2004 'National Survey on Drug Use and Health' in the US in which 21 967 out of 130 152 respondents reported lifetime psychedelic use and no associations between lifetime use and increased rates of mental illness were found (Krebs & Johansen, 2013). In fact, lifetime use of psychedelics was associated with lower rates of mental health problems. This is not, however, evidence that psilocybin is risk-free. Psilocybin can lead to psychologically challenging experiences, especially when not used in a proper therapeutic setting where introduction, support, and integration are incorporated. The most likely psychological risk would be known as a "bad trip" which is characterised by anxiety, fear/panic, dysphoria, aggression, and/or paranoia. The person having a bad trip might experience frightening illusions, disturbing hyperawareness of physiological processes, troubling thoughts or feelings concerning one's life and about evil forces (Grinspoon & Bakalar, 1979; Strassman, 1984).

Short-term adverse effects that are usually reported after a therapeutic dose of psilocybin (but are transient, tolerable, and normally return to baseline within 24-hours) are tiredness, exhaustion, headaches, anxiety, psychological discomfort, confusion, nausea, and paranoia (Carhart-Harris et al., 2018; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Psychedelics also have a tendency to modestly raise blood pressure and heart rate. For that reason, people with severe cardiac disorders should be excluded from clinical trials (Grob et al., 2011). Distortions of the visual field and detachment can also occur, which some can experience as negative and stressful (Carod-Artal, 2015).

The four presented studies on clinical populations (Carhart-Harris et al., 2018; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016) did not report any serious adverse events, either physiological or psychological, in their subjects and any mild complications were almost completely restored within 24-hours after drug administration. Studerus et al. (2011) reported no serious adverse events in their healthy participants. They also found that a carefully monitored administration of psilocybin to healthy volunteers did not increase the risk of abuse of psilocybin or other illicit drugs. Their results are consistent with the widely accepted view that classical psychedelics have very low abuse potential. They found that most of their subjects welcomed the 'coming down' effect after psilocybin because the experience was tiring, even though it had been a pleasant experience. This goes along with the argument that psilocybin is not an addictive and dependence-inducing drug.

One potential adverse long-term risk is HPPD. In order to meet the 'Diagnostic and Statistical Manual of Mental Disorders: IV' (DSM-IV) criteria for this disorder, a hallucinogen user must re-experience perceptual effects similar to those experienced under the drug. The symptoms mentioned in DSM-IV are geometric hallucinations, false perceptions of movement in the peripheral visual fields, intense colours, flashes of colours, trails of images of moving objects and after-images, macropsia, and micropsia (American Psychiatric Association, 2013; Studerus et al., 2011). These effects must also be clinically distressing or impair functioning, and the effects must not be caused by a medical condition or be better explained by another psychiatric disorder or hypnopompic hallucinations (American Psychiatric Association, 2013). HPPD is considered a risk, but is thought to be very uncommon given the relatively few cases reported since the 1960s (Halpern & Pope, 2003). This is also supported by the fact that none of the participants experienced HPPD in the studies mentioned above (Carhart-Harris et al., 2018; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016; Studerus et al., 2011).

Another risk is that psychedelics can instigate a prolonged state of psychosis. For cases where psychotic reactions within a lifetime occur after taking a psychedelic, a psychotic vulnerability is suspected. However, it is impossible to know whether a given individual would eventually have a psychotic reaction if that person would not have taken the drug (Grinspoon & Bakalar, 1979).

The Therapeutic Potential of MDMA

In the current review, four original studies conducted with MDMA in patients with PTSD are included (see Table 3). However, three more studies have been conducted but have been excluded based on very small sample sizes and/or because they have not been published as original studies and have only been included in pooled analyses (Bouso, Doblin, Farré, Alcázar, & Gómez-Jarabo, 2008; studies NCT01958593 and NCT01689740 included in Mithoefer et al., 2019). The four studies included in this review were all sponsored by MAPS and have therefore almost entirely the same design and form of psychotherapy. MAPS developed a manual that all studies followed and that is available on their website (Multidisciplinary Association for Psychedelic Studies, 2017). Participants in all studies were required to have chronic PTSD with treatment-resistant symptoms defined with Clinician-Administered PTSD Scale (CAPS) as a score of ≥50 (signifying moderate to severe symptoms), no response to selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) treatment, in addition to at least six months of psychotherapy. All participants were required to abstain from all psychotropic medication during the study (with exceptions).

MDMA for Post-Traumatic Stress Disorder. The first study (Mithoefer et al., 2010) was a randomised, double-blind, inactive placebo-controlled, crossover trial that included 20 participants (17 females) (see Table 3). Subjects were randomised into two groups, one group who received two experimental sessions with MDMA (N = 12; 125 mg of MDMA with the possibility of a supplemental dose of 62.5 mg), and another group who had two sessions with

the inactive placebo (lactose) (*N* = 8). Each subject had two 90-min introductory sessions, two experimental sessions (lasting 8-10 hours followed by an overnight stay), and eight integration sessions starting immediately after the first experimental session and up to two months after the second experimental session. CAPS scores improved over time in both groups, but the MDMA group showed significantly greater improvements than the placebo group (see Table 3). Two months after the second experimental session, ten out of the twelve (83%) subjects in the MDMA group no longer met the criteria for a PTSD diagnosis, compared to two out of eight (25%) in the placebo group. There was also a crossover arm where seven out of the eight placebo subjects enrolled and received two MDMA sessions. In all seven, the CAPS scores decreased from end of the control trial to four-six weeks after two MDMA sessions (see Table 3).

A LTFU study (Mithoefer et al., 2013) was conducted with 16 of the original participants from the Mithoefer et al. (2010) study between 17 and 74 month after the completion of the MDMA-assisted psychotherapy session. The original results were sustained four years later without any further MDMA intervention. Altogether, 85% of the participants remained PTSD-free. All subjects reported benefit from participation in the study and also believed that more MDMA sessions would have been helpful.

The next study (Oehen, Traber, Widmer, & Schnyder, 2013) had 12 participants (10 females) with chronic PTSD (mean PTSD duration of 18.3 years) (see Table 3). The design was similar to the previous study (Mithoefer et al., 2010), but one difference was that Oehen et al. used an active placebo of 25 mg of MDMA. Eight subjects were randomised to the experimental group (125 mg + 62.5 mg 2.5 hours later), and four to the active placebo group (25 mg + 12.5 mg 2.5 hours later). The drug was administered in three full day MDMA-assisted psychotherapy sessions (the participants in the placebo group would later receive two full MDMA sessions). Each subject received a minimum of 12 non-drug psychotherapy sessions. A clinical response was seen for four out of the eight participants in the experimental group, however, all of them still fulfilled PTSD criteria but with a reduction in severity from 'severe' to 'mild' or 'moderate' after undergoing three blinded drug-assisted sessions and 12 non-drug psychotherapy sessions. Three full-dosage participants were non-responders to the MDMA so they received two additional high dose sessions, but no improvements in CAPS scores were observed (mean CAPS score change of 0.2 points). Changes in CAPS scores from baseline to post-treatment were small in these participants, but although Oehen et al. did not find statistically significant reductions in CAPS scores, the subjective ratings (measured by self-report questionnaires) showed a significant symptom reduction. They also found that three MDMA sessions were more effective than two. At the one-year follow-up, CAPS scores improved further (see Table 3). Five participants no longer met the criteria for PTSD, two had switched to mild PTSD, four had moderate PTSD, and one had died due to cancer.

The next study (Ot'alora et al., 2018) included 28 participants (19 females) with chronic PTSD (mean duration of 29.4 years) who were randomised in a double-blind dose response comparison of two active doses, 100 mg (*N* = 9) and 125 mg (*N* = 13), with the active placebo of 40 mg (*N* = 6) (see Table 3). Three 90-minutes introductory sessions were conducted to prepare the participants before the two 8-hour experimental sessions started. Participants in the 40 mg group crossed over after the two initial experimental sessions and

had three open-labeled sessions (100-125 mg) with associative integrative sessions. The experimental groups had the largest reduction in CAPS scores, from baseline to after the second blinded session. These scores further declined two months after the final open-label session (one additional MDMA session for the experimental group, and three for the placebo group), and additionally 12 months after the last active dose of MDMA. At that point, the average CAPS scores had declined for the participants that completed the 12 month follow-up (N = 25), with 76% of participants (N = 19) no longer meeting the criteria for a PTSD diagnosis (see Table 3).

The last study (Mithoefer et al., 2018) was a Phase II trial that included military veterans, firefighters, and police officers with chronic PTSD (N = 26; 19 males) (see Table 3). They were randomised into three groups, 30 mg (active placebo) (N = 7), 75 mg (N = 7), or 125 mg (N = 12) of MDMA that was administered in three 8-hours sessions with 18 hours of non-drug psychotherapy sessions (double-blind). The primary outcome was mean change of CAPS scores from baseline to one month after the second double-blinded experimental sessions. Participants in the 30 and 75 mg groups underwent an open-label crossover with three additional 100-125 mg experimental sessions. The 125 mg group had one additional experimental session. The CAPS mean score decreased from baseline to one month after the second blinded experimental session for all groups (see Table 3). At this point, two of seven participants in the 30 mg, six of seven participants in the 75 mg group, and seven of twelve participants in the 125 mg group did not meet the criteria for a PTSD diagnosis anymore. At the crossover, PTSD symptom severity decreased further for the group that had previously received 30 mg dose (see Table 3). The 75 mg group did not have any further improvements. Compared with baseline, PTSD symptoms were significantly reduced at the 12 month follow-up and 16 out of the 24 who completed the follow-up no longer met PTSD criteria.

Table 3. Summary of completed MDMA clinical trials for chronic PTSD.

Study	**(*N*)**	**Dosage**	**Sessions (follow-up)**	**Outcome**
Mithoefer et al., 2010 + 2013 (LTFU)	20	125 mg (62.5 mg extra if advisable), or placebo (lactose)	2 introductory + 2 experimental + 8 integration sessions (1.4 - 6.1 year follow-up)	Average CAPS scores decreased with 53.7 points in the MDMA group compared to 20.5 points in the placebo group; At crossover, CAPS decreased from 65.6 to 33.9
Mithoefer et al., 2018	26	75 mg, 125 mg, or 30 mg (placebo)	3 introductory + 3 - 5 experimental + 9 - 12 psychotherapy sessions (1 year follow-up)	Average CAPS scores decreased from baseline to 1 month after the second drug session (11.4: 30 mg; 58.3: 75 mg; 44.3: 125 mg); After crossover, the 30 mg group decreased with 27 points
Oehen et al., 2013	12	125 + 62.5 mg, or 25 + 12.5 mg (placebo)	2 introductory + 3 experimental + 12 or more psychotherapy sessions (1 year follow-up)	Average CAPS scores decreased with 24 points from baseline to 1 year follow-up for the experimental group, and 35 points for the crossover group who had received the active placebo first
Ot´alora et al., 2018	28	100 mg, 125 mg, or 40 mg (placebo)	3 introductory + 4 experimental + 8 - 11 integrative sessions (1 year follow-up)	Average CAPS scores decreased from 92 (baseline) to 31 at the 12 month follow-up

Note. PTSD: Post Traumatic Stress Disorder; CAPS: Clinician-Administered PTSD Scale.

Limitations. Some important methodological limitations require noting. For instance, these limitations include patient selection and sample size, the lack of a true control group in three out of the four studies, difference in the amount of psychotherapy between the groups, no control group for the follow-up in all studies because of crossover, and observer expectancy bias. Similar to psilocybin, the profound effects of MDMA compared to a placebo make it impossible to keep therapists and participants blind from the treatment condition. Even with an active placebo, keeping the study blind could only be partially accomplished. As with psilocybin, any potential expectancy bias that can alter the results of the study is also an issue with MDMA. Lastly, since all studies were sponsored by MAPS and also conducted by similar research teams, the reliability could be questioned.

Adverse Physiological and Psychological Effects of MDMA. Many neuroimaging studies have been published over the past 20 years that have caused an ongoing debate whether MDMA may be neurotoxic. Studies have provided results that MDMA impairs memory and vision, increase psychiatric symptoms, distress, pain, meta-cognition, sleep apnea, reduce immunocompetence (Parrott, 2013), and that MDMA has neurotoxic effects at high doses (Johnson, Richards, & Griffiths, 2008). MDMA has also shown signs of stimulating difficult feelings and memories, especially during neurochemical recovery after the effects of MDMA have diminished and when the supply of serotonin is low (Parrott, 2014). However, these studies are either animal studies or conducted with subjects who have used *Ecstasy* recreationally (not always exclusively MDMA), usually in heavy doses and in an environment that is far from a therapeutic setting (Parrott, 2013).

Opposite results have also been presented. More than 850 subjects have safely participated in regulatory-approved MDMA research with no persistent drug-related harm reported (Doblin et al., 2014). In a systematic review article by Mueller et al. (2016), any evidence for negative long-term brain alterations induced by MDMA was not found. Still, these are factors that need to be considered before MDMA can be accepted as a safe co-drug for psychotherapy. However, MDMA has been judged safe to use in a controlled therapeutic and research setting where the doses are regulated and administered in a safe amount (Johnson et al., 2008). MDMA-assisted psychotherapy is not 100% risk-free, but the benefits seem to outweigh the risks. Research on treatment-resistant PTSD patients has therefore been approved around the world, on the grounds that the potential benefits outweigh the risks.

The most frequent reported adverse short-term effects after a therapeutic dose of MDMA are lack of energy, headache, lack of appetite, anxiety, insomnia, jaw clenching, and muscle tension (Kalant, 2001; Mithoefer et al., 2010; Mithoefer et al., 2018; Oehen et al., 2013; Ot'alora et al., 2018; Vizeli & Liechti, 2017). However, these symptoms were usually restored within 24-hours. Other studies have found symptoms of depressed mood, including irritability, brooding, and bad dreams that lasted up to three days in some subjects (Liechti, Gamma, & Vollenweider, 2001). Also anxiety, difficulty concentrating, and irritability have been noted in the week following MDMA use in psychotherapy (Mithoefer et al., 2010).

No serious drug-related adverse events or HPPD were reported in any of the four studies included in this review (Mithoefer et al., 2010; Mithoefer et al., 2018; Oehen et al., 2013; Ot'alora et al., 2018). However, one patient had a pre-existing heart condition that needed medical attention during the Mithoefer et al. (2018) study (the patient fully recovered

during the study). HPPD has been reported in MDMA use, although rarely (Litjens, Brunt, Alderliefste, & Westerink, 2014). In a study by Vizeli and Liechti (2017), out of their 141 participants 12 experienced flashbacks, but only within 8-50 hours after drug administration, which is not long enough to be considered HPPD.

Dependence is unlikely to happen with MDMA, partly because frequent use of the drug decreases the pleasurable or rewarding effects of MDMA. Methamphetamine causes dependence, but it may be that MDMA is more like mescaline in this respect (Kalant, 2001). In the LTFU study by Mithoefer et al. (2013), none of the participants reported any dependency or addictive behavior. The participants commented that the therapeutic elements were essential and that MDMA simply should not be taken alone without clinical monitoring and therapeutic support.

Discussion

The aim of this thesis was to review whether psilocybin- and MDMA-assisted psychotherapy have the potential to safely and efficaciously reduce depression/anxiety and PTSD symptoms, respectively. All psilocybin studies conducted with TRD and cancer patients have evidenced a significant reduction in the patients' depression and anxiety symptoms from baseline to six months post-treatment (Carhart-Harris et al., 2018; Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), with one LTFU study showing that the reductions seen after six months were sustained 3.2 years post-treatment (Agin-Liebes et al., 2020). MDMA-assisted psychotherapy for chronic PTSD (Mithoefer et al., 2010; Mithoefer et al., 2018; Oehen et al., 2013; Ot'alora et al., 2018) has showed a significant positive effect on PTSD symptoms after two doses of MDMA (with a third dose further decreasing the symptoms). The majority of participants no longer met the criteria for a PTSD diagnosis after two doses, with one LTFU study showing that the effects were sustained 4 years later (Mithoefer et al., 2013). Overall, psilocybin- and MDMA-assisted psychotherapy were deemed safe and efficacious (with no serious long-term adverse events, and short-term adverse events restored within 24-hours) for patients most of whom had not previously responded to pharmacotherapies and psychotherapy. All this suggests that psilocybin- and MDMA-assisted psychotherapy have the potential to reduce depression/anxiety and PTSD symptoms in a safe and efficacious manner.

Why Psilocybin Alleviates Depressive and Anxiety Symptoms. The pathophysiology of depression has not been fully elucidated. However, a decrease in the level of serotonin in synaptic clefts has been shown to correlate with symptoms of depression (Dean & Keshavan, 2017). Psilocybin's main effect on neurochemistry is the activation of several serotonin receptors (5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}) (Ruban & Kołodziej, 2018), leading to the assumption that psilocybin's way of targeting these receptors is responsible for the positive outcomes on depressive symptoms. The 5-HT_2 receptors are found throughout the brain, including parts of the DMN where *decreased* activity in conjunction with psilocybin has been found (Carhart-Harris et al., 2012; Muthukumaraswamy et al., 2013), and subjects with MDD have been shown to have *increased* activity within (Berman et al., 2011; Greicius et al., 2007). The

DMN activity has been correlated with increased rumination and worrying (Berman et al., 2011; Pollan, 2018), which are characteristics often seen in people with depression and anxiety (American Psychiatric Association, 2013; Berman et al., 2011).

According to the Entropic Brain Theory (EBT) people with depression could be characterized as having low level of brain entropy, that is, an excess amount of order in the brain that could be the result of a hyperactive DMN (Carhart-Harris, Leech, et al., 2014; Carhart-Harris, 2018). The EBT is a novel theory on conscious states that proposes that the subjective quality, or *qualia*, of any given conscious state can be indexed by a quantitative measure of the magnitude of *entropy*, where entropy is being synonymous with randomness, uncertainty, or disorder (Carhart-Harris, 2018). In line with the EBT, psilocybin seems to increase the amount of entropy by disorganizing brain activity, dissolving fixed networks and creating new communication pathways. This has been empirically investigated by Petri et al. (2014) who found that following the administration of psilocybin, the brain became more globally interconnected, and that these connections were persistent. The fluid and flexible brain state induced by psilocybin can therefore help patients and therapists to work together to break down rigid thinking styles and treat conditions like depression and anxiety.

The ability of psilocybin (as well as psychedelics in general and also MDMA) to create new connections are supported by Ly et al. (2018) who found that psychedelics enhance neuroplasticity. This leads to the impression that the antidepressant and anxiolytic effects of psilocybin might result from their ability to promote structural and functional plasticity in the brain. This "rewiring" of connections and the promotion of neuroplasticity could arguably be beneficial for people with depression and anxiety who normally suffer from mental rigidity.

Further, psilocybin can produce a mystical-type experience, a profound and potentially transformative psychological experience. A high-dose of psilocybin can rather reliably produce these types of experiences in both healthy volunteers and patients (Johnson, Hendricks, Barrett, & Griffiths, 2019). Such experiences are often described as *"being among the most personally meaningful experiences of their lives"* (Griffiths, Richards, McCann, & Jesse, 2006). Importantly, the having of mystical experiences has been positively correlated with the anxiolytic and antidepressant effects seen with psilocybin-assisted psychotherapy (Griffith et al., 2016; Ross et al., 2016). These experiences, however abstract, thus seem to correlate with symptom reduction.

Why MDMA Alleviates PTSD Symptoms. PTSD is characterized by an increase in the activity of a few key brain regions including the amygdala, medial PFC, anterior cingulate cortex, insula, and hippocampus (Garfinkel & Liberzon, 2009). These regions have a high affinity for 5-HT_2 receptors (Graeff, Guimarães, De Andrade, & Deakin, 1996) that has been found to decrease following MDMA administration (Carhart-Harris et al., 2015; Gamma et al., 2000; Walpola et al., 2017). This reduction has been correlated with reduced depression and anxiety symptoms, and increased positive mood (Graeff et al., 1996). Trauma exposure sets off a cascade of neural changes that are expressed as an oversensitivity to perceived threats, hyper-arousal, and vigilance in subjects with PTSD. For instance, hyperresponsivity can be seen in the amygdala, a brain structure that activates in response to perceived threats, and triggers the neurobiological response to fear (Garfinkel & Liberzon, 2009).

Administration of MDMA has been seen decreasing amygdala activity which might underlie mood enhancements, increased extraversion, and decreased anxiety (Gamma et al., 2000). MDMA also decreases amygdala's reactivity to angry faces and increases the striatum's response to happy faces. This had led to the assumption that MDMA alters processing of emotionally salient social information by reducing responses to threats and by enhancing response to reward (Bedi et al., 2009).

The hormone oxytocin, involved in trust, empathy, social closeness, and prosocial behavior could be a key factor in the treatment of PTSD with MDMA. MDMA has been shown to lead to an increase in oxytocin (Dumont et al., 2009; Harris et al., 2002), which in turn markedly dampens amygdala activity (as the amygdala has a high amount of oxytocin receptors), causing a decrease in stress response, social anxiety (Kirsch et al., 2005), and an increase in prosocial effects (Dumont et al., 2009). Dumont et al. (2009) found that MDMA's prosocial effects were attenuated by co-administration of the oxytocin antagonist tocinoic acid, which had no effect on social behavior when given alone. They therefore drew the conclusion that oxytocin mediates MDMA's effect on prosocial behavior. MDMA's ability to increase the release of oxytocin is not only beneficial for the patient as such, but may be beneficial also during the MDMA-assisted psychotherapy. The therapeutic relationship is an important factor in achieving the best outcome (Charuvastra & Cloitre, 2008), and MDMA is proposed to be a prominent factor in improving the relationship between the therapist and the patient because it enhances trust, closeness, and prosocial behavior (Johansen & Krebs, 2009). MDMA does this by putting the PTSD patient into a state where they are appropriately alert and motivated to engage in the therapy session (through the release of noradrenaline), but not overly stimulated that they become hypervigilant (through the α2-adrenoceptors) (Lavelle, Honner, & Docherty, 1999), and in a psychological state where they are able to address their traumatic memories while reducing the fear associated with the trauma (Sessa, 2017).

Limitations of Drawn Conclusions. While significant positive effects of psilocybin on depression and anxiety symptoms, and MDMA on PTSD symptoms, have been presented in the current thesis, it is important to acknowledge that the total number of participants in these studies is too small to confidently draw any strong conclusions. These substances are known to promote suggestibility and expectancy bias which undoubtedly may have distorted the results towards a more positive outcome, similar to the placebo-effect that might be strong at first but with questionable long-term effects. Because psilocybin- and MDMA-assisted psychotherapy are novel treatment methods, any true results will not be obtainable until such treatments are available to larger patient groups. On the population level, the reductions in symptoms could very well be lower and less significant, and taking into account both cost and time commitment, these therapies might not be a better treatment option over current treatments and medications.

Results that have shown decreased DMN activity after ingestion of psilocybin, which is suggested to underlie the positive effects, have caused a big commotion and have even been publicized in mainstream media (Pollan, 2018). Yet, any conclusions previously drawn might have been too early because diverging results have been found (Carhart-Harris et al., 2017), making it obvious that we simply do not have enough information. The neurotropic effects of psilocybin and MDMA cannot be interpreted as hard evidence since many more replication

studies need to be made before making claims. Similarly, the EBT is just a theory at the moment, with very little empirical evidence directly supporting it, leaving the exact workings of psilocybin and MDMA not fully known yet. The positive outcomes could very well result from a mix of expectancy bias, psychotherapy, and the activation of the serotonin receptors. If that would be the case, then current antidepressants, such as SSRIs (used both for depression and anxiety) could be just as beneficial if administered with psychotherapy. It is of course possible that psilocybin and MDMA might generate similar therapeutic effects, but with less frequent consumption and less side effects compared to the long-term use of SSRIs which also has its side-effects, such as sexual dysfunction, weight gain, and sleep disturbance (Ferguson, 2001).

The Future of Psilocybin- and MDMA-Assisted Psychotherapy. The negative public image of mind-altering substances throughout history has contributed greatly to both psilocybin and MDMA being placed in the most restrictive drug category where they are regarded as *"drugs with no currently accepted medical use"*. As steps are being taken towards legalization in medical use, with this comes the concern that it might come across as if these substances would be safe for personal or recreational use. This might lead people to "self-medicate", which could be dangerous since no regulations of content and dosage would be possible. If psilocybin and MDMA are ever to be accepted as medical agents, there will be a need to emphasize that these substances are for use in a therapeutic setting, under strict monitoring, and *not* for self-medication.

Further, the therapeutic part is an essential component for the positive effects of these treatments, but also time consuming and certainly expensive. It would be expensive to train therapists for when, or if, legalization for therapeutic purposes occurs. Training programs would have to be implemented (something that MAPS has already started with on a larger scale) which would be costly. However, the amount of money that can be saved by patients not having to consume daily medications as well as more people being able to return to work from sick leave would be economically beneficial in the long-run. The therapists are an essential part of the treatment because they provide the patients with support throughout the whole experience, they help unfold and analyze the experience, they are there to turn to if and when needed, they monitor physiological signs, they provide a safe space to take the substance in, and they administer doses that have been screened for purity and measured for right amount. The psychotherapy sessions should therefore not be underestimated or cut down based on cost if these treatment would become available to larger patient groups.

Professional assistance is also needed before the therapeutic part even begins, to monitor and help wean the patients off any current antidepressant treatment because psilocybin/MDMA are not recommended to be taken simultaneously with SSRI/SNRI medication. Antidepressants block or desensitize the interaction of psilocybin/MDMA with the serotonin receptors, and SSRIs/SNRIs diminish the effects of MDMA (Liechti & Vollenweider, 2000) and psychedelics (Bonson, Buckholtz, & Murphy, 1996). Having the patients stop their current medications comes with the risk of worsening the depression/anxiety which might induce withdrawal, but letting the patients continue with their current medication may prevent the therapeutic effect of the psilocybin/MDMA. For the best

outcome, the patient needs to stop their antidepressants which is a process that needs to be done slowly, carefully, and with professional supervision (Nutt, 2019).

The research on these substances is moving forward fast, with 11 studies currently ongoing throughout the world (see Table 4), including seven studies with psilocybin for depression, and four studies with MDMA for PTSD. This could very well be the result of both substances receiving 'Breakthrough Therapy' designation by the FDA.

Table 4. Ongoing psilocybin and MDMA studies for depression and PTSD.

Sponsor *(Location)*	**Diagnosis** *(Substance)*	**(*N*)**	**Study design**	**Ending***	**Trial number**
Imperial Collage *(UK)*	**MDD** *(psilocybin)*	59	Phase II, randomised, double-blind, placebo-controlled trial, comparing psilocybin and escitalopram	May, 2020	NCT03429075
MAPS *(International)*	**PTSD** *(MDMA)*	100	Phase III, double-blind, placebo-controlled (mannitol and magnesium stearate), randomised trial	June, 2020	NCT03537014
Compass Pathways *(International)*	**TRD** *(psilocybin)*	216	Phase II, randomised, double-blind, dose ranging study	December, 2020	NCT03775200
John Hopkins University *(USA)*	**MDD** *(psilocybin)*	24	Phase II, randomised, assessor-blinded, controlled (treatment-delay) trial	December, 2020	NCT03181529
Usona Institute *(USA)*	**MDD** *(psilocybin)*	80	Phase II, randomised, double-blind, placebo-controlled (niacin) trial	February, 2021	NCT03866174
MAPS *(International)*	**PTSD** *(MDMA)*	100	Phase III, double-blind, placebo-controlled (mannitol and magnesium stearate), randomised trial	June, 2021	NCT04077437
MAPS *(Europe)*	**PTSD** *(MDMA)*	40	Phase II, open-label, active placebo (half dose of MDMA), trial	June, 2021	NCT04030169
Helsinki University *(Finland)*	**Severe depression** *(psilocybin)*	60	Phase II, randomised, double-blind, placebo-controlled trial, comparing psilocybin, ketamine, and no treatment	September, 2021	NCT03380442
University of Zürich *(Switzerland)*	**MDD** *(psilocybin)*	60	Phase II, randomised, double-blind, placebo-controlled (mannitol) trial	October, 2021	NCT03715127
Yale University *(USA)*	**MDD** *(psilocybin)*	18	Phase I, randomised, double-blind, placebo-controlled (inactive), crossover trial	April, 2023	NCT03554174
VA Loma Linda Health Care System *(USA)*	**PTSD** *(MDMA)*	10	Phase II, open-label, active placebo (half dose of MDMA) trial	December, 2023	NCT04264026

Note. *Estimated study completion date; MDD: Major Depressive Disorder; PTSD: Post-Traumatic Stress Disorder; TRD: Treatment Resistant Disorder; MAPS: Multidisciplinary Association for Psychedelic Studies.

Psilocybin- and MDMA-assisted psychotherapy have the potential to become the backbone of a new emerging research field that can expand to different sub-fields and include a larger patient population. One emerging new sub-field is microdosing, i.e., the regular

consumption of small amounts of psychedelic substances. The first published study on healthy participants who microdosed with psilocybin or LSD found that the microdosers had more positive emotional valence, lower levels of dysfunctional attitudes, and lower negative emotionality compared to the control group (Anderson et al., 2019). Microdosing for patients with depression/anxiety or PTSD in conjunction with psychotherapy would be an interesting future study, since at the moment, no conclusions can be drawn based on recreational microdosing.

A future society where psilocybin- and MDMA-assisted psychotherapy have been legalized for medical use is not an unreasonable future if new studies emerge that demonstrate efficacy and safety. We might soon be witnessing an integration of psilocybin- and MDMA-assisted psychotherapy into existing healthcare infrastructures, as well as the emergence of new treatment centers and private clinics to treat patients with depression/anxiety and PTSD. Other mental disorders, such as tobacco addiction (Johnson, Garcia-Romeu, Cosimano, & Griffiths, 2014), obsessive-compulsive disorder (Moreno, Wiegand, Taitano, & Delgado, 2006), and alcohol dependence (Bogenschutz et al., 2015; Sessa, Sakal, O'Brien, & Nutt, 2019) have already been investigated as targets of treatment with psilocybin and MDMA. Studies on treating, for example, anorexia nervosa, various substance abuse and addiction disorders, obsessive-compulsive disorder, and migraine and cluster headaches with psilocybin and MDMA are also ongoing (Clinicaltrials.gov), indicating that this field has the potential to expand to include patients suffering from other conditions than depressive/anxiety symptoms and PTSD.

Conclusion

The aim of this thesis was to review whether psilocybin- and MDMA-assisted psychotherapy has the potential to safely and efficaciously reduce depression, anxiety, and PTSD symptoms. Psilocybin has been proven to produce significant antidepressant and anxiolytic effects, and similarly, MDMA to significantly decrease PTSD symptoms. Both substances have been shown to have good tolerability and to lead to persistent positive long-term effects. However, only two long-term follow-up studies have been conducted thus far. The alleviation of depressive/anxiolytic and PTSD symptoms is a promising sign, although repeated treatment would probably be necessary for the effects to be continuous. Regardless, research in this field is still in its infancy so caution is therefore needed when making claims about the potential usefulness of psilocybin and MDMA in the treatment of depression, anxiety, and PTSD. Based on the studies presented, evidence points to the conclusion that both therapies have the potential to significantly reduce symptoms. As there are currently no effective treatments for people suffering from treatment-resistant symptoms, any promising substances should not be dismissed, or research on them prevented, on the basis of history, stigma, or ill-informed opinions.

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