UNIVERSIDADE
BEIRA INTERIOR

MDMA as an enhancer of psychotherapy for PTSD

Carolina Morais Correia Cordeiro Rodrigues

Dissertação para obtenção do Grau de Mestre em
Medicina

abril 2024

MDMA as an enhancer of psychotherapy for PTSD

Carolina Morais Correia Cordeiro Rodrigues

Dissertação para obtenção do Grau de Mestre em
Medicina
(mestrado integrado)

Orientador: Mestre João Campos Mendes
Co-orientador: Prof. Doutor Francisco José Alvarez Pérez

abril de 2024

Declaração de Integridade

Eu, Carolina Morais Correia Cordeiro Rodrigues, que abaixo assino, estudante com o número de inscrição 41274 do Mestrado Integrado em Medicina da Faculdade de Ciências da Saúde, declaro ter desenvolvido o presente trabalho e elaborado o presente texto em total consonância com o Código de Integridades da Universidade da Beira Interior. Mais concretamente afirmo não ter incorrido em qualquer das variedades de Fraude Académica, e que aqui declaro conhecer, que em particular atendi à exigida referenciação de frases, extratos, imagens e outras formas de trabalho intelectual, e assumindo assim na íntegra as responsabilidades da autoria.

Universidade da Beira Interior, Covilhã 08 /04 /2024

Carolina Rodrigues

Dedicatória

A todos que sempre me apoiaram e nutriram a minha vontade de tornar o mundo que me rodeia um lugar mais feliz.

Agradecimentos

Aos meus pais que sempre estiveram presentes para mim, mesmo quando não sabia que era a presença deles da qual realmente precisava, e que nunca desistiram da tarefa que é ajudar-me a crescer. Obrigada por tudo o que fizeram, por tudo o que ainda farão. Vão ser sempre a minha casa e a razão para o meu sucesso.

À minha irmã, que estando longe ou perto sempre me ensinou tanto, e quem admiro imensamente.

A todos os meus amigos e amigas, que foram tão essenciais para mim nesta jornada, e para o bem ou para o mal me apoiaram e ajudaram. Sem vocês não estava aqui porque sem vocês não teria conseguido superar o que superei. Em especial à Gabriela e à Lídia, que desde o 3º fim-de-semana da praxe e para sempre estarão no meu coração, e espero que também estejam na minha vida.

Aos meus avós, tanto os que cá continuam como os que partiram, por me terem providenciado com tanta alegria e terem-se certificado que acompanhavam tudo estando longe ou perto. Em particular ao meu avô, com quem partilhei mais histórias e conversas, e de quem me faz falta o abraço.

A quem já cá não está, independentemente do tempo ou distância que nos separam partilho convosco esta conquista por tudo o que fizeram por mim.

Ao Gui, por nunca me deixar sentir sozinha.

Ao meu orientador Dr. João Mendes, por me ter proporcionado esta oportunidade, ter a disponibilidade para me ajudar a aprender, e me ter apoiado durante todo este processo.

Ao meu coorientador Prof. Dr. Francisco Alvarez, por me ter ajudado com este grande projeto.

Obrigada a todos, e espero relembrar a todos do vosso valor e importância tanto na minha vida como em todas as minhas conquistas.

Resumo

Introdução: A PSPT é uma perturbação psiquiátrica cada vez mais prevalente, que se manifesta após um trauma pessoal ou de exposição grave, e que tem um impacto negativo na vida das pessoas que lhe são diagnosticadas. Embora existam opções aprovadas de psicoterapia e farmacoterapia para o tratamento desta doença, muitas vezes não são bem toleradas ou não são eficazes no tratamento da mesma. O MDMA, mais conhecido pela sua utilização recreativa como ecstasy, é um composto psicoativo, com uma semi-vida curta, que induz breves estados de perceção alterada e abertura, que podem ser utilizados para melhorar as intervenções psicoterapêuticas, com um impacto duradouro.

Objetivo: Identificar e avaliar a possível utilização do MDMA como potenciador de tratamentos psicoterapêuticos em pacientes diagnosticados com PSPT.

Métodos: Coleta de dados usando Google Scholar, PubMed, SCOPUS, National Library of Medicine e Elsevier, de julho de 2022 a janeiro de 2024. Os critérios para a escolha dos artigos incluíram data de publicação anterior a 2017 (permitindo exceções contextualmente necessárias), escritos em inglês e com foco no uso de MDMA em associação com psicoterapia em pacientes diagnosticados com PSPT.

Resultados: Os estudos e artigos analisados mostram resultados promissores da utilização de MDMA como potenciador da psicoterapia de doentes com PSTP, com vários estudos a registarem diminuições significativas nas suas medidas de sintomatologia e critérios de diagnóstico. As populações estudadas, as técnicas de *blinding*, as medidas de resultados e os métodos apresentaram várias limitações, o que justifica a continuação da investigação sobre o tema.

Conclusão: Esta tese concluiu que os resultados positivos dos estudos avaliados justificam uma investigação mais aprofundada sobre o potencial de alavancagem do tratamento psicoterapêutico, de modo a estabelecer protocolos e efeitos dose-dependentes da administração de MDMA.

Palavras-chave

PSPT; psicoterapia assistida por MDMA; MDMA; tratamento farmacológico da PSPT; intervenções psicológicas na PSPT; PSTP resistente ao tratamento; psicadélicos;

Abstract

Introduction: PTSD is an increasingly prevalent psychiatric disorder that manifests after severe personal or expositional trauma, and gravely negatively impacts the lives of those who are diagnosed with it. Though there is approved psychotherapy and pharmacotherapy options for the treatment of this disease, they often are not well tolerated or not effective in the treatment of the disease. MDMA, most known for its recreative use as ecstacy, is a psychoactive compound, with a short half-life, that induces brief states of altered perception and openness, which can be used to improve psychotherapeutic interventions, with enduring impact.

Objective: Identify and assess the possible use of MDMA as an enhancer for psychotherapy treatments in patients diagnosed with PTSD.

Methods: Collection of data using Google Scholar, PubMed, SCOPUS, National Library of Medicine, and Elsevier, from July 2022 to January 2024. Criteria for the choice of articles included publishing date before 2017 (allowing for contextually needed exceptions), written in English and with focus on the use of MDMA in association with psychotherapy in patients diagnosed with PTSD.

Results: The studies and articles analyzed show promising results of the use of MDMA as an enhancer of psychotherapy for PTSD patients, with several studies noting significant decreases in their measures of symptomology and diagnostic criteria. There were several limitations in the populations studied, blinding techniques, measures of outcomes and methods, which further justifies ongoing research on the subject.

Conclusion: This thesis has found that the positive outcomes of the studies assessed justify further investigation into this potencial boost of psychotherapy, in order to establish set protocols and dose-dependent effects of the administration of MDMA.

Key terms

PTSD; MDMA assisted psychotherapy; MDMA; pharmacological treatment of PTSD; psychological interventions in PTSD; treatment-resistant PTSD; psychedelics;

Table of Contents

Figure Index

Table Index

CHAPTER 1: INTRODUCTION

1.1. Post-Traumatic Stress Disorder

Post-Traumatic Stress Disorder (PTSD), a psychiatric disorder contemplated in the DSM-5, is described as a psychiatric disorder that may occur in people who have experienced or witnessed a traumatic event, series of events or set of circumstances. An individual may experience this as emotionally or physically harmful or life-threatening and may affect mental, physical, social, and/or spiritual well-being (1).

It combines signs and symptoms of other major psychiatric disorders such as depression and anxiety, as well as characteristic behaviours observed in other disorders such as recurring and persistent thoughts, and avoidance behaviours (1). The existence of an association between the development of PTSD and other pathologies, like substance abuse disorders, has also been noted, and according to the DSM-5 approximately 80% of PTSD cases are accompanied by other psychiatric comorbidities (2).

Essentially PTSD can be thought of as an imbalance between the activity of the fear centres of the brain, principally the amygdala, and the parts of the brain where one can logically reason, rationalise and overcome that fear response (3).

Like most psychiatric disorders, each person's experience with PTSD is unique and subjective, hence encountering different symptoms of different magnitudes in terms of personal and relational impact is frequent. This makes PTSD somewhat complicated to diagnose as it must account for different presentations of the disease, and it is therefore important to correctly use the DSM-5 guidelines of diagnosis (4).

The clinical criteria for the diagnosis of PTSD can be found in Appendix 1.

1.1.1. Epidemiology of PTSD

PTSD is one of many psychiatric disorders which have become increasingly prevalent in the worldwide population, with a 3,9% lifetime prevalence and a 5,6% prevalence amongst people exposed to trauma (5). Significant variations are noted according to income stratification – higher income countries had increased rates of PTSD when compared to moderate income or low-income countries (6)– as well as other less statistically significant factors such as sex, employment status, relationship status and literacy level (7).

Though many people experience trauma, not all end up suffering from PTSD, indicating that there might be predisposing factors which increase the probability of a PTSD outcome. Some of these factors include genetics, the features of the trauma, environmental exposures, stage of life, social and economic context as well as the post-trauma aid that is provided. Some characteristics that have been linked to PTSD occurrence include female sex, history of early life stress, or predisposing neuronal disturbances (7).

Within victims of trauma, it is estimated that less than 10% of people will develop PTSD, these numbers rising to 20% in victims of assault violence, 50% in victims of sexual assault and 4 to 86% amongst refugees. A study found that victims of the Holocaust, in specific Auschwitz prisoners who had survived, 80% experienced intrusive memories, 90% had complaints of nightmares and 100% suffered from sleep disorders or disturbances (7).

Very often PTSD becomes chronic, and is accompanied by high rates of comorbidities, both psychiatric and medical (6) hence causing a significant strain on human and economic resources, there having been an estimated economic cost of $34.9 billion for hospitalizations between 2002 and 2011 (in inflation-adjusted charges) found in one cost-effectiveness study conducted in the United States (5).

1.1.2. Neurobiology of PTSD

In neurobiological terms, PTSD is associated to a failure in fear extinction as well as augmented perceptions of fear and danger, even when confronted with neutral non-threatening stimuli (8).

Essentially it can be thought of as an over-activation of the amygdala (9) resulting in exaggerated responses to cues related to trauma, worsened by a lack of top-down inhibition by the ventromedial prefrontal cortex (vmPFC), hippocampus and orbitofrontal cortex (6).

PTSD is usually caused by a life-threatening or determining event, which in most cases are associated to prolonged stress responses, independently of the duration of the causal event. While brief neurological stress responses may increase neuronal plasticity and enhance cognition to counter the stressor, prolonged stress is known to lead to detrimental neurological effects and occurrence of behavioural changes (7).

These detrimental neurological effects may include neuronal loss, reversible up until 4 weeks after the primary stressor, however when dealing with stress caused by life-threatening

or determining events, the stress response may last longer due to the larger magnitude of impact on the psychological plane.

In the case of repeated or continued stress such as the one involved in the appearance of PTSD symptomology, the neuronal networks are reformed, following alternate pathways to 'survive' the perceived aggression or threat.

These alternate pathways often involve an increase in immediate body response to stress, favouring neuronal synaptic connections to brain areas such as the basolateral amygdala (key part of the fight or flight instinct) and nucleus accumbens (which connects the motor and limbic systems, promoting action from emotions), rather than areas associated with cognition and emotional regulation such as the PFC and hypocampus (9).

In terms of neurophysiological changes postulated in PTSD, the reduction in quantity of serotonin transporters – leading to excessive extracellular serotonin – is thought to be a predictor for the development of the disease. An increased cerebral blood flow (CBF) to the amygdala during the exposure to fear-inducing stimuli has also been observed and thought to be part of the neurophysiological mechanism of PTSD (7).

However clinical symptoms and changes in brain activity are not homogenous across patients, and different patterns of neurophysiological alterations or symptomology may be observed (9). It is also important to mention that these alterations have been suggested as characteristic of PTSD presentation, yet neuroimaging findings have not yet been confirmed.

The neurophysiological models that explain PTSD symptomology can be found in Appendix 1 – Neurobiology of PTSD.

1.1.3. Cognitive Mechanisms of PTSD

PTSD can be explained by neurobiological changes in the brain, however, to understand the persistence of the symptoms and the difficulty in the treatment of this disease, we need to understand the cognitive mechanisms behind this disease.

It is proposed that a traumatic event changes the way information is processed and coded by the brain through a stronger link to sensory perceptions, and a pattern of encoding described as fragmented. This helps to explain why traumatic memories are often disorganized and hard to integrate (10).

Another model describes two different pathways for memory processing: the verbally accessible processed memory (VAM) and the situationally accessible processed memory (SAM). The first is made up of context rich and consciously processed information, while the latter is sensory rich and more fragmented information. The existence of these two memory processing systems may give rise to some of the classic PTSD symptoms as the SAM is associated with intrusive thoughts and recollections, as well as the existence of sensory triggers (10).

On the other hand, fear conditioning, another mechanism involved in PTSD, can be thought of as the re-experiencing of traumatic memories when confronted with triggers that someone may associate to their trauma (10).

Psychologically, PTSD is correlated to inadequate interpretations and emotional control, and emotion is at the centre of these pathological manifestations. For example: cognitively mediated emotions, which can be defined as emotions arising from a specific thought, are correlated with symptoms presented.

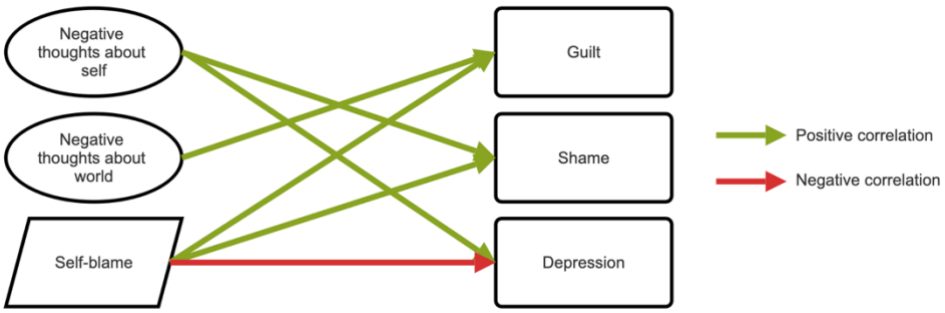

Figure 1: PTSD Cognitively-Mediated Emotion Correlations adapted from LoSavio et al. (2017) (11)

As can be seen in the diagram above, thoughts or cognitions of negative connotation about the self are positively associated with feelings of shame and depression, meaning the presence of negative thoughts about oneself makes it more likely for there to be feelings of shame and guilt. On the other hand, negative feelings about the world do not seem to show any association with depression or shame feelings, but rather are positively associated with guilt feelings. Finally, self-blame cognitions are positively associated with guilt and shame feelings, but strangely, seem to be negatively associated with depression. This suggests that negative thoughts about oneself and self-blame may not coexist in certain presentations of the pathology of PTSD (11).

Also, strategies associated with trying to cope with PTSD, including rumination, thought suppression and experiential avoidance are correlated with presenting PTSD symptoms (11). All these processes are used as a defence mechanism for the patient to avoid feeling more pain. However, many times they have the exact opposite effect, isolating the person from others and somewhat trapping them in their own mind.

While experiential avoidance or the avoidance of circumstances which remind the patient of their trauma is an extremely natural response it is very limiting as not all triggers for the remembrance of traumatic events are obvious or consciously known, making it hard to avoid every trigger and many times leading to anxiety-related pathologies such as social anxiety. Thought suppression, or the avoidance of thinking about certain topics and ideas that are related to the traumatic event, does not work often, and it is common for the patient to be so preoccupied avoiding triggers that they get lost within their thoughts which significantly diminishes concentration and cognitive abilities.

Lastly, rumination is the repetitive thoughts about the reasons and consequences surrounding traumatic events, which not only perpetuates the impact of the event but also many times acts as a 'distorted lens' through which other experiences are analysed and perceived. A specific type of rumination called counterfactual thinking is especially significant in its association with PTSD symptomology, which is described as above and beyond the effects of age, number of traumatic events, and depression symptoms (12), particularly in the intrusive thoughts and avoidance behaviours. It has also been related that rumination mediates the relationship between low emotional regulation and PTSD symptoms, and the use of this strategy is increased in people who have more self-blame cognitions.

1.1.4. Treatment of PTSD

The preconized treatment for PTSD currently includes 2 different approaches – psychological-oriented and pharmacotherapy. According to the APA Quick Guide on PTSD Management (13), the choice of initial treatment depends on the mental health status of the patient, using psychopharmacological approaches to control physical and mental symptomology that causes distress and once stabilized begin introducing psychotherapy and psychoeducation, to facilitate the full reintegration in society and recovery to full health.

The complex involvement of different types of memories and circuits in the symptomology of PTSD is more effectively addressed through psychotherapy to reintegrate fragmented memories and try to recode the brain to learn how to deal with triggers.

Within the psychological treatments exposure therapies are preferred, including Cognitive Behaviour Therapy (CBT), Prolonged Exposure (PE), Cognitive Processing Therapy (CPT) or Eye Movement Desensitization and Reprocessing (EMDR) (14). Each of these therapies presents with different levels of recommendation as a consequence of the evaluation of their immediate and long-term outcomes: PE is the only therapy with a high level of recommendation in terms of PTSD symptom reduction, it does however not assure improvements in other areas such as depression and anxiety; CBT on the other hand, though only moderately recommended in terms of PTSD symptomatic reduction, does have a moderate effect on anxiety and depression symptoms; EMDR has a lower level of recommendation due to imprecision and inconsistency findings in trials assessing its efficacy; finally, CPT also appears as moderately recommended in terms of PTSD symptomology reduction, however with minimal effect on depression and anxiety (15).

These have been proven in various studies to be the most effective method of treatment (15), and the approaches with the most significant reduction of symptoms amongst patients, however they do also have a high drop-out rate as they might initially worsen anxiety and memory recollection symptoms through the confrontation with the trauma experience. In the meta-analysis by Cusack et al. (2016), mentioned above, there are mentions of suicide attempts (1 in a PE study, and 3 in CPT studies), a successful suicide (in a CPT study) and hospital admissions for suicidal thoughts (in an alternate therapy, Narrative Exposure Therapy) (15).

In terms of pharmacological treatment, so far, the only drugs specifically approved for the treatment of PTSD have been sertraline and paroxetine, two selective serotonin reuptake inhibitors, though other medication is used off-label to control symptomology. Nonetheless, this medication regimen simply reduces PTSD symptoms rather than stopping them completely (16), leading patients to need additional medication such as anxiolytics, mood stabilizers or antipsychotics, which, though having positive results for some patients, come with many unwanted and problematic side-effects (17).

Some alternative drugs have begun being studied for their potential in the treatment of PTSD, such as ketamine, which has been found to have anti-depressant effects lasting for up to 2 weeks after the infusion[1], and whose proposed mechanism for the improvement of PTSD symptoms is due to a structural and functional reversal of synapses related to stress within the first 24h after administration (18–22). Cannabinoids and cannabinoid-like drugs have also proven to be a possible avenue to explore as their anxiolytic effects have been

demonstrated in several studies and may help the extinction of fear or stress-related neural pathways**Error! Bookmark not defined.**.

The reality is that most of the psychopharmacological medication used in the treatment of PTSD and its symptoms has not performed adequately or sufficiently, as studies indicate insignificant or small to moderate effects on populations studied (6), meaning that compared to the control group the drugs have a highly limited impact on symptom reduction. Therefore, it is extremely important to investigate new pharmacological and psychological approaches to PTSD.

1.2. MDMA

1.2.1. The Chemical Compound

MDMA (*3,4-Methylenedioxymethamphetamine*) is a chemical compound which is usually know as *Ecstasy* or *Molly*, used as a party drug, and illegal worldwide. This compound is called an empathogen or entactogen due to its ability to induce states openness, connection with the world and others and heightened emotions. Unlike other psychedelic drugs, MDMA does not cause cognitive impairment, but rather simply alters the perception and insight of the person (23). It is a very short acting drug, with primary effects lasting only about four hours and gradual return to baseline over the course of another two hours (24), however allowing for the memories of all that happened whilst feeling the drug's effects to be kept.

In a healthy population it has been described that MDMA causes an easily controlled and reversible state of altered consciousness characterized by euphoria, empathy, well-being, insightfulness, extraversion, positive mood, gregariousness, feelings of authenticity, increased access to emotionally intense material, increased interpersonal trust, and compassion for oneself and others (25).

MDMA also has some physical effects due to the release of hormones and neurotransmitters induced by the drug. These include (26):

- Release and reuptake inhibition for serotonin molecules.
- Release and reuptake inhibition dopamine and norepinephrine molecules (moderate).
- Release of oxytocin, prolactin, cortisol, and vasopressin.
- Decreased synapse activity in the amygdala and hippocampus, as well as an increase in resting state functional connectivity (RSFC) between them.

- Increased synapse activity in the medial prefrontal cortex, as well as decreased RSFC between this cortex and the posterior cingulate cortex.

A diagram of the mechanism of action of MDMA on the brain is shown below and as can be observed, it differs greatly from other psychedelic drugs such as DMT, psylocibin ketamine and LSD, acting on neurohormonal mechanisms and mostly on inhibiting transporters.

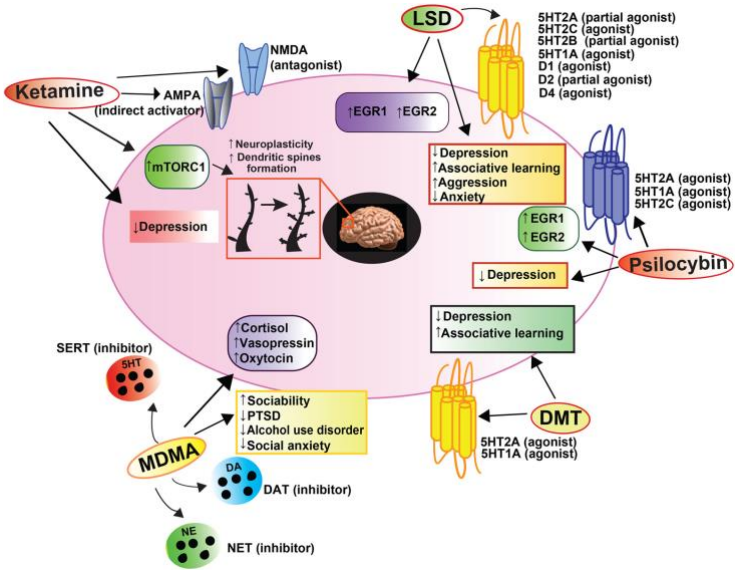

Figure 2: Schematic overview of the main pharmacological targets of LSD, psilocybin, DMT, MDMA, and ketamine, the signaling cascades involved, hormonal modulation, as well as main behavioural outcomes following their administration in both animals and humans (26)

In terms of physical symptoms, the increase in cortisol and vasopressin will lead to increases in blood pressure and heart rate, as well as an increase in bodily temperature.

1.2.2. MDMA History

MDMA is a chemical compound first synthesized by the chemist Anton Köllisch in 1912 and patented in 1914 as a precursor for the synthesis of haemostatic medication by the German company MERK (27). Due to its problems in studies with animals it was cast aside, only to be rediscovered again in 1962 by Alexander T. Shulgin to synthetically replicate the mescaline derivate MDA (methylenedioxy-amphetamine).

At the time Shulgin was working with the Chilean psychiatrist Claudio Naranja, who had a keen interest in the therapeutic use of the mescaline derived MDA. The mescaline derivate MDA (methylenedioxy-amphetamine) provided a similar effect to mescaline without

as much hallucinating and cognitive impairment, making it a useful tool in assisting psychotherapy (28).

In time, however, MDA proved to have significant side-effects which effectively deterred further use in pharmacologically assisted psychotherapy. It was then discovered that MDMA provided the same effect as MDA, without the health risks. It was Naranja who first incorporated MDMA into psychotherapy sessions, as well as Shulgin's wife, Ann Shulgin, who also began using it in therapy sessions (28).

MDMA began being disseminated amongst the psychotherapeutic community and many started to use it for research and others for enhancement of psychotherapy. These professionals included researchers such as Grof, Yensen, DiLeo and Lynch, as well as psychotherapists such as Greer, Downing and Ingrasci. Many of these professionals began comparing their notes and sharing experiences, leading to the creation of the "Boston Group", a collective of interested researchers and practitioners which believed MDMA, and other psychedelic substances, could be used in a therapeutical manner (27).

Though these investigators and medical professionals saw the benefit in the use of MDMA, the drug was scheduled as category I, defining it as a drug with no currently accepted medical use and a high potential for abuse (29), in 1985. The Boston group and other professionals collected their data and experiences with the use of MDMA in psychotherapy, presenting the therapeutical advance that it had created to the Drug Enforcement Administration (DEA). Even though the hearings conducted advised against its placement in Category I due to the potential therapeutic benefit, the DEA overruled the decision of their appointed judge (28).

1.2.3. MDMA as a Category I Drug

Due to its classification as a category I drug, the use of MDMA in psychotherapy stopped. Consequently, MDMA was made illegal, and it became much more complicated to study its properties and therapeutic benefits.

Though much evidence regarding MDMA use in psychotherapy had been gathered before the decision of the DEA, researchers and psychotherapists were reluctant to share their findings with the public, fearing that, like other psychedelic compounds, MDMA would be banned. During their investigations, many therapists developed protocols for the use of MDMA, preferring to use it in group sessions. These guidelines established preparatory

sessions with the patients, the calm and comfortable environment where the MDMA session would take place, and most important of all, agreements as to what the participants would do. These agreements included, for example, that no participants would perpetrate destructive actions towards themselves, other or property, and that they would follow any instructions given by the facilitator of the therapy (28).

In the next decades, organized and formal studies became harder to conduct due to its classification and the FDA's (Food and Drug Administration) concern about neurotoxicity, resulting in the clinical hold or rejection of most proposals (28). It was only in the late 1990's that initial clinically driven studies began emerging, beginning the revival of psychedelics in Medicine.

1.3. Failure of PTSD-approved therapies

PTSD, like all other mental health conditions, is an ever-evolving entity which is mutable and subject to changes as time and society progresses. As mentioned previously, PTSD is not a separate entity or pathology anymore, but rather it has many links with physical and mental diseases. In any case, it seems that the study of the treatment of this disease has, on many occasions, not considered the different presentations of PTSD and their unique resistances to certain medication.

1.3.1. Inadequate Treatment

In terms of pharmacological treatments, the advancement has somewhat stalled, there being a lot of unfruitful enterprises and culminating in only moderate improvements. Though many patients may respond well to treatment as evidenced by Murphy, et al. (2015)(15) and Williams, et al. (2022) (30), a subgroup of these PTSD patients appears to not benefit from the traditional therapeutic options, hence being designated as treatment refractory PTSD (TRPTSD) (31).

It is notable that most psychopharmacological options are the cause of unwanted short-term side effects such as constipation, diarrhoea, anxiety, and irritability among others (32), as well as long-term effects namely intense dreams, making them undesirable in long-term treatment. Not only that but the experimental trials with these pharmacological options have demonstrated a significant drop-out rate, sertraline with 28% drop-out and paroxetine with 11,7% drop-out rate (33).

As seen in the table below, though several trials have been undertaken to find new medication or confirm utility of existing medication for PTSD, a majority yielding negative results (16).

Table 1: Phase II Investigator-Initiated Drug Clinical Trials for PTSD in the United States since 2006 (16)

Table 4. Phase II Investigator-Initiated Drug Clinical Trials for PTSD in the United States Since 2006

Study Name	Intervention	Status	Funding Agency	Results
Pharmacogenetic Clinical Trial of Nepicastat for PTSD	SYN117 (nepicastat) vs. placebo	Completed (11/2009)	Department of Defense	Negative[a]
Risperidone Treatment for Military Service Related Chronic PTSD (CSP 504)	Risperidone vs. placebo	Completed (1/2011)	VA Office of Research & Development, Janssen provided drug	Negative (36)
Iloperidone for Symptoms of Arousal in PTSD	Iloperidone vs. placebo	Completed (2/2014)	University of Colorado, Novartis Pharmaceuticals (collaborator)	No published results
Ganaxolone in Posttraumatic Stress Disorder	Ganaxolone vs. placebo	Completed (3/2014)	Department of Defense, Marinus provided drug	Pending-results not published yet
Nepicastat for PTSD in OIF/OEF Veterans	Nepicastat vs. placebo	Completed (6/2014)	Department of Defense	Negative[a]
Evaluation of GSK561679 in Women With PTSD	GSK561679 vs. placebo	Completed (8/2014)	VA Office of Research & Development, National Institute of Mental Health	Negative
Glial Regulators for Testing Comorbid PTSD and Substance Use Disorders	*N*-acetylcysteine vs. placebo CPT	Completed (9/2014)	Medical University of South Carolina, Department of Defense, Institute for Translational Neuroscience	Participants treated with *N*-acetylcysteine compared with placebo evidenced significant improvements in PTSD symptoms (65).
Trial of Mifepristone in Combat Veterans With PTSD	Mifepristone vs. placebo	Recruiting	James J Peters VA Medical Center (Bronx, NY)	Ongoing
A Randomized Clinical Trial of Mifepristone in PTSD	Mifepristone vs. placebo	Recruiting	Bronx VA Medical Center, San Diego VA Medical Center, Durham VA Medical Center	Ongoing
Novel Therapeutics in PTSD: A Randomized Clinical Trial of Mifepristone	Mifepristone vs. placebo	Recruiting	VA Office of Research & Development	Ongoing
Repeated-Dose Intravenous Ketamine for PTSD	Ketamine vs. midazolam (active comparator)	Recruiting	Icahn School of Medicine at Mt. Sinai	Ongoing
CAP-Ketamine for Antidepressant Resistant PTSD	Ketamine vs. placebo	Recruiting	VA Office of Research & Development	Ongoing
Zonisamide in Addition to E-CPT-C for Veterans With PTSD and Comorbid Alcohol Dependence	Zonisamide vs. placebo E-CPT-C	Recruiting	Department of Defense	Ongoing

CPT, Cognitive Processing Therapy; E-CPT-C, Enhanced Cognitive Processing Therapy-C; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; PTSD, posttraumatic stress disorder; VA, Veterans Affairs.
[a]L. Davis, M.D., personal communication, Feb 17, 2017.

Table 2: Phase III Investigator-Initiated Drug Clinical Trials for PTSD in the United States since 2006 (16)

Table 5. Phase III Investigator-Initiated Drug Clinical Trials for PTSD in the United States Since 2006

Study Name	Intervention	Status	Funding Agency	Results
Levetiracetam in PTSD	Levetiracetam vs. placebo	Completed (3/2008)	Duke University, UCB Pharma	No published results
CSP 563: Prazosin and Combat Trauma PTSD	Prazosin vs. placebo	Completed (5/2013)	VA Office of Research & Development	Negative[a]
Prazosin for Treatment of Patients With Alcohol Dependence and PTSD	Prazosin vs. placebo	Completed (10/2014)	Department of Defense and VA VISN 1	Negative (59)
Prazosin for Nightmares and Sleep Disturbance	Prazosin vs. placebo	Completed (2/16/2006)	VA Office of Research and Development and NIMH	Positive (40)
Prazosin for Combat Trauma PTSD	Prazosin vs. placebo	Completed (8/29/2012)	VA Office of Research (VISN 20 MIRECC)	Positive (41)

CSP, Cooperative Studies Program; MIRECC, Mental Illness Research, Education and Clinical Centers; NIMH, National Institute of Mental Health; PTSD, posttraumatic stress disorder; VA, Veterans Affairs; VISN, Veterans Integrated Service Network.
[a]M. Raskind, M.D., personal communication, Feb 1, 2017.

In terms of psychological treatments, though they evolve and may adapt to each person, as well as having become more widely available, there are not many possibilities for reformation of the guidelines. It should also be mentioned that CBT therapy, one of the types of psychotherapy indicated in the treatment of PTSD, has a 20% drop-out rate (9), meaning a lot of people are not able to endure it. It is, however, an option to add elements or change the administration of this therapy. This seems like a good investment option, as psychological treatments are proven to be more effective than psychopharmacology (34), and their

enhancement could improve on the common complaint that normal psychotherapy may be triggering.

Psychotherapy is known to be helpful in most psychiatric disorders, and it is, in fact, very common for PTSD to be associated with other psychiatric illnesses, such as substance abuse or depression. While it may be argued that the high extent of comorbidity between these psychiatric diagnoses may suggest an imprecision by the DSM-5 criteria for diagnosis of PTSD or major depressive disorder (MDD), for example, it is more likely that it reflects a fundamental dimension of risk for psychopathology following trauma exposure (35). This being said, if the same stimuli that may lead to PTSD represents a predisposing factor to the appearance of other mental disorders, such as MDD, the real problem is not whether there are any comorbidities but rather which ones and how they relate to the trauma and PTSD that may have allowed for them (35).

Another problem is the event of self-medication to deal with symptoms of PTSD. These methods may include the use of dangerous substances and may lead to comorbidities such as substance abuse to deal with or numb symptoms of PTSD. This use of illegal substances to cope with psychiatric diseases and their symptoms has been the case studied by Daisy Lutyens in her thesis for a master's in criminology in the Te Herenga Waka Victoria University of Wellington. She addresses the use of psychedelics as self-therapy in Aotearoa (the Māori designation for New Zealand) and found several incidences of the use of psychedelics as enhancer of self-therapy (36). In this study, the use of psychedelics such as MDMA, psylocibin and LSD was evaluated in a select group of people who had experience with the use of these substances as a method for self-healing and improvement. From the interviews conducted it was be concluded that, in the case of MDMA, though not one of the most used psychedelics amongst the group, had positive results in all proposed self-therapies. One of the cases presented was of a patient diagnosed with PTSD after a sexual assault, and her opinion was that MDMA provided her with an experience which she was able to reflect on and analyse with the help of conventional therapy (6 months), and hence she was able to progress and reach "a breakthrough" (sic.)(36). Unlike what is observed with the use of alcohol and other recreative drugs to induce numbness and reduce symptoms, it seems that the use of these compounds, particularly MDMA, has been successful in progressing therapeutically and induced prolonged benefits in the life of the patient. We can then assume that there might be a therapeutic power in the use of these substances, though in controlled and safe environments, as described by the study subjects in this thesis (36).

All in all, new treatments should address and try to improve upon the common reasons for treatment avoidance, failure, and dropout (37). This is an extremely important endeavour as if the currently available and approved treatments do not have sufficient impact on the health of patients, they will begin turning to non-approved and possibly dangerous methods to relieve their PTSD symptoms (36). It seems that, currently, the most viable option is to enhance the impact of psychotherapy, targeting cognitive distortions associated with PTSD and its symptoms, to reframe the traumatic experience and help unchain themselves from it (11).

1.3.2. Possible Treatment Improvement Strategies

The problems faced by patients include trauma memory fragmentation, emotional detachment, poor emotional regulation, and intrusive thoughts (9). These symptoms exist in a vicious cycle, one augmenting the other, and making the success of psychotherapy attempts more limited to the individual capacity and resources to deal with these pathological thought processes.

Having these mechanisms in mind, new therapeutic options should target them and take them into account. By doing so the treatment would not only be mitigating the symptomology and consequences of altered thought processes, but it would also provide an intentional reframing of said thought processes.

With MDMA the ability to influence these possible therapeutic targets and reframe thought processes is enhanced due to the altered insight and perception.

1.4. Therapeutic potential of MDMA

MDMA is referred to as an entactogen, which means it is a drug which promotes self-reflection and inner awareness (17). It has a small time frame of action, the effects lasting about 4 hours before slowly returning to baseline over the next 2 hours, and does not induce any cognitive impairment, hence the user is able to remember what happened during the psychedelic experience without trouble.

The psychological impacts of MDMA have been described as warm and social openness experience, in which self-acceptance is augmented and both fear and defensiveness are reduced (38). The ability to remember the experience felt during MDMA allows for the easy integration of feelings and thoughts, leading to benefits and improvements in psychological processing in the long term.

In terms of neurophysiological changes, MDMA has been credited with increasing activity in vmPFC and decreasing activity in the left amygdala (26), which counters the usually observed pattern of PTSD (an increase in amygdala activity causing increased fear triggered reactions, and a decrease in the connectivity with the vmPFC and hence decreasing the more logical interpretations of events).

Another pattern of PTSD that is changed using MDMA is the diminished serotonin transporter levels, which are linked to a propensity for PTSD manifestations, and have been known to increase activity in the amygdala and anxiety related behaviours (8). Most of the positive symptoms of MDMA use, such as increased sociability and reduced fear, are attributed to its impact on 5HT receptors, which causes activation of these receptors due to increased release of serotonin (8). This counters the symptomology of PTSD (fearful and anxious behaviours) and allows for the modulation or reintegration of previously traumatic memories.

Finally, MDMA also has an impact on the release of oxytocin, increasing it, thus allowing for a further decrease in amygdala activity (9) and countering fear-related symptoms of PTSD.

Due to the psychological changes produced by MDMA, it appears to be a suitable drug to lower resistance and improve the quality and impact of psychotherapy in patients suffering from PTSD. The positive and warm emotional state, as well as the reduction in anxiety and fear, all contribute to the facilitation of the processing or reprocessing of traumatic memories (6), allowing for a less self-criticizing reflection on the events.

This is important as “therapeutic exposure to traumatic memories should be kept in an “optimal arousal zone,” avoiding the extremes of eliciting overwhelming anxiety and other painful emotions that may lead to dissociation on the one hand and emotional numbing on the other (39).

It has been observed that MDMA may lessen feelings of shame or guilt related to the traumatic event (11), and hence it makes it easier for patients to access and deal with the traumatic memories that usually would result in emotional distress (38), and re-encode them within the brain as still bad memories, however with a different degree of importance and relevance, making them less emotionally charged.

Additionally, the impact MDMA has on the release of hormones such as oxytocin, cortisol and epinephrine may also be a benefit to therapy. MDMA has been credited with improving the therapeutic alliance between therapist and patient due to its increase in the release of oxytocin and therefore pro-social, less fear-driven, behavior (8). In terms of the elevation in cortisol levels, MDMA-stimulated enhancement of cortisol may increase extinction learning by allowing for emotional engagement without interference of avoidance mechanisms commonly applied by individuals with PTSD (9). Finally, during traumatic experience recollection there is a physiological increase in cortisol and epinephrine levels, and MDMA mimics that effect allowing for the replacement of the older traumatic memories for newer less negative ones (8).

Overall, due to its extensive activity on neurotransmitters and brain pathways, MDMA appears to have the potential to allow for the recoding or relearning of memories and the emotions attached to them. MDMA's action on different brain regions enables the strategic enhancement of cognitive areas while emotion-related networks, such as the amygdala, may be attenuated, resulting in a relearning of memories with a less anxious or fearful perception, reframing traumatic experiences into less overwhelming emotionally charged cognitions**Error! Bookmark not defined.**.

Though there aren't many proven health risks, it is important to consider the context in which this drug can be administered as, if MDMA is taken in an uncontrolled environment it may have detrimental effects on the psychological wellbeing of the patient.

During the therapy it is important to allow for periods of inner focus and reflection and have a less directive approach to let the patient spontaneously address his thoughts and cognitions (17). It is important to let patients freely explore their thoughts during an MDMA experience as they may gain valuable insight not only into their traumatic memory but also other topics that they might not recognize as problems while not under the influence of the psychedelic.

MDMA is also known to slightly increase anxiety, and hence it becomes important for therapists to teach patients stress and anxiety management techniques in the case that they become anxious during the MDMA session**Error! Bookmark not defined.**.

1.5. Justification for Topic Choice

Over the past decades there has been an increasing tendency in mental illness in the world population and due to its relative novelty when compared with other medical specialties, there is much work to be done in trying to understand the etiology, treatment, and management of psychiatric disorders. PTSD, like many other mental illnesses has been increasing in incidence and prevalence, however the treatment options available do not seem to be responding to the problem effectively. Hence, it is important to further investigate possible new treatment avenues while also considering other psychiatric comorbidities and their impact on the response to traditional or innovative treatments.

CHAPTER 2: METHODS

In the following chapter the methods of the organization and preparation of this thesis will be discussed. The studies included in this thesis were evaluated and integrated several eligibility criteria to be included (40), to make this thesis unbiased and provide a global outlook on the topic addressed.

2.1. Eligibility Criteria

For their inclusion in this analysis, articles had to conform to the following eligibility criteria:

2.1.1. Topic

The studies had to discuss the use of MDMA (both recreative and in medical contexts), the neurohormonal effects of MDMA on openness and neuroticism traits, the description of PTSD and its symptomology, the current therapeutic options in the treatment of PTSD and their effectiveness, and the use of MDMA-assisted psychotherapy in the treatment of PTSD patients.

2.1.2. Date

The studies had to be published within 5 years of the beginning of this investigation (2017 – today). Exceptions for this rule were only considered in the acquisition of knowledge on the past use and history of MDMA and other psychedelic substances, and to contextualize MDMA effects and PTSD as a disease.

2.1.3. Type of Study

Different types of studies were accepted in this analysis, though there was a preference for recent clinical trials to assure the most recent and accurate data was presented. For context systematic reviews, descriptive reviews and other types of articles were accepted, however in terms of data analysis, as mentioned previously, clinical trials (phase II and III) were preferred.

2.2. Exclusion Criteria

The criteria for exclusion from this study include focus on other areas of medicine, written in languages other than English and published before 2017 (allowing for the exceptions mentioned above).

2.3. Article Research

The analysis presented in this thesis used articles acquired from the following databases: Google Scholar, PubMed, SCOPUS, National Library of Medicine, and Elsevier. These databases were chosen for their extensive collection of articles on the subject analyzed,

and the possibility of a broader outlook on the topic of MDMA- assisted psychotherapy in patients diagnosed with PTSD. Upon several preliminary research attempts, the following terms were deemed as best for gathering information and articles on the proposed topic: (MDMA [Title/Abstract] AND ptsd [Title/Abstract] AND psychotherapy [Title/Abstract]). Other research results were gathered using the terms individually or in different combinations of the three or in combination with terms such as "history" (in terms of the history of MDMA USE), "effects" (in terms of the neurohormonal effects of MDMA), "biology" (in terms of the biological alterations in PTSD patients), and "pharmacotherapy" as well as "treatment" (in terms of the current pharmacotherapy approved for treatment of PTSD).

The research was conducted between August of 2022 and December of 2023.

2.4. Article Selection

In a first phase for the selection of the articles, all the articles that met the first research terms were collected and any that were repeated were eliminated. After this, the abstracts of the remaining articles were analyzed and all that did not conform with the eligibility criteria mentioned above (did not address the topic, was published before 2017, etc.) was excluded. Finally, the articles that were eligible were thoroughly examined to see the quality of the information extracted from these articles.

It must also be considered that from this first research, during the examination of the individual articles, there was the discovery of other articles cited, some of which may not conform to the eligibility criteria but were however used in terms of contextualization of the pathology and use of MDMA.

2.5. Quality Control

In terms of quality control there were no set criteria that were analyzed and compared between articles, as it was considered that the newer studies utilized represented the most recent and informed perspective and knowledge on the topic. The eligibility and exclusion criteria were deemed to be sufficient to ascertain a good quality of the articles. Any biases, design flaws or factors which may have impacted the quality of the data presented are discussed in the **Error! Reference source not found.** section of this thesis.

CHAPTER 3: RESULTS

3.1. Results of Tests on Healthy Individuals

To test the premise that MDMA can be useful in addition to psychotherapy several studies have been conducted. As with all scientific investigations, the first step in understanding whether a compound can be useful or not therapeutically is to understand its effects on healthy individuals.

It is important to make sure that the doses administered during psychotherapy sessions would not have negative effects on healthy people before experimenting on individuals diagnosed with PTSD. With that thought in mind, phase 1 trials were conducted from the 1980's to the early 2000's, associated to a significant investment to test the safety of the compound (17).

Neuroimaging studies were amongst the type of studies conducted as phase 1 studies aiding scientists in the understanding of neuronal impacts of MDMA in the different areas of the brain. These studies have shown that, when under the effect of MDMA, healthy subjects' "left anterior temporal cortex or temporal pole" have reduced activation levels when thinking about negative or traumatic memories. This is indicative of diminished emotional impact of the negative thoughts. Not only does MDMA have this 'desensitising' effect, but it also helps with anxiety symptomology, as evidenced by the reduction of activity in the insular cortex. In summary, the previously mentioned changes in cerebral blood flow seen in PTSD patients (1.1.2. Neurobiology of PTSD) are reverted by the use of MDMA, which reduces CBF to the left amygdala and increased it to the ventromedial prefrontal cortex**Error! Bookmark not defined.**.

It was theorized that psychotherapy could be made for effective when accompanied by MDMA due to its effects on inner and outward awareness, including social behaviour and openness, hence the designation as an empathogen. During the several trials it was found that while MDMA did appear to increase sociability, it does not increase empathy *per se*. Although there were self-reports of friendliness and loving feelings, there was a decrease in the recognition of fear in others. This increase in sociability may be precisely because of the decreased recognition of fear or other negative emotions in others, which many times inhibit us from social connections (41). When it comes to psychotherapy, this would be positive in the sense that it might inhibit guilt and shame feelings during therapy sessions, allowing the patient to address more traumatic or negatively charged memories. Not only that but it might

incite the patient to be more truthful and express emotions that they otherwise would inhibit (41) due to societal norms or their own preconceptions.

One study also decided to address the effect of MDMA administration on "socioemotional feelings, authenticity, and autobiographical disclosure" to further understand the changes in social behaviour induced by the compound (38). This study was designed to assess changes in self-appraisal, in this case using the construct of authenticity, which can be thought of as knowing one's thoughts and feelings and acting in accordance with them (42–44). This study asked the healthy participants to describe 4 different situations: one in which they felt fear, one in which they felt joy, one in which they felt sadness and one in which they felt safe. These autobiographical recollections were discussed at baseline and while on MDMA or placebo, and the data is shown below.

Table 3: Autobiographical memories used in placebo and 3,4-methylenedioxymethamphetamine (MDMA) conditions were comparable in multiple dimensions. (38)

Table 1. Autobiographical memories used in placebo and 3,4-methylenedioxymethamphetamine (MDMA) conditions were comparable in multiple dimensions.

	Fear		Joy		Sad		Safe	
	Placebo	MDMA	Placebo	MDMA	Placebo	MDMA	Placebo	MDMA
How long ago event occurred (years)	8.7±7.9	9.7±9.1	3.4±4.8	3.1±3.3	7.5±6	6.3±6.7	5.6±8.3	6.3±8.2
Confidence in accuracy of memory (0–100)	87.4±12.5	88.4±13.1	95.1±5.4	91.2±11.2	86.3±14.3	90.9±7.8	93.7±6.2	87±19.9
Level of detail of memory (0–100)	88±10.1	87.9±14.1	93.5±8.2	93.2±11	85.4±16.4	90.9±17.8	92.7±8.4	89.2±15.3
Nature of personal involvement (0–100)	96.8±4.9	90.7±15.1	96±8	91.2±17.5	82.3±34.2	96.4±4.3	97.2±2.9	97.5±4.5
Emotional impact (0–100)	78±16.9	75.2±19.9	74.9±25.8	75.5±23.9	86.4±17.1	79.8±22.3	75.2±30.1	67.8±27.1
Other impacts (e.g. financial, health) (0–100)	61.2±29.8	55.8±31.4	64.6±32.7	49±41.6	64±31.7	51.8±29.7	66.8±34.3	50.5±45
PANAS, Positive scale (1–5)	2.6±0.9	2.8±0.8	4.1±0.7	4±0.6	2.6±0.9	2.4±0.7	3.5±1	3.2±1.1
PANAS, Negative scale (1–5)	3.4±0.7	3.6±0.6	1.3±0.3	1.3±0.4	3±0.9	2.7±0.8	1.4±0.5	1.4±0.7
Impact of events scale, intrusions scale (0–4)	2.5±0.5	2.5±1	2.1±0.7	2.1±0.6	3.2±0.6	2.8±0.5	1.9±0.7	1.9±0.6

PANAS: Positive and Negative Affect Schedule. Values are given as mean±standard error of the mean (SEM).

The results of this study are shown in Figure 3, which demonstrates a reduction in both the negative emotional impact of discussing the memories as well as the ability to fully relive and experience these memories. This is compatible with other results which indicate that while under MDMA there is an attenuation of the emotional weight attached to memories, making it less upsetting to discuss traumatic memories and not as overwhelmed by their description. In addition, MDMA does seem to improve the ability to describe, remember and understand emotions, and comfortability in talking about the autobiographical events.

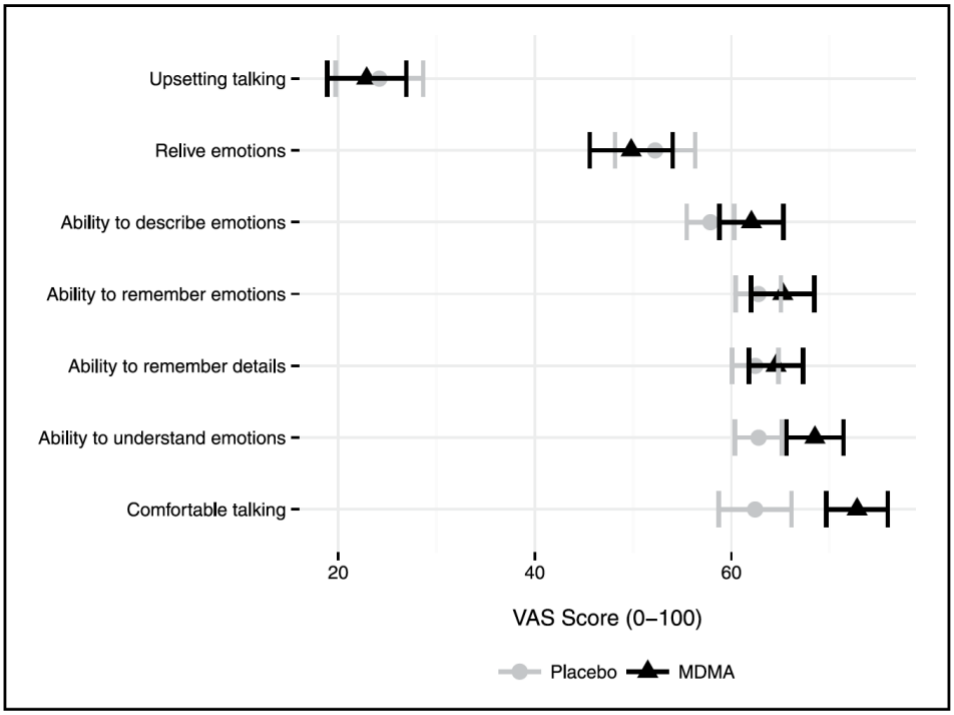

Figure 1. 3,4-Methylenedioxymethamphetamine (MDMA) increased participants' comfort describing emotional memories. Drug effects on participant visual analog scale (VAS) ratings of the experience describing autobiographical memories. Placebo is shown by gray circles, MDMA by black triangles.

Figure 3: 3,4-Methylenedioxymethamphetamine (MDMA) increased participants' comfort describing emotional memories. Drug effects on participant visual analog scale (VAS) ratings of the experience describing autobiographical memories. Placebo is shown by gray circles, MDMA by black triangles.

During the discussion of these autobiographical events self-reports of levels of anxiety, sociability, and authenticity were measured. One of the most significant conclusions of this study was that MDMA does not worsen all types of anxiety, but rather it decreases social anxiety. It does so through the increase of sociability and altered, usually positively toned, perception of others and their actions. This contradicts the findings that attribute a decrease in threat sensitivity to MDMA as it often may increase overall anxiety. The coexistence of increased anxiety and increased sociability may, at first, seem contradictory, yet it may serve the purpose of triggering a "protective sociability" which thereby may augment therapeutic alliance. So, this increase in sociability may counter the anxiety caused by MDMA administration by inducing a "tend-and-befriend" response to said anxiety, helping to strengthen the bond between patient and therapist (38).

One of the most important concerns surrounding MDMA use as an enhancer of psychotherapy was its effects on serotonin and dopamine neurotransmitters, as it was feared

that the release of these compounds might cause neurotoxicity (17). This neurotoxicity was thought to provoke a serotonin storm in acute cases and long-term neuronal damage in the chronic users. This problem arose from studies of recreational users of MDMA which demonstrated poorer performance in memory tests when compared to non-users. This concern was further augmented by the rare, however still present, instances of death after MDMA use in high-risk situations and contexts (24).

In conclusion, all these trials it has been attested that the administration of MDMA in controlled doses and controlled settings does not seem to have any dangerous side effects, as all drug-related events reported were moderate to mild, mostly expected and prepared for. Overall, more than 1100 healthy subjects have participated in these trials, and it was concluded that the administration of MDMA was safe (17).

3.2. Results of Phase 2 Trials

After having the needed assurances that the MDMA administration would not have any negative unforeseen effects, phase 2 trials were approved and began collecting information.

One trial was comprised of data collected from 20 patients who had not responded to psychotherapy or pharmacotherapy and with an average duration of PTSD symptoms of more than 20 years. Participants in this study were randomly assigned to MDMA and placebo groups, having received two or three doses of MDMA weeks apart and having integrative psychotherapy sessions in between sessions.

The MDMA sessions lasted about 8 hours and followed a non-directive approach, with the main goal being making use of the "optimal arousal zone" created by the administration of MDMA wherein it was easier to explore feelings related to the traumatic events. The participants reported "deeply meaningful therapeutic experiences", mentioning that the effect of the MDMA-assisted psychotherapy sessions lasted well beyond the physical and mental effects of the drug itself (17). During the MDMA sessions it was also observed that patients appeared to have less avoidance behaviours and defensiveness, as well as a clearer memory of the traumatic events, not clouded by emotion, and an increased willingness and capacity to process said memories. This new interpretation of the memories was accompanied by an increased awareness of their own cognitive and emotional escape mechanisms and a much more compassionate attitude.

Their overall results revealed that the MDMA group had a significant decrease in PTSD symptomology, so much so that, at the end of the study, approximately 83% of participants no longer met PTSD diagnosis criteria, and 74% reported remission of symptomology on the long-term (45,4 months) (17).

Another study decided to divide participants by the dose of MDMA received, all 12 participants having been exposed to the compound. The doses administered were 25mg and 12,5mg supplemental for the low dose and 125mg and 62,5 supplemental for the full dose. Much like the previous study, MDMA was administered in two or three separate occasions weeks apart, with weekly traditional psychotherapy sessions to integrate the progress made in the drug sessions. There was an assessment of the patients at baseline, 3 weeks after the second and third drug-assisted sessions, 2 month and 1 year long-term follow up, where the outcome measured was the Clinician-Administered PTSD Scale (CAPS) as well as the Posttraumatic Diagnostic Scale (PDS) (6). The CAPS scale is the most used tool to quantify the presence of PTSD symptomology, and is the standard measurement used in clinical trials.

As to the findings, this study did not find statistically significant reductions in CAPS scores ($p = 0,066$) but did find a clinically and statistically significant reduction in the self-reported PDS scores ($p=0,014$). It was also found that the reduction in CAPS scores continued through the long-term follow-up period, and that 3 MDMA sessions were more effective than 2 ($p=0,016$). It is also important to mention that some study subjects required the use of benzodiazepines as SOS medication after the MDMA-assisted session due to excessive anxiety symptoms, and that most of these people had been previously treated with anxiolytics (benzodiazepines) or antidepressants with anxiolytic properties (9).

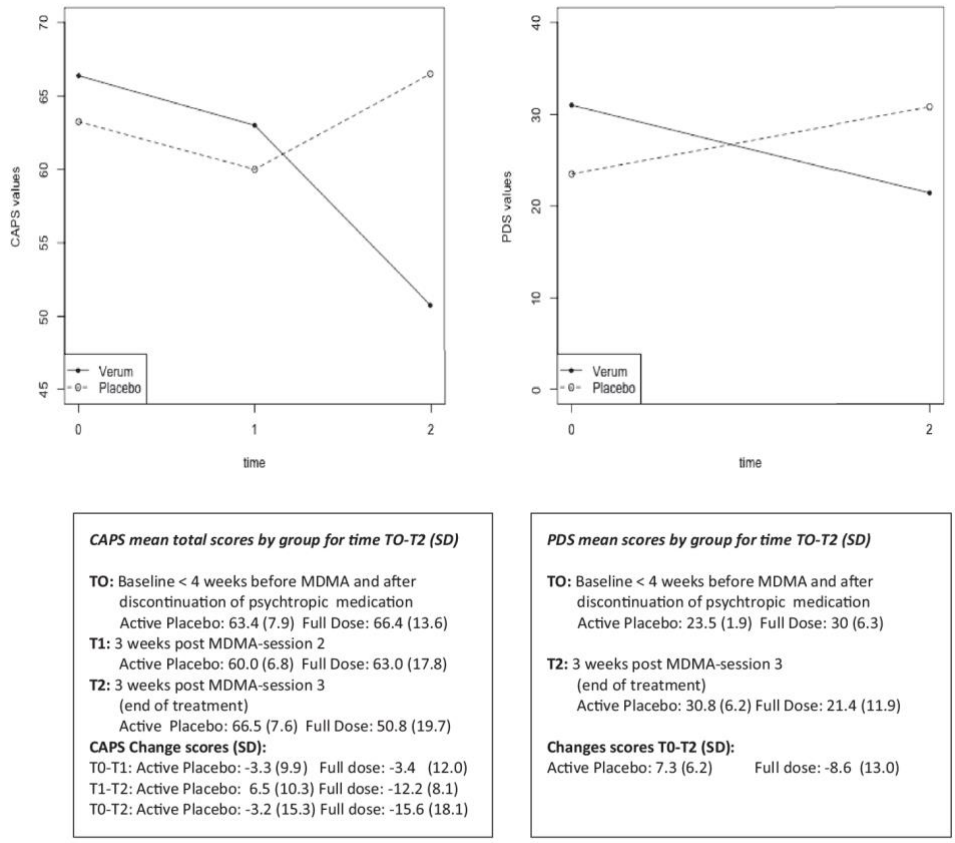

Figure 2. CAPS and PDS scores by group for time T0-T2.

Figure 4: CAPS and PDS scores by group for time To-T2. (6,37)

Illustrated above we can see the graph which plots the changes in CAPS and PDS scores along the 3 measured occasions, and we can observe a reduction in both CAPS and PDS scores in the MDMA group, though as previously mentioned, the reduction in CAPS scores was not found to be statistically significant. As for the placebo group, we can see that there was an increase in PDS scores and overall CAPS scores.

A third study, focused on military, firefighters, and police veterans, intended to analyse the impact of MDMA-assisted psychotherapy in this group of people which, due to their line of work, is significantly more prone to the expression of PTSD. As in the previous study, there were set occasions for the measurement of their variables. In this case, CAPS score was measured, as well as secondary outcomes listed below (37).

- Depression symptoms → measured with the self-reported Beck Depression Inventory-II (BDI-II)
- Sleep quality → self-reported using the Pittsburgh Sleep Quality Index (PSQI)
- Perceived growth following trauma → measured with the Post-Traumatic Growth Inventory (PTGI)

- Personality factors → assessed by the Neuroticism-Extroversion-Openness-Personality Inventory-Revised (NEO-PI-R)
- Symptoms of dissociation → only in a small group of patients which had previously reported dissociative experiences, using the self-reported Dissociative Experiences Scale II (DES-II)
- General psychological function → scored by independent raters using the single item Global Assessment of Functioning (GAF)

Below we can see the graph representing the data collected in this study (37).

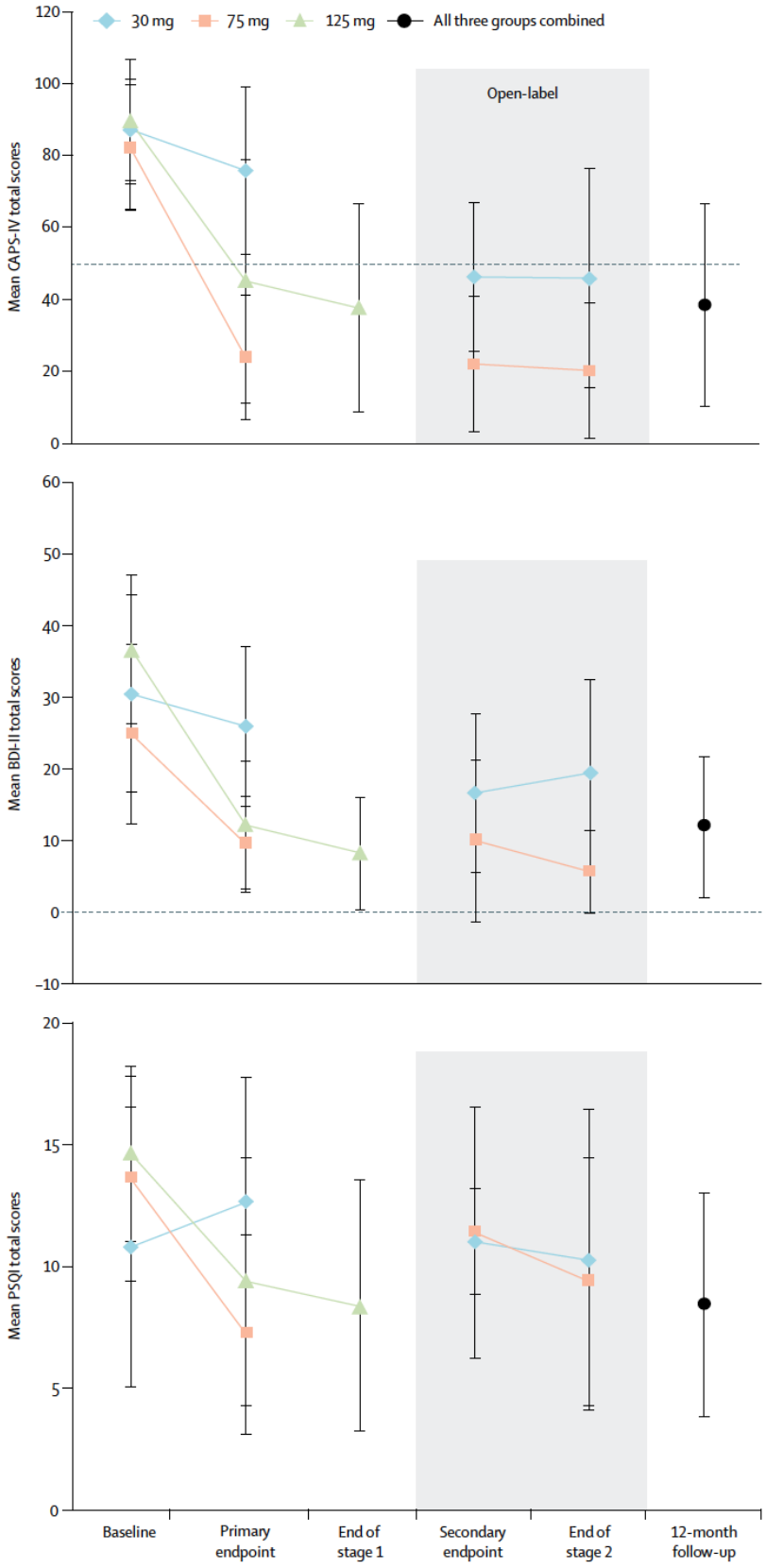

Figure 5: Mean CAPS-IV, BDI-II, and PSQI scores over time from baseline to endpoints (intention-to-treat population). (37)

In Figure 5, a mean change in CAPS scores from baseline to 1 month after the second MDMA session of -11,4 (±12,7) for the 30mg group, -58,3 (±9,8) for the 75mg group, and -44,3 (±28,7) for the 125mg group can be noted. As we can observe, both the 75mg and 125mg group had significant decreases (p=0,0005 and p=0,004 respectively) and Cohen's d effect for both values was large (2,8 and 1,1 respectively), giving further credibility to the extrapolation of these results to a larger population. On the other hand, a significant decrease in the 30mg group was not observed. At the primary endpoint it was also observed that a larger percentage of participants in the active dose groups did not meet PTSD diagnostic criteria on CAPS-IV (37) when compared to the 30mg group (control group). Moreover, a larger percentage of patients assigned to the active doses of MDMA seemed to reach a decrease of 30 or more percent after the second MDMA-assisted session (37). The table with the final CAPS results for this study is shown below.

Table 4: Primary outcome measures at the primary endpoint of 1 month after the second experimental MDMA. (37)

	30 mg MDMA plus psycho-therapy (n=7)	75 mg MDMA plus psycho-therapy (n=7)	125 mg MDMA plus psycho-therapy (n=12)	Total (n=26)	p value†
Primary efficacy measure					
Mean CAPS-IV total score					
Baseline	87·4 (14·1)	82·4 (17·3)	89·7 (17·3)	87·1 (16·1)	..
12-month follow-up	52·7 (41·2)	28·3 (23·0)	37·8 (21·4)	38·8 (28·1)	<0·0001

The re-examination of the data collected in the Mithoefer phase 2 study allowed the comparison of the decrease in CAPS scores, accounting for the neuroticism and openness traits, resulting in the following graphs (4):

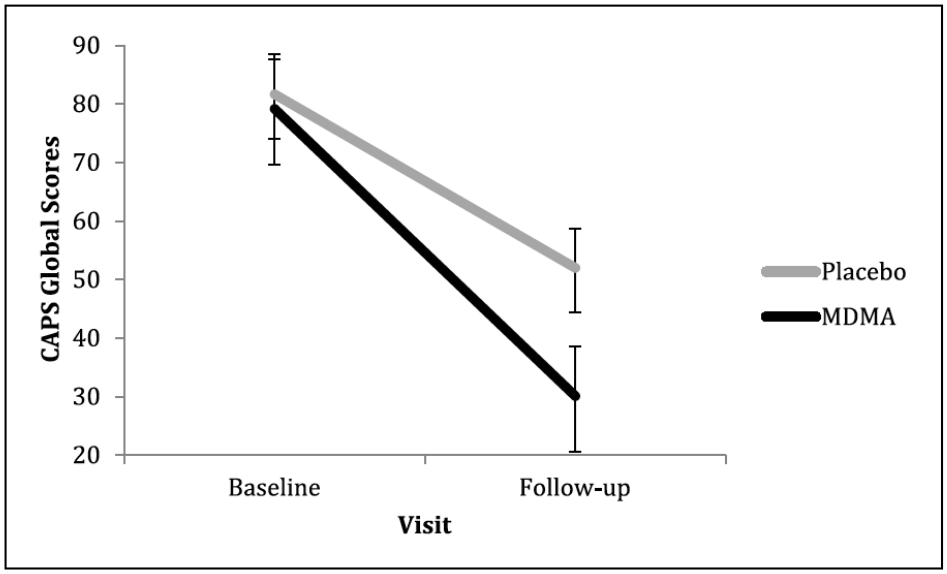

Figure 1. Placebo vs. MDMA-treatment group means and standard errors for Clinician-Administered PTSD Scale (CAPS) Global Scores at baseline and 2 months.

Change in Openness served as a covariate. Results represent the main effect of PTSD symptom reduction and the moderating effect of increased openness on therapy outcomes; all *p* values < .05.

Figure 6: Placebo vs. MDMA-treatment group means and standard errors for CAPS Global Scores at baseline and 2 months. Change in Openness as a covariate. (4)

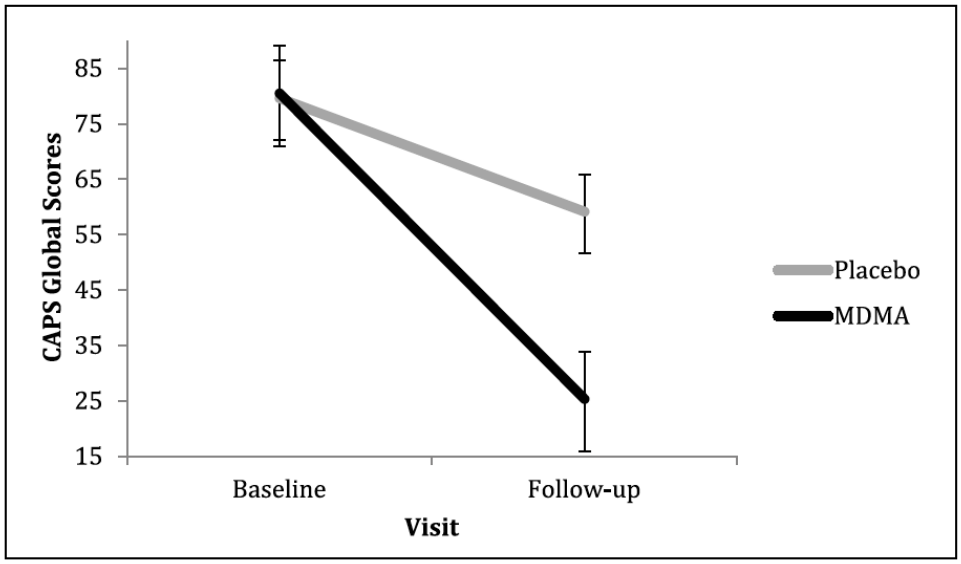

Figure 2. Placebo vs. MDMA-treatment group means and standard errors for Clinician-Administered PTSD Scale (CAPS) Global Scores at baseline and 2 months.
Change in Neuroticism served as a covariate. Results represent the main effect of group and the effect of decreased Neuroticism on therapy outcomes; all *p* values < .05.

Figure 7: Placebo vs. MDMA-treatment group means and standard errors for CAPS Global Scores at baseline and 2 months. Change in Neuroticism as a covariate. (4)

As shown in Figure 6 and Figure 7, when accounting for the traits of openness and neuroticism, there is a very significant decrease in mean CAPS scores. This is further highlighted by the correlations between the difference in openness as well as neuroticism and the decrease of the CAPS scores. It is noted that people whose openness trait had a more substantial increase experienced bigger reductions in CAPS scores, and people whose neuroticism trait decreased more also experienced a bigger decrease in CAPS scores. It was also noted that the degree of openness rose in the MDMA group while the placebo group did not have the same degree of increase. When it came to neuroticism both groups showed a decrease, meaning that MDMA could not be causally related to the reduction of this trait. While these changes observed between the baseline and the 2-month follow up did not have significant power to indicate correlation, the changes between the baseline and the long term follow up did show a much more statistically significant decrease in CAPS score amongst patients (4).

Table 5: Changes in openness and neuroticism personality traits from baseline to LTFU. (4)

Table 2. Changes in openness and neuroticism personality traits from baseline to LTFU.

Variable mean (SD)	Baseline	LTFU	$p \leq$
Openness	56.40 (15.03)	59.67 (11.91)	.032
Neuroticism	69.00 (13.85)	59.07 (11.76)	.003

Another study targeted individuals diagnosed with life-threatening or terminal diseases, as, due to the recent approval of MDMA as a breakthrough therapy for PTSD, it was theorized that this compound might also have a positive impact in the life-threatening disease related anxiety. People with life-threatening illnesses do not simply experience physical symptoms of the disease that define their fate but have an associated elevation of risk for psychopathology such as depression, anxiety, and anger-related disorders, these being designated comorbidities in a lot of these patients. It is therefore extremely important to address these psychological symptoms, as even if the life-threatening disease disappears or enters remission, they may persist and have long-lasting effects. This was tested using the STAI-Trait anxiety scale, and the results were as follows (45):

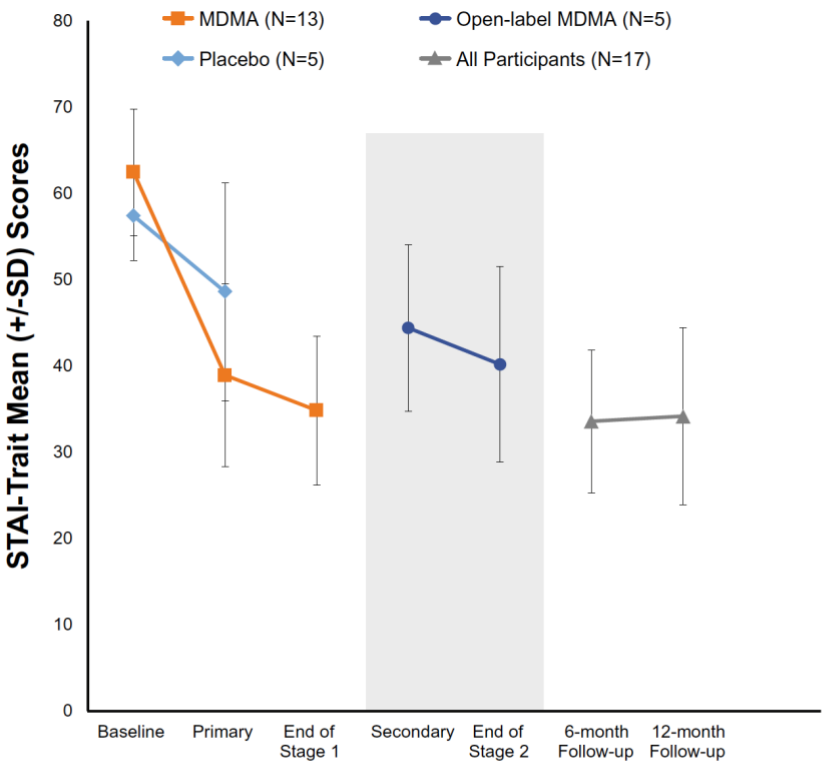

Figure 2. Mean (SD) STAI Trait scores for MDMA and Placebo groups at baseline and post treatment. Mean (SD) State Trait Anxiety Inventory scores across time at baseline, primary endpoint (one-month post second blinded experimental session), end of stage 1 (one month post third MDMA session, i.e. treatment exit for MDMA 125 mg group), secondary endpoint (one month post second open-label session), end of stage 2 (one month post third open-label session, i.e. treatment exit for control group), 6-month follow-up, and 12-month follow-up. The grey box represents the open-label crossover after placebo group was unblinded at the primary endpoint. Groups were collapsed for long-term follow-ups since all participants had received active doses of MDMA in either the blinded or open-label stage

Figure 8: Mean (SD) STAI Trait scores for MDMA and Placebo groups at baseline, primary endpoint, end of stage 1, secondary endpoint, end of stage 2, 6-month follow-up and 12-month follow-up. (45)

The mean (SD) change in STAI-Trait anxiety score was greater for the MDMA group -23.5 (13.2) compared to the placebo group -8.8 (14.7), but these group differences were not statistically significant ($p = 0.0558$). If the one potential placebo outlier was removed, the STAI-Trait change scores between treatment groups in Stage 1 would have been statistically significant ($p = 0.0066$). Results on the STAI-State anxiety, depression, sleep quality, and global functioning (46–51) followed the same trajectory, indicating greater improvement in the MDMA group vs. the control group but failed to reach statistically significant between-group differences (45).

Table 6: Outcome measures at baseline and post two blinded experimental sessions. (45)

	Placebo (n = 5)			MDMA (n = 13)			*p*-value
	Baseline	Post two experimental sessions	Change[b]	Baseline	Post two experimental sessions	Change[b]	
Primary efficacy variable							
STAI Trait, mean (SD)	57.4 (5.2)	48.6 (12.6)	− 8.8 (14.7)	62.5 (7.3)	38.9 (10.6)	− 23.5 (13.2)	0.06
Secondary efficacy variables							
STAI state, mean (SD)	51.8 (5.3)	45.8 (12.5)	− 6.0 (15.8)	59.5 (11.9)	37.5 (13.6)	− 22.1 (17.9)	0.10
BDI-II, mean (SD)	30.0 (11.4)	15.4 (9.9)	− 14.6 (8.6)	30.2 (11.0)	9.3 (10.4)	− 20.9 (13.8)	0.36
PSQI, mean (SD)	7.0 (6.6)	6.8 (5.7)	− 0.2 (1.3)	10.9 (3.5)	7.3 (4.5)	− 3.6 (5.4)	0.05
PTGI, mean (SD)	64.0 (19.1)	61.4 (24.9)	− 2.6 (6.1)	58.1 (19.9)	71.0 (18.8)	12.9 (23.2)	0.04
MADRS, mean (SD)	19.2 (9.3)	12.2 (5.3)	− 7.0 (7.2)	19.5 (7.1)	9.0 (9.0)	− 10.5 (8.2)	0.41
GAF, mean (SD)	69.8 (13.4)	72.8 (7.7)	3.0 (12.5)	68.5 (5.4)	75.1 (9.9)	6.6 (9.7)	0.52
SCS, mean (SD)	2.8 (0.8)	2.7 (0.9)	− 0.04 (0.5)	2.8 (0.6)	3.3 (0.6)	0.4 (0.7)	0.21
FFMQ, mean (SD)	3.3 (0.4)	3.3 (0.4)	0 (0.2)	3.3 (0.4)	3.7 (0.5)	0.4 (0.6)	0.04
DAP, mean (SD)							
Fear of death	5.1 (1.1)	4.5 (0.7)	− 0.6 (1.0)	3.8 (1.6)	3.7 (1.4)	− 0.1 (0.6)	0.25
Death avoidance	3.5 (1.9)	2.4 (0.9)	− 1.1 (1.8)	3.1 (1.7)	3.1 (1.6)	0 (0.8)	0.26
Neutral acceptance	5.4 (1.0)	5.6 (0.5)	0.2 (0.6)	5.8 (0.5)	5.9 (0.7)	0.1 (0.6)	0.88
Approach acceptance	3.2 (1.3)	3.0 (0.7)	− 0.1 (1.1)	3.2 (1.8)	3.5 (1.6)	0.3 (0.7)	0.32
Escape acceptance	3.4 (1.3)	3.4 (1.3)	0 (0.9)	3.5 (1.4)	3.9 (1.0)	0.4 (1.0)	0.85
FACIT, mean (SD)[c]							
Physical well-being	19.8 (6.7)	21.4 (3.0)	2.8 (5.0)	21.6 (4.2)	23.0 (4.3)	1.4 (4.4)	0.61
Social/family well-being	20.0 (9.7)	17.6 (6.3)	− 2.0 (2.9)	17.6 (2.9)	18.5 (3.8)	0.8 (3.4)	0.15
Emotional well-being	14.0 (5.9)	15.0 (3.9)	1.0 (2.2)	14.7 (3.0)	16.3 (6.7)	1.6 (7.1)	0.87
Functional well-being	19.5 (5.9)	18.8 (7.1)	1.0 (1.6)	14.5 (2.8)	19.3 (6.3)	4.8 (5.8)	0.22
Additional concerns	24.8 (14.4)	24.2 (10.3)	− 0.3 (5.0)	24.0 (9.2)	28.5 (14.1)	4.5 (11.9)	0.45

Table 2. Outcome measures[a] at baseline and post two blinded experimental sessions. *STAI* State-Trait Anxiety Inventory, *BDI-II* beck depression inventory-II, *PSQI* Pittsburgh Sleep Quality Index, *PTGI* Post Traumatic Growth Inventory, *MADRS*, Montgomery-Asberg Depression Rating Scale, *GAF*, Global Assessment of Functioning, *SCS* Self-Compassion Scale, *FFMQ* Five-Facet Mindfulness Questionnaire, *DAP* Death Attitudes Profile, *FACIT* Functional Assessment of Chronic Illness Therapy Scale. [a]All outcomes were based on an intent-to-treat set. [b]Independent group *t*-test on change from baseline to post 2 experimental sessions. [c]Missing FACIT data at baseline for placebo group (n = 4).

Since some of the patients had also been diagnosed with PTSD, the impact of the MDMA shown in Table 6, could also have been caused by an improvement specifically PTSD symptoms. It is likely, however, that since MDMA is thought to act as an enhancer of psychotherapy due to its ability to induce openness and increase rapport between patient and therapist, it can be assumed that MDMA could work on several pathologies by inducing a more effective psychotherapy. Its impact on the patients' capability to analyse and rethink perceptions they have related to their illness and thoughts of anxiety and fear in a more empathetic way may allow for a better resolution and integration of one's fears (45).

3.3. Results of Phase 3 Trials

More recently the first results of phase 3 trials have begun being released. So far there have been two phase 3 trials, whose study methods were based on the analysis of the pooled phase 2 studies conducted to decrease confounding factors and biases. Both trials have been sponsored by MAPS (Multidisciplinary Association for Psychedelic Studies), an organization dedicated to the study of therapeutic uses of psychedelic substances.

The first trial, MAP1, similarly to other phase 2 studies before it, administered three doses of MDMA or placebo, separated in time and with psychotherapy sessions before and after to integrate the experiences. A properly trained therapy team was always present, and sessions occurred with one male and one female therapist. The study span across countries, having included patients from the US, Canada, and Israel. In total 91 patients were admitted to the study, 46 in the MDMA group and 44 in the placebo group (one participant dropped out of the study after having felt triggered during one of the CAPS interviews). The impact of MDMA-assisted psychotherapy was assessed by the change in CAPS score as a primary outcome and SDS (Sheehan Disability Scale) scores as a secondary outcome. The results of the trial are presented below (8):

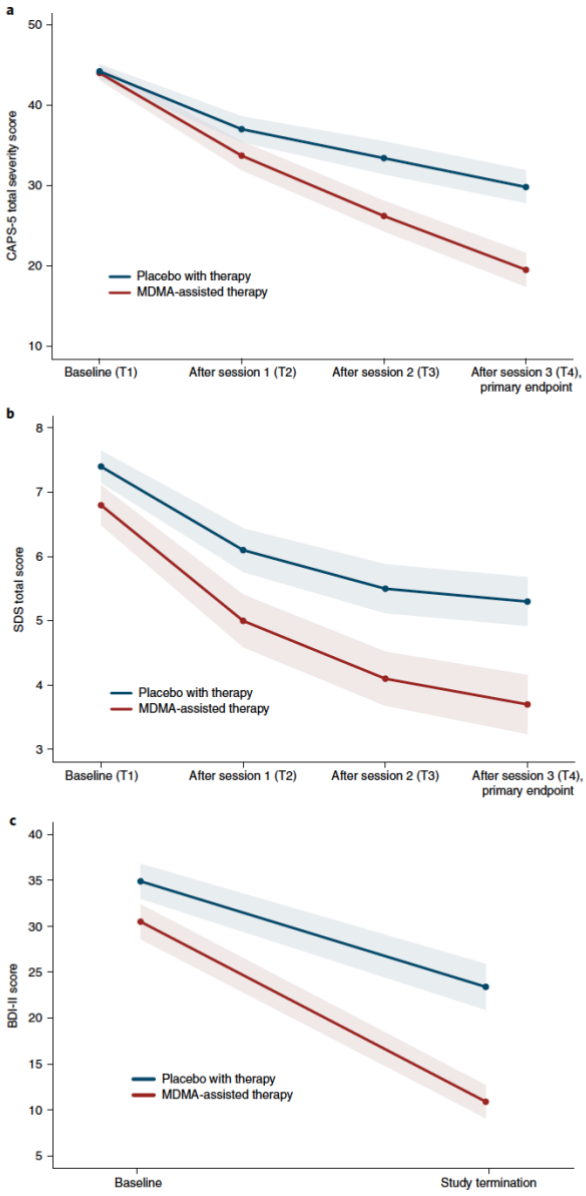

Fig. 2 | Measures of MDMA efficacy in the MDMA-assisted therapy group and the placebo group. a, Change in CAPS-5 total severity score from T1 to T4 ($P<0.0001$, $d=0.91$, $n=89$ (MDMA $n=46$)), as a measure of the primary outcome. Primary analysis was completed using least square means from an MMRM model. **b**, Change in SDS total score from T1 to T4 ($P=0.0116$, $d=0.43$, $n=89$ (MDMA $n=46$)), as a measure of the secondary outcome. Primary analysis was completed using least square means from an MMRM model. **c**, Change in BDI-II score from T1 to study termination ($t=-3.11$, $P=0.0026$, $n=81$ (MDMA $n=42$)), as a measure of the exploratory outcome. Data are presented as mean and s.e.m.

Figure 9: Measures of MDMA efficacy in the MDMA-assisted therapy group and the placebo group. (8)

In terms of occurrences during the study it is important to mention secondary or adverse effects, which were typically transient and not serious, including muscle tightness, decreased appetite, nausea, hyperhidrosis and feeling cold (8). The only severe adverse effects reported were by two participants allocated to the placebo group. It is also important to mention that though there was a variation in the quantity of patients reporting suicidal thoughts during the trial, the number never exceeded the baseline and there were no significant differences between the placebo and MDMA groups. As the study included different sites and populations it is also interesting to note that the results did not seem to be affected

by personal history, such as alcohol or substance abuse and childhood trauma, making them consistent across the 15 sites. Notably, many of the patients in the trial had other comorbidities, such as other psychiatric pathologies or a dissociative PTSD type, which were not deemed to be exclusion criteria, and that the MDMA was effective in the improvement of PTSD symptomology, even with these additional comorbidities. This can be concluded from the reductions in the MDMA group (mean MDMA Δ = −30,8 (±9,0)) and in the placebo group (mean placebo Δ = −12,8 (±12,8)) (8). The changes in CAPS scores from baseline to 18 after was of -24,4 (±11,6) in the MDMA group compared to a -13,9 (±11,5) decrease in the placebo group. In terms of the quality of the data, the effect size of the MDMA-assisted therapy treatment compared with placebo with therapy was d = 0.91 (95% CI = 0.44–1.37, pooled s.d. = 11.55) in the de jure estimand and d = 0.97 (95% CI = 0.51–1.42) and the effect size was 2.1 (95% CI = −5.6 to 1.4) in the MDMA group and 1.2 (95% CI = −4.9 to 2.5) in the placebo group (8). In relation to the secondary outcome, the mean change in SDS scores was -3,1 (±2,6) in the MDMA group and -2,0 (±2,4) in the placebo group.

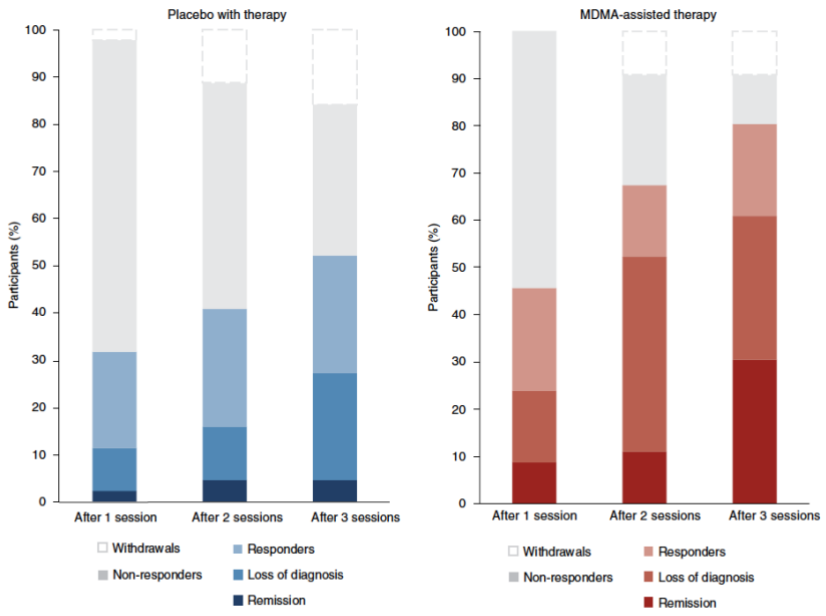

Fig. 3 | Treatment response and remission for MDMA and placebo groups as a percentage of total participants randomized to each arm (MDMA, *n* = 46; placebo, *n* = 44). Responders (clinically significant improvement, defined as a ≥10-point decrease on CAPS-5), loss of diagnosis (specific diagnostic measure on CAPS-5), and remission (loss of diagnosis and a total CAPS-5 score of ≤11) were tracked in both groups. Non-response is defined as a <10-point decrease on CAPS-5. Withdrawal is defined as a post-randomization early termination.

Figure 10: Treatment response and remission for MDMA and placebo groups as a percentage of total participants randomized to each arm (MDMA, n=46; placebo, n=44). (8)

Overall, this study recorded several instances of clinical improvement (decrease in ≥10 points on the CAPS-5) and loss of diagnostic criteria met and remissions (CAPS-5 score ≤ 11). Eighteen weeks after the baseline, 67% of the participants in the MDMA group didn't meet PTSD diagnosis criteria, compared to 32% of the participants in the placebo group. 33% of

the participants in the MDMA group, at 18 weeks after baseline, were considered in remission while only 5% of the placebo group went into remission.

The second MAPS trial, MAP2, aimed to test their hypothesis on a more diverse population, including representation of different ethnicities and races. The primary outcome was still the change in CAPS scores and the secondary outcome was the change in SDS scores, and the rest of the trial design was very similar to the first study. The results of the study can be observed in Figure 11 (52).

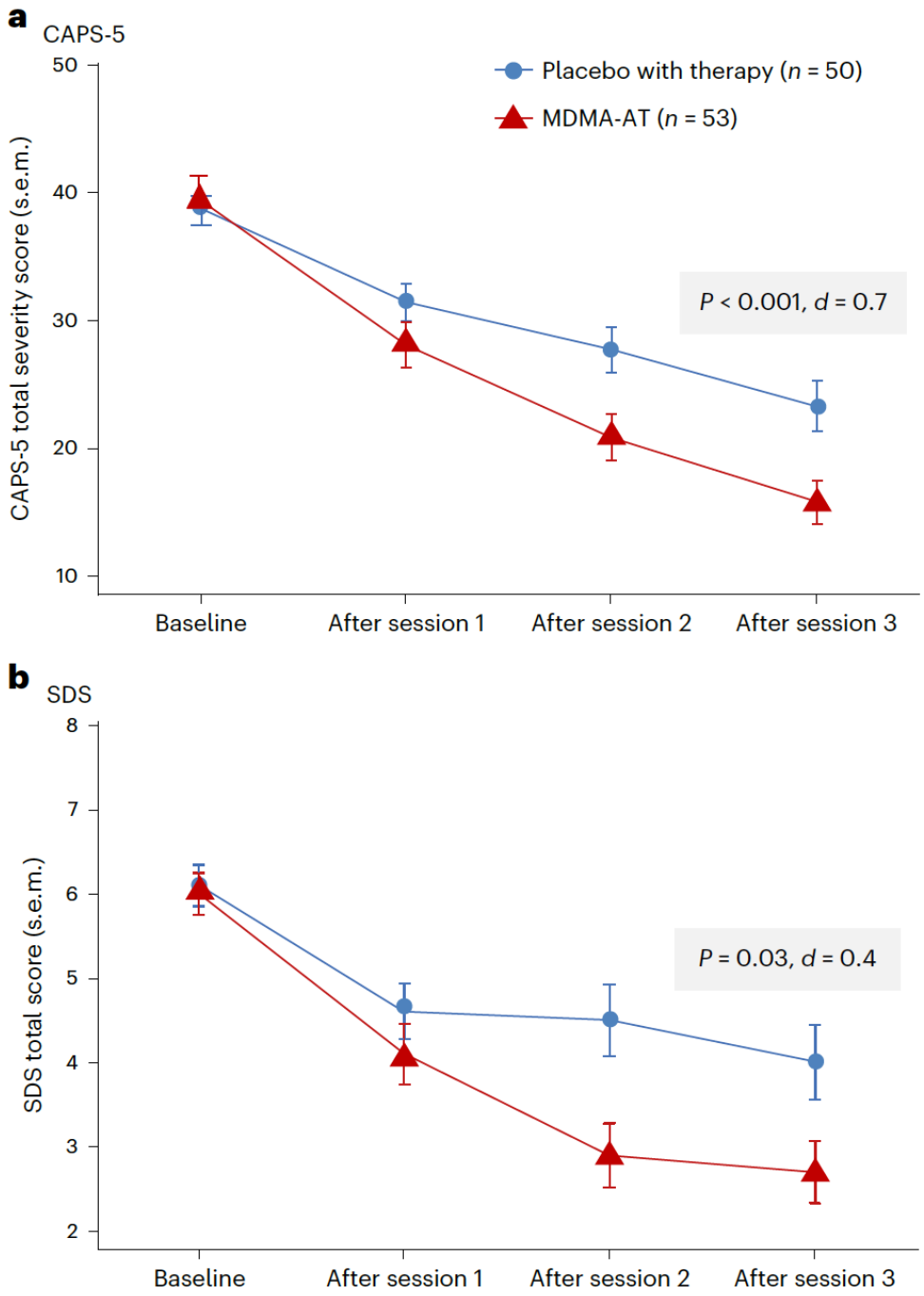

Fig. 2 | Measures of efficacy in the MDMA-AT and placebo with therapy groups. a, LS mean change (±s.e.m.) in CAPS-5 total severity score from baseline to after session 3 (primary outcome) for placebo with therapy ($n = 50$) versus MDMA-AT ($n = 53$, $P < 0.001$, Cohen's $d = 0.7$). **b**, LS mean change (±s.e.m.) in SDS total score from baseline to after session 3 (key secondary outcome) for placebo with therapy ($n = 50$) versus MDMA-AT ($n = 53$, $P = 0.03$, Cohen's $d = 0.4$).

Figure 11: Measures of efficacy in the MDMA-AT and placebo with therapy groups. (52)

Above you can observe the reductions in CAPS score and SDS score as the sessions occurred. As can be seen, both groups experienced a reduction in both outcomes, however the

MDMA group seemed to have a more significant decrease in symptomology and PTSD criteria. Within the MDMA group, 86,5% of participants demonstrated significant clinical improvements at the 18-week endpoint, compared to 69% in the placebo group. At the end of the study, 71,2% of participants in the MDMA group no longer met the criteria for PTSD diagnosis compared to 47,6% of the placebo group (52).

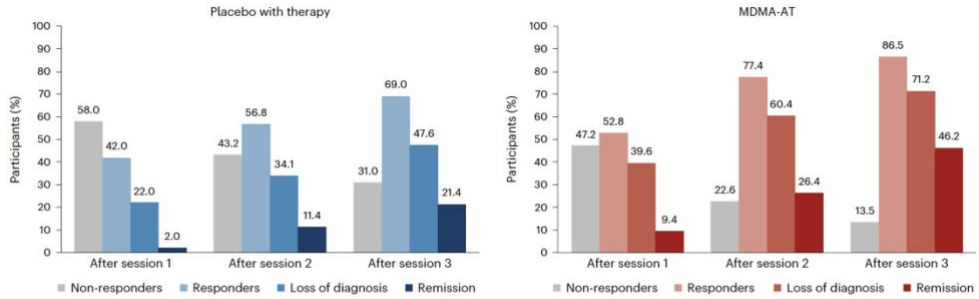

Fig. 3 | Treatment response and remission in the MDMA-AT (n = 53) and placebo with therapy (n = 50) groups. A ≥10-point reduction in CAPS-5 total severity score was considered to be clinically meaningful. Responders (≥10-point reduction from baseline), loss of diagnosis (≥10-point reduction from baseline and no longer meeting PTSD diagnostic criteria) and remission (loss of diagnosis and CAPS-5 total severity score of 11 or less) were tracked in both groups as a percentage of participants. Non-responders were defined as any CAPS-5 total severity score change <10-point reduction from baseline.

Figure 12: Treatment response and remission in the MDMA-AT (n=53) and placebo with therapy (n=50) groups. (33,52)

This was a confirmatory study with the intent of validating the results from the first phase 3 trial, MAP1 (mentioned above), with a more diverse population. As can be seen, both studies demonstrated positive results, and support the hypothesis of a therapeutic potential in the use of MDMA when combined with psychotherapy in patients diagnosed with PTSD (52).

3.4. Results of Comparative Reviews

In a review article comparing the effect of SSRIs and MDMA (33) it is mentioned that the MDMA-consequent decrease in CAPS scores was not only significant with a p-value of <0,001, but also demonstrated a large between-group effect size (0,9 Cohen's *d* effect size) that was approximately double that of paroxetine (0,45–0,56) and triple that of sertraline (0,31–0,37), which can be observed in the table below.

Table 7: Comparison of sertraline, paroxetine, and MDMA mean CAPS reduction LOCF, intent-to-treat. (33)

TABLE 3 | Comparison of sertraline, paroxetine, and MDMA mean CAPS reduction LOCF, intent-to-treat.

	Sertraline		Paroxetine		MDMA	
	CAPS-2 (sertraline–placebo)[a]	Dropout %	CAPS-2 (paroxetine–placebo)[a]	Dropout %	CAPS-IV (MDMA–control)[b]	Dropout %
Study 1	–6.8 (effect size 0.31)	29.3%	–14 (effect size 0.56)	35.5%	–26.2 (effect size 0.9)	7.6%
Study 2	–9.8 (effect size 0.37)	28.4%	–11 (effect size 0.45)	39.0%	—	
Study 3	—		–6 (effect size 0.09)	33.0%	—	

[a]*Effect sizes were not reported in FDA statistical package for paroxetine. Placebo subtracted effect. Size were determined from CAPS scores by calculating the change from baseline divided by the standard deviation.*
[b]*Primary endpoint was 1–2 months after 2–3 blinded experimental sessions.*

3.5. Results of Cost-Effectiveness Studies

According to Elliot Marseille et.al. (5), mentioned previously in 1.1.1. Epidemiology of PTSD, the cost of this intervention is recovered at 3,8 years, at which point it would have already prevented 10,8 deaths and generated 887 QALYs (Quality-Adjusted Life Years) in a cohort of 1000 patients. This study also predicts that, over 30 years in a 1000 patient cohort, MDMA-assisted therapy could save approximately $132.9 million while averting 61.4 premature deaths and generating 4,856 discounted QALYs, in the context of the United States on which this study was based (5).

CHAPTER 4: DISCUSSION

As of right now, most trials on the topic of MDMA use in patients diagnosed with PTSD have been phase 2 trials, as research on this topic only really begun taking off in the late 1990's and 2000's. Many conclusions may be drawn from the studies presented above, and the impacts of the results may be significant for global health improvement.

4.1. The Impact of MDMA on Psychotherapy

As can be clearly noted, MDMA has had a significant impact on the psychotherapy delivered in patients diagnosed with PTSD. There were promising and positive effects identified, however, as we are considering the use of a substance for the resolution of symptoms or treatment of a disease, we must also consider negative findings to make an informed decision on whether it should be further investigated.

4.1.1. Positive Impacts

As can be inferred from the results demonstrated above, MDMA has shown very positive effects when used in conjunction with psychotherapy to address PTSD symptomology. The positive effects are translated in the objective results – the difference in CAPS scores and other secondary measures – and in the specificities of MDMA administration and its impact on emotional and cognitive functioning. Not only that but it has, on several occasions, allowed for the study of more complicated socioemotional states like trust, blame, and empathy, having the potential to be used to study the neurobiology of these entities (38).

The studies presented above have demonstrated that the administration of MDMA significantly increases the magnitude of the reduction in CAPS scores (the most used primary measure of PTSD symptomology). According to Mitchell et.al (2023), it was found that the implementation of three MDMA-assisted psychotherapy sessions caused a notable decrease in CAPS scores, as well as SDS scores, with an effect size of 0,91, which is larger than any other PTSD pharmacological treatment (52).

A third study that used different doses of MDMA to evaluate dose-dependent effects found, interestingly, that a smaller 75mg dose of MDMA led to a more substantial reduction in CAPS scores when compared to the 125mg dose. It should be considered that these results arise from a phase 2 trial and may have been due to a small sample size or the fact that the 125mg group had a higher depression score at baseline when compared to other groups. Nevertheless, it is postulated that the 75mg dose may have had greater effects on CAPS score

since it allowed patients to focus more on the processing of the traumatic memories and experiences, with diminished interference from the physiological and emotional effects of MDMA. Not only does this result further accentuate the positive correlation between MDMA administration and reduction in PTSD symptomology, but it attests that smaller doses with less physiological impact may have sufficient effects (37).

In these studies, another important objective result is the duration of the effect of MDMA on PTSD symptomology reduction. These results have also been very positive overall, with many accounts of improvements or additional reductions in the long-term follow-up. Studies found benefits from this type of therapy last a minimum of 12 months (33,37), others claiming a duration of the benefits of this treatment of 3,5 years after the end of MDMA-assisted therapy sessions**Error! Bookmark not defined.**. Another conclusion draw was that these long-term results did not simply refer to a reduction in symptomology, but to changes in personality which further enhance the success of traditional therapy sessions (4). These results suggest the possibility of personality alterations, something that was assumed to be stable during most of the adult life. Questions about personality formation and adaptations can then arise, promptly giving way to more research in the use of MDMA-assisted psychotherapy in PTSD or even other psychiatric diagnosis where this effect could have positive clinical significance.

Another objective change that should be noted is the decrease in drop-out rates in MDMA trials when compared to other therapies. The drop-out rate for participants in MDMA-assisted psychotherapy studies is significantly lower than that of the pharmacotherapeutic options or the psychological therapies alone: cognitive-behavioural therapy (CBT) demonstrated high drop-out rates of 20% (9), sertraline trials demonstrated a drop-out rate of 28% and paroxetine had a 11,7% drop-out rate (33). In comparison, MDMA-assisted psychotherapy trials showed a 6,8% drop-out rate, indicating this therapy may have been better tolerated by subjects.

In terms of the impact of MDMA administration, there are several advantages relatively to other treatments. Firstly, MDMA-assisted psychotherapy requires only 2 to 3 administrations of MDMA while pharmacotherapy implies a continued use of SSRIs which, as mentioned previously, may cause several uncomfortable side effects (17). It has also been found that MDMA use does not seem to produce withdrawal symptoms when compared to other pharmacological options (33).

In light of the reduction in addiction potential and side effects, we must also consider that 80% of the patients diagnosed with PTSD are additionally diagnosed with at least one other comorbid disorder (8), and therapies must account for the impact of these comorbidities on the evolution of PTSD symptomology and response to treatment. MDMA-assisted psychotherapy has been shown to have positive results in PTSD patients with comorbidities such as depression, history of alcohol and substance use disorders (8). This success may be because many of the comorbidities associated with PTSD are psychological and, by treating the root cause, we consequently address pathological cognitions and behaviours related to the comorbidities. Moreover, it is also understood that this therapy mitigates depression (8) and its symptoms, further increasing the scope of action of MDMA on psychiatric disorders.

In an economical perspective, MDMA-assisted psychotherapy also has several advantages, as it provides a directed therapy which not only occurs in a small window of time but also appears to be extremely effective in the long run. The fact that two to three sessions of MDMA-assisted therapy sessions interspersed with normal psychotherapy, a process that takes about 12 weeks, might have such positive results on the long term supports the cost-effectivity of this therapeutical option.

It is the action mechanism of MDMA that facilitates addressing traumatic experiences, especially those with a lot of emotional charge, and this may not only be useful in the treatment of PTSD but in many other psychiatric disorders that thrive on pathological cognition pathways. It is hypothesized that the administration of MDMA allows for the temporary activation of oxytocin-dependent neuroplasticity, which for most people has a peak of activity during adolescence and becomes more inactive in adulthood (53,54). This neuroplasticity allows for the reencoding of memories and alteration of neural pathways which might determine fear responses and hence PTSD symptoms. In conjunction with the emotional effects of MDMA, a 'window of tolerance' is created, enabling patients to reprocess traumatic occurrences and not experience the usual symptoms of hyperarousal or dissociation (8). It is extremely beneficial for patients to have the opportunity to recode the memories with a different emotional charge, in effect numbing the emotions attached to these memories and allowing for the cessation of the connection between these memories and the anxiety response they used to induce (9).

Finally, the MDMA sessions provide an opportunity to revaluate and recode the memories, while also allowing for the usual cognition directed intervention of psychotherapy. During psychotherapy sessions for patients suffering of PTSD, the aim is usually to take notice of and reformulate negative cognitive processes which lead to hyperactivation of the fear

response. One of the pathological cognitive processes that psychotherapy aims to treat in PTSD is over-accommodation (i.e. exaggerated negative beliefs). Although psychotherapy does have positive results by itself, as in the long-term levels of over-accommodation do not exceed baseline, by administering MDMA during sessions, these results could be greatly improved (55). It has been noted that the decrease in negative thoughts about the world and oneself could be used as a predictor for the decrease of PTSD symptomology. Hence, we can use this as a target, aiming to diminish these thoughts during MDMA-assisted psychotherapy sessions, and use the psychological and emotional effects of MDMA to do so.

4.1.2. Negative Impacts

Though MDMA may have had many positive impacts on the result of psychotherapy in the studies mentioned above, it is also important to assess its negative impacts, not only on the results but also the individual patients that endured the therapy.

One such problem is the fact that prior research indicated that patients who had recently been on SSRIs might not respond as well to MDMA as patients without any previous pharmacotherapy (8). On the same note, as previously mentioned, Mithofer et al. (2018), found that a 75mg dose of MDMA seemed to have better results than a 125mg dose. This fact may indicate that there is a further need to stratify doses according to weight, sex and other factors. It also may indicate that the people in the 125mg group were in increased risk for dose dependent physiological effects.

In terms of the physiological impact of the MDMA administration, several side effects were mentioned in the different clinical trials. Though, as previously stated, MDMA would, on one hand, have fewer long-term side effects due to its interval administration and fewer doses when compared to SSRIs, the acute effects of its administration are still important and should be considered. These physiological effects included diarrhea, difficulty concentrating, anxiety, dizziness, heavy legs, impaired gait/balance, jaw clenching/tight jaw, lack of appetite, nausea, nystagmus, paresthesia, perspiration, sensitivity to cold, thirst, and weakness (33). These side effects have been noted to be the reason for patients to drop out, particularly the anxiety MDMA may induce. Although this does not support the use of MDMA as an enhancer of psychotherapy, it must be considered that the positive emotional and social effects of MDMA do counter many of the complaints patients have about psychotherapy alone, such as the extreme emotional responses elicited by the reexperiencing of traumatic memories necessary to recode them and assign a different meaning to them.

Besides the acute effects of MDMA ingestion, the long-term physiological impacts of MDMA use must also be considered. So far, most of the studies that address chronic MDMA effects have been based on recreative users who, many times, pair the use of MDMA with other drugs, making results unreliable. Hence, there are no real studies about the impact of MDMA, by itself, on human physiology, meaning the long-term impact of the therapy is not yet known. In time, the subjects of the phase 2 and 3 trials of MDMA-assisted psychotherapy may be tested to assess the difference in physiological levels of neurotransmitters and hormones implicated in the neurochemical effects of MDMA, such as cortisol, oxytocin, serotonin, and norepinephrine. A concern about the possible increase in cortisol levels rose from studies on recreational users, mentioned previously. These studies found that the use of MDMA caused an acute increase in cortisol levels and that heavy users when compared to light users or non-users had significantly higher cortisol levels at 3-month follow-up (56). Sustained increased levels of cortisol may have several impacts on the health of patients such as lowered immune response, sleep dysregulation and weight gain. Other harmful effects of the use of MDMA on the long-term are based on individual cases, and to be sure that these negative health impacts are caused by MDMA, other prospective studies would have to be conducted. In these prospective studies physiological parameters impacted by the administration of MDMA would have to be measured, as well as the administration of neurological tests and the accounting for aging and conflicting factors.

In a wider scope, the use of MDMA may be hindered as it will not benefit all *stratum* of the population. Even though the use of MDMA to enhance psychotherapy may be useful for patients, we must consider that its advantage of only having to be administered two to three times may also present a disadvantage to the pharmaceutical companies since they would most likely ensure a higher profit by continually supplying SSRIs to patients diagnosed with PTSD for many years. Additionally, due to the illegal nature of MDMA there are no approved protocols for its synthesis, and because of the novelty of its use in the medical field, a significant amount of money would need to be invested in exploring the best process of synthesis of medical grade MDMA. For this reason, in terms of cost-effectivity, the production of MDMA for the treatment of PTSD patients could be smaller than that of the production of sertraline or paroxetine, established SSRIs whose production process has been optimized and approved worldwide. On the other hand, since most of the patents for these SSRIs have expired, the economic gain from their sale is not as significant, which might, in turn, incentivize the investigation of a synthesis protocol for medical grade MDMA, if FDA approval is granted.

The organization of the MDMA-assisted therapy sessions must also be considered as these sessions involve many people, require a specific environment which may be hard to create and maintain. This type of therapy involves at least two therapists as well as an overnight stay, meaning that many resources must be available at any time, demanding significant funding. It is thought that the prevalence of PTSD on the world population is 3,9%, meaning out of 8,1 billion people, about 300 million would be diagnosed with PTSD (57), out of which a third, or 100 million, may not respond to therapy (58). Ensuring the treatment of all these people with MDMA-assisted therapy would be an extremely difficult undertaking, especially accounting for differences in economic conditions between countries and populations. Though promising trial results have been made public until now, the dissemination of this treatment would most likely not reach all people suffering from PTSD, especially since the percentage of people seeking treatment is lower in low-income countries, most likely due to lack of access to health services (6).

As well as economic interests we also must consider our societal regulations and expectations. Since the 1980's MDMA has been considered an illegal drug, designated as Schedule I in the United States, making the consumption of this chemical a very controversial action. Supposing the intent of the use of MDMA in patients diagnosed with PTSD is the reduction of symptoms or cessation of symptoms altogether, this may be poorly regarded in the traditional society due to the fringe culture association of MDMA. Since MDMA is associated with youth culture, raves, and anti-establishment ideology due to its recreational use and association with other psychedelic drugs and the settings in which they are consumed, its therapeutic potential is tarnished with its reputation of being a party drug. This may cause a negative social response to its therapeutic use, specifically the discreditation of its therapeutic potential as an 'excuse' to defy regulations put in place that make it an illegal substance. This can lead to prejudice towards people who undergo MDMA-assisted psychotherapy and hence cause more psychological damage, worsening the psychiatric disorder that led them to the sessions in the first place.

Finally, the possibility of illegal activities must also be considered. Although ecstasy may not be the most expensive illegal recreative drug, the existence of a storage of medical grade ecstasy could make it into a possible target for contraband. Safety measures should be put into place to avoid the entrance of medical grade MDMA into the illicit market and avoid other safety risks that may impact the patients or the society, meaning more additional costs. A screening process for the MDMA used in therapy sessions should also be implemented to make sure of the quality of the MDMA being administered and be assured there was no adulteration of the chemical compounds.

4.2. Experimental Trial Limitations

4.2.1. Impact on Conclusions

Though these studies appear to have extremely positive results, we must not only consider the limitations and effects of MDMA on the patients but the way that these trials have been designed and whether it may cause any biased results or conclusions. There are several factors to consider when evaluating the design of the studies and the way in which it might impact the validity of the conclusions drawn from them.

Firstly, most trials have been sponsored by MAPS, which presents an ethical dilemma as this organization was derived from the group of professionals that intended to pursue MDMA research before it was classified as a Category I substance. As this organization's focus is on the use of psychedelic substances in medicine, they clearly have a conflict of interests.

The fact that most of these studies have been phase 2 trials, and thus lacked diversity within the pool of subjects studied (6,8), is a factor that should be considered. Though PTSD may be developed by anyone who undergoes a stressful situation, there are certain factors which may make the development of this disorder more likely, as described in the introduction of this thesis (1.1.1. Epidemiology of PTSD). The populations observed in the phase 2 studies were limited geographically to the countries wherein the studies were conducted, and selection of participants was sometimes conducted by contacting psychiatric units, hospitals, psychiatrists, psychotherapists, and trauma counselling centres (6). The lack of diversity of the population as well as the small number of participants means that the studies lacked statistical power, only being able to detect large effects and not being enough to extrapolate to other populations (6).

MDMA-assisted psychotherapy trials have also been hindered by extenuating circumstances which could not be surpassed. These include the acquisition of MDMA being extremely difficult derived from its legal status as a Category I drug as well as licenses needed to make or use this substance being costly and very hard to receive (28). Another unsurpassable problem is the fact that these trials begun not long ago in the 2000's, meaning that the long-term follow-up in the correspondent studies is brief, namely between 1 to 3 years. The longer-term effects should be collected**Error! Bookmark not defined.**, and durability of the treatment should be 'checked' as well as continuously revising the possibility of chronic impacts. This is extremely important in order to control possible physical and biological impacts of the administration of MDMA, notably on account of the results of previous MDMA

use studies which focused on recreative users and found negative health impacts such as increased suicidality, abuse potential and cardiovascular risk (56). Most of these previous studies had many problems, including being retrospective and there being uncertainties about drug composition and polydrug use (56), however to prevent any negative side effects the health of the study participants should be monitored for longer. The fact that many of the participants in the trials had already had experiences with MDMA may also prove to be a limitation as the effect in MDMA-naïve individuals may be different (41).

Another challenge during these trials was the fact that as MDMA is a psychoactive drug, blinding was much harder to accomplish. MDMA's effects are quite extravagant when compared to other substances, and hence there was a difficulty faced in blinding both patients and researchers to which subjects were assigned to the placebo and which subjects were assigned to MDMA (6,8,37). This problem was countered by the introduction of active placebos in some studies, though the effectiveness of this precaution was not measured in these trials. The fact that the condition of each subject could be more easily guessed due to the visible effects of MDMA ingestion causes expectation bias, thus leading to a significant impact on the results of the studies and the conclusions drawn from them. Besides the difficulty in blinding researchers and subjects, one of the studies also referred an imbalance in the amount of people assigned to placebo and the active compound, further impacting the validity of the data collected (6).

As to the design of the studies, there are a few details which may have had an impact on the conclusions, making the studies criticisable. As a consequence of a crossover in some of the studies, some people assigned to the placebo had the opportunity to try MDMA-assisted psychotherapy sessions possibly causing the results of both the endpoint and long-term follow-up data to have been impacted (37). This may have led to an approximation of the values of CAPS scores of controls and active substance groups at LTFU, therefore diminishing the effect of MDMA on CAPS scores. This approximation however would most likely not be extremely significant as, like previously discussed, the MDMA seems to have peak effect after three sessions. An additional possible design flaw is the use of inadequate behavioural assessment tasks, such as static images when assessing the psychosocial impacts of MDMA, which may not be the appropriate task as it is less natural than dynamic or spontaneous facial reactions (41).

It is important to note that discrepancies exist in the conclusions of different studies, as most of the studies assessed only active substance versus placebo (active or inactive), except for one which decided to see the impact of different doses of MDMA and found that a lesser

quantity had more positive effects (37). This study showed that dose-dependent effects should be further investigated and that different doses might be adequate for different people due to their individual characteristics. This was also seen in another study where 4 participants assigned to the active compound did not demonstrate a 'sufficient' response and were assigned to Stage 3 which consisted of either more MDMA-assisted sessions or higher dose MDMA-assisted sessions. Stage 3 did not produce any significant results, meaning the three-session protocol with the previously designed dose had a larger impact and was more helpful than any of the succeeding sessions (9).

An added challenge faced is the fact that most of the people participating in these trials have a history of previous SSRI use and psychotherapy. These are confounding factors as the results may be impacted by long-term SSRI use or previous psychotherapeutic experiences, not allowing for a definite assumption of a causal relation between the decrease in CAPS scores and administration of MDMA-assisted psychotherapy sessions (8). The employment of psychotherapy sessions between MDMA-assisted sessions also makes the comparison between MDMA studies and SSRI studies difficult because, in SSRI studies, neither the active substance group nor the placebo group received any type of psychological intervention (33).

Though the previously stated challenges could have hindered the collection of reliable data, other factors such as the thorough exclusion criteria conducted in these studies might have helped the credibility of the data. These criteria included significant medical conditions, history of psychotic episodes or illness, borderline personality disorder, substance abuse/dependence within 60 days before the beginning of the trials, bipolar disorder type I, dissociative identity disorder, history of MDMA consumption of more than five times or in the 6 months before the beginning of trials. Comorbidities like eating disorders without purging, anxiety disorders and depression were allowed to be in the study, as these are commonly related to the PTSD disorder and its cause (6).

Furthermore, there is a positive and global conclusion from these trials that three MDMA-assisted psychotherapy sessions had more impact than only two sessions. This was seen across the phase 2 studies and even further reinforced by the 2013 study by Peter Oehen, et al., showed that the majority of the MDMA effects were felt between the second and third session. It also revealed that more sessions did not have a positive impact or significance on the results as some of the participants advanced to a Stage 3, where more sessions were conducted, but the data did not show any significant decrease in CAPS scores (6).

The design of the MDMA trials must also be acknowledged as a positive factor. All the MAPS scientific studies into the use of MDMA as a psychoactive support in psychotherapy have been designed since 2001, concurrently based on the designs of the sertraline and paroxetine studies. This effort is made to achieve a fair and complete comparison of all the different outcomes measured and observed during the trials (24). These designs use the already existing risk-profile assessment of MDMA in previous non-therapeutic focused trials to optimize the conditions of the therapy sessions and to prevent potentially harmful side-effects (24).

4.2.2. Improvements to Study Design

As can be inferred from the section above, though the data conclusions of the MDMA-assisted psychotherapy trials seemed to be very positive, there were several factors which may have had a significant impact on the conclusions drawn from the data. There are several ways whereupon the studies could be improved to attain more credibility and weight to their conclusions.

Some easy improvements to implement would be to encourage other entities to pursue research in the MDMA-assisted psychotherapy field, particularly organizations which do not have an economical interest and may approach the research more objectively. Adding to this there should be an increase in the number of trials, with different populations and doses. The trials could help ascertain whether effect of this treatment is universal in all patients with PTSD or whether there are populations, be it defined by prior experiences, sex, race, or biological factors, that differ in their response. These factors, along with the different subtypes of PTSD identified in previous trials (8) should be further investigated and more Phase 3 trials should be conducted, as well as considering the beginning of Phase 4 trials. Other investigations should be conducted to better understand the mechanism that makes psychotherapy effective in the treatment of PTSD and any other ways we might be able to enhance it, either with psychological, technological, or biological tools**Error! Bookmark not defined.**. It is also important to reinforce that all trials conducted from now on would benefit from following up for longer follow-up periods of MDMA administration and durability of treatment.

As a compound with a possible positive impact in Medicine, another possible improvement, one which might help encourage other professionals to pursue research in this field, would be to make pure medical grade MDMA easier to access. While doing so, protocols

to ensure the right usage of this compound should also be created, making sure all laws are abided and no legal issues are created.

Regarding design alterations with the purpose of improving the validity of the data, several alterations could be made. To account for the fact that most patients diagnosed with PTSD have already been subjected to pharmacotherapy and psychotherapy, and to ensure fair comparisons, a comparison only between people who have had similar, or the same previous treatment should be made. Also, investigating whether the MDMA-assisted psychotherapy is useful at any stage of the disease and including patients who have not had any exposure to the pharmaceutical treatment or previous psychotherapy could be a relevant step forward in the investigation of MDMA's medical usefulness.

Delving deeper into the issue of blinding raters and patients as to their condition, this was approached by the introduction of an active placebo, an approached that proved to be complicated by the fact that each person may respond optimally to a different dose of MDMA. To solve this problem studies about the relative impact of MDMA in different populations should be conducted and a system of designating the dose administered according to personal characteristics should be attempted. As to the blinding of the raters, due to the psychoactive nature of the compound it would be extremely hard to totally blind evaluators, however the continuation of an active placebo may prove to be the best solution. By randomly assigning the patient assessments to blinded raters coming from one centralized pool, we will be assuring maximum impartiality (8).

The introduction of crossovers in the studies also proved to be a disadvantage in terms of data as the placebo or active placebo data was 'contaminated'. This problem can easily be fixed by restricting crossovers in further studies. Though this might be somewhat debatable, as the people assigned to placebo may not have the same magnitude of effects on their CAPS scores, and hence symptomology, as people assigned to the active substance, it is needed to confirm the efficacy of the treatment. Other improvements include the adaptation of tasks performed during the influence of MDMA and making sure they are as dynamic or natural as they can be, for example with the inclusion of emotional interpretation of videos rather than photos.

Additionally, it is necessary to introduce different doses of MDMA into these trials as dose-dependent effects and efficacy have not yet been properly studied. The introduction of different or adjusted doses should be considered and implemented, all while making sure the safety conditions are maintained for each test subject. The analysis of this data will help

further understand not only the impact of different doses on the human body but also recognize which, if any, physical or biological characteristics can affect the dose needed for full effect. Defining which doses are appropriate for each population as well as finetuning counterindications of MDMA administration is extremely important in the advancement of this research and the possibility to institute MDMA-assisted therapy as a PTSD treatment.

4.3. Own Analysis Limitations

As all studies or revisions, there are limitations to the thesis conducted. This review had several limitations, be them methodological or circumstantial. These limitations may have had an impact on the conclusions drawn, and certainly there are a lot of improvements that could be made to achieve a more impartial perspective.

Firstly, there was a limited number of articles and data that could be analysed as there was the impossibility to access certain articles due to their access fee, making it unfeasible to include every article due to the financial burdens. Also, particularly in the case of clinical trials, very few exist as the research into this topic is novel. A better review of this topic should be conducted once more studies and clinical trials, ideally phase IV, are developed and published to make sure all the results are applicable to a larger world population and no significant side effects are caused.

A particularly significant limitation on this analysis is the fact that the method of data collection could have been improved, including more specific eligibility criteria, and following harsher exclusion criteria, making this review much more superficial and broader, rather than applied to a specific population. The use of systematic revision criteria would also improve the conclusion drawn since a more rigorous process would allow for further dissipation of the effect of biases.

It must also be mentioned that, thanks to the relatively new nature of this line of investigation, there may be a lot of confounding factors that have not been identified and might be skewing the data. These confounding factors may include different types of PTSD, the fact that everyone in the trials benefit from non-pharmaceutical psychotherapy, in between other problems described above. These factors require further investigation to get answers as to their role in way MDMA does or does not help to boost psychotherapy results in PTSD patients.

As stated previously, this thesis and analysis had several limitations which could be further improved or worked upon. However, due to the information available at this time, the

type of research conducted and the overall goal to showcase the available results of MDMA-assisted psychotherapy with the objective of drawing a conclusion from them was achieved.

Considering that many improvements could be made to the collection of the data regarding this topic, most of the articles used were from reputable sources, met several inclusion criteria which assured that the data was the most trustworthy it could be, and were published within the last 5 years, making most of the data available very dependable and the most accurate found to the date. The assumption of the validity of the data and articles described in this thesis can be made, and so it can be concluded that this thesis presents valid and accurate information which exhibits the reality of MDMA-assisted psychotherapy.

Overall, within the framework and design of this thesis, it can be stated that this analysis conforms to several veracity criteria and hence, conclusions from this thesis may be considered credible and fair.

4.4. Future Studies

Future studies following in this theme should include research on the long-term impact of MDMA administration, the quantification of psychotherapy intervention in CAPS scores of PTSD patients, comparative studies of the combination of MDMA and psychotherapy and SSRI use and psychotherapy, and finally the further confirmation of the dose-dependent effects of MDMA as well as an algorithm for the correct dose of each patient.

CHAPTER 5: CONCLUSION

5.1. Future Use of MDMA in addition to Psychotherapy

MDMA-assisted psychotherapy is a different therapeutic model in that we are using its chemical properties to induce a mental state in which psychotherapeutic interventions become more significant and impactful.

With the information presented previously and gathered from the several trials for MDMA-assisted therapy it can be concluded that there is evidence to attest the fact that MDMA may be a good alternative treatment when compared to the traditional pharmacotherapy. Even so, all negative impacts of MDMA use or possible safety concerns must be addressed and prepared for, including conducting further physiological tests on trial subjects exposed to MDMA to ascertain long-term impacts of MDMA use.

All the findings examined in the previous chapters are extremely important as the intended use of MDMA would be as an enhancer of psychotherapy, which has thus far proven to be the most effective treatment for PTSD, rather than traditional pharmacotherapy. The augmentation of openness and the decrease of neuroticism allows the psychotherapy to not only go more smoothly but also for the patients to more easily approach memories and situations that, in another state, would most likely be triggering. This triggering effect could potentially hinder their ability to process and integrate new insights, as they would be dealing with physical and mental symptoms that would require their full attention to control, undermining the effect of standalone psychotherapy. The results demonstrate that MDMA allows for a prolonged effect on personality which allows the psychotherapy to be more effective and less painful for the patients, therefore improving results and reducing CAPS scores**Error! Bookmark not defined.**.

The introduction of MDMA-assisted psychotherapy, particularly in patients with high CAPS scores and a resistance to pharmacotherapy, seems to be a solid investment for the improvement of mental health worldwide. Though this therapy may have some problems in its implementation in different countries and health systems, justified by the conflicting idea of MDMA use with societal norms and prejudices, it appears to be a promising therapy which may revolutionize mental health treatments of PTSD.

This therapy also presents a unique economic opportunity, both in the sense that it is an untapped market and advancements in such a field might lead to profitable enterprises, since this treatment improves upon the disadvantages of others currently available. It also

enables economic gains from the improvement of workers' mental health and maximization of their productivity. According to the projection presented in Marseille et al. (2022), the decrease in premature deaths and QALYs would allow for people affected by this disease to achieve more in all areas of their lives, including contributing to global economy, but not limited to it (5).

Besides the improved resolution of PTSD symptoms, might have an even bigger effect on the patients' health, by additionally addressing other psychiatric comorbidities that might coexist. Psychotherapy is one of few treatments recognized to aid in many psychopathologies thanks to its capacity to modulate cognitive processes that perpetuate psychiatric illnesses and lead to their exacerbation. By amplifying the impact of this technique with the use of MDMA, its usefulness increases in the discipline of medicine, targeting more population and possibly allowing for the treatment of other psychiatric diseases. This major positive impact on the populations' mental health and productivity makes it an even more enticing treatment to establish as future solution.

In conclusion, the exploration of MDMA-assisted psychotherapy not only offers a promising alternative to conventional pharmacotherapy but also provides a starting point in the mitigation of the adverse effects of psychiatric medications. By pushing the boundaries and testing new hypothesis, we give rise to new discoveries which might make the world a better and healthier place, particularly in such an upcoming subject as mental health.

CHAPTER 6: APPENDIX

Appendix 1 – Clinical Criteria for the Diagnosis of PTSDError! Bookmark not defined.

The following criteria apply to adults, adolescents, and children older than 6 years. For children 6 years and younger, see corresponding criteria below.

A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:
   1. Directly experiencing the traumatic event(s).
   2. Witnessing, in person, the event(s) as it occurred to others.
   3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
   4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains: police officers repeatedly exposed to details of child abuse).

   Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
   1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).

      Note: In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.
   2. Recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s).

      Note: In children, there may be frightening dreams without recognizable content.
   3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)

      Note: In children, trauma-specific reenactment may occur in play.
   4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
   5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).

C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
    a. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
    b. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
    a. Inability to remember an important aspect of the traumatic event(s) (typically due to dis sociative amnesia and not to other factors such as head injury, alcohol, or drugs).
    b. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," 'The world is completely dangerous," "My whole nervous system is permanently ruined").
    c. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
    d. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
    e. Markedly diminished interest or participation in significant activities. 6. Feelings of detachment or estrangement from others.
    f. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings).
E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
    a. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
    b. Reckless or self-destructive behavior.
    c. Hypervigilance.
    d. Exaggerated startle response.
    e. Problems with concentration.
    f. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).
F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.
G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.

Specify whether:

With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

1. Depersonalization: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).

2. Derealization: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if:

With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate).

Appendix 2 – Neurobiology of PTSD

Dual Pathology Model

There are two models which intend to explain the neurophysiological changes that occur in PTSD, as well as many other psychiatric diseases, the dual pathology model and the triple network model.

According to the dual pathology model, there are two proposed mechanisms for the biological pathophysiology of PTSD:

- Amino Acid-Based mechanism related to the "glutamate dysregulation and excitotoxicity" and more associated with loss of synaptic power.
- Monoamine-Based mechanism related to the "disruption in catecholamine" theory, accounting for the gain in synapses in other brain areas such as the amygdala and striatum, as well as the hypertrophy of grey matter.

It is thought that depending on the stressor or trigger, the biological characteristics of each PTSD patient will fall into one of these 2 categories. The identification of the subtype present in each patient may then be used as a guideline for pharmaceutical therapeutics as one subtype may react favourably to a certain drug while the other might not react at all.

It is also postulated that an initial monoamine related pathology may worsen the quantity of stress, therefore leading to an amino acid related pathology, hence the possibility of the presence of both or simply one of the subtypes in one person. This is also relevant in explaining the differences observed in the studies of the amygdala in PTSD patients, as different findings may be related to the time course of the disease and its progression[1].

Triple Network Model

Another model which intends to explain the pathophysiology of PTSD is the "triple network model", which identifies three synaptic networks, each with their own particular purpose.

The impact of the loss of synaptic connections in each of these networks, leads to the different parts of the symptomology of PTSD. The three networks are:

- Default mode network – which comprises the "posterior cingulate cortex, medial PFC, and medial temporal lobe including the hippocampus", has an

[1] The Neurobiology and Pharmacotherapy of Posttraumatic Stress Disorder (PTSD)

autobiographical and introspective function and when preserved is more active in states of rest and hypoactive during goal-specific tasks.

- Central executive network – which comprises the dlPFC, mediates goal-oriented actions as well as regulation of emotions, and when preserved is more active during completion of goal-oriented tasks and hypoactive at rest.
- Salience network – which comprises the "insula, dorsal anterior cingulate cortex, and possibly the amygdala", whose function is to alternate between the two previously mentioned networks depending on the task at hand.

The loss of synapses in each of these networks has pathological consequences correlated with symptoms experienced by PTSD patients:

- The hypoactivity of the default mode network is related to dissociative and avoidance symptoms.
- The lack of connectivity in the central executive network is related to a lesser extent of emotional control and inability to distinguish between threatening or fearful situations and non-threatening or fear-inducing situations.
- The loss of function of the salience network is thought to have a negative impact in the capacity of choice between the other two networks, resulting in wrong activation of the networks, hypervigilance, and low tolerance for alteration between networks[1].

References

1. American Psychiatric Association [Internet]. 2022. What is Posttraumatic Stress Disorder (PTSD)?
2. American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders : DSM-5. 5th ed. American Psychiatric Association, editor. American Psychiatric Association; 2013. 271–273 p.
3. Sessa B. MDMA and PTSD treatment: "PTSD: From novel pathophysiology to innovative therapeutics." Neurosci Lett. 2017 May 10;649:176–80.
4. Wagner MT, Mithoefer MC, Mithoefer AT, MacAulay RK, Jerome L, Yazar-Klosinski B, et al. Therapeutic effect of increased openness: Investigating mechanism of action in MDMA-assisted psychotherapy. Journal of Psychopharmacology. 2017 Aug 1;31(8):967–74.
5. Marseille E, Mitchell JM, Kahn JG. Updated cost-effectiveness of MDMA-assisted therapy for the treatment of posttraumatic stress disorder in the United States: Findings from a phase 3 trial. PLoS One. 2022 Feb 1;17(2 February).
6. Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (±3,4- Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). Journal of Psychopharmacology. 2013 Jan;27(1):40–52.
7. Abdallah CG, Averill LA, Akiki TJ, Raza M, Averill CL, Gomaa H, et al. The Neurobiology and Pharmacotherapy of Posttraumatic Stress Disorder (PTSD). Annu Rev Pharmacol Toxicol. 2019 Jan 19;59:171–89.
8. Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat Med. 2021 Jun 1;27(6):1025–33.
9. Feduccia AA, Mithoefer MC. MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms? Prog Neuropsychopharmacol Biol Psychiatry. 2018 Jun 8;84:221–8.
10. Bryant RA. A critical review of mechanisms of adaptation to trauma: Implications for early interventions for posttraumatic stress disorder. Clin Psychol Rev. 2021 Apr 1;85.
11. LoSavio ST, Dillon KH, Resick PA. Cognitive factors in the development, maintenance, and treatment of post-traumatic stress disorder. Curr Opin Psychol. 2017 Apr 1;14:18–22.
12. Mitchell MA, Contractor AA, Dranger P, Shea MT. Unique relations between counterfactual thinking and DSM–5 PTSD symptom clusters. Psychol Trauma. 2016 May;8(3):293–300.
13. American Psychiatric Association. Treating Patients with Acute Stress Disorder and Post Stress Disorder - A Quick Reference Guide [Internet]. Available from: http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm.
14. Lewis C, Roberts NP, Andrew M, Starling E, Bisson JI. Psychological therapies for post-traumatic stress disorder in adults: systematic review and meta-analysis. Eur J Psychotraumatol. 2020 Dec 31;11(1).
15. Cusack K, Jonas DE, Forneris CA, Wines C, Sonis J, Middleton JC, et al. Psychological treatments for adults with posttraumatic stress disorder: A systematic review and meta-analysis. Clin Psychol Rev. 2016 Feb 1;43:128–41.
16. Krystal JH, Davis LL, Neylan TC, A. Raskind M, Schnurr PP, Stein MB, et al. It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group. Biol Psychiatry. 2017 Oct 1;82(7):e51–9.
17. Mithoefer MC, Grob CS, Brewerton TD. Novel psychopharmacological therapies for psychiatric disorders: Psilocybin and MDMA. Lancet Psychiatry. 2016 May 1;3(5):481–8.

18. Abdallah CG, Averill LA, Collins KA, Geha P, Schwartz J, Averill C, et al. Ketamine Treatment and Global Brain Connectivity in Major Depression. Neuropsychopharmacology. 2017 May 8;42(6):1210–9.
19. Abdallah CG, Averill CL, Salas R, Averill LA, Baldwin PR, Krystal JH, et al. Prefrontal Connectivity and Glutamate Transmission: Relevance to Depression Pathophysiology and Ketamine Treatment. Biol Psychiatry Cogn Neurosci Neuroimaging. 2017 Oct;2(7):566–74.
20. Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, et al. Glutamate N-methyl-D-aspartate Receptor Antagonists Rapidly Reverse Behavioral and Synaptic Deficits Caused by Chronic Stress Exposure. Biol Psychiatry. 2011 Apr;69(8):754–61.
21. Abdallah CG, Jackowski A, Salas R, Gupta S, Sato JR, Mao X, et al. The Nucleus Accumbens and Ketamine Treatment in Major Depressive Disorder. Neuropsychopharmacology. 2017 Jul 8;42(8):1739–46.
22. Melo A, Kokras N, Dalla C, Ferreira C, Ventura-Silva AP, Sousa N, et al. The positive effect on ketamine as a priming adjuvant in antidepressant treatment. Transl Psychiatry. 2015 May 26;5(5):e573–e573.
23. The Little Book Psychedelic Substances. Psychedelic Support; 2022.
24. Doblin R. A Clinical plan for MDMA (Ecstasy) in the treatment of posttraumatic stress disorder (PTSD): Partnering with the FDA. J Psychoactive Drugs. 2002 Jun;34(2):185–94.
25. Reiff CM, Richman EE, Nemeroff CB, Carpenter LL, Widge AS, Rodriguez CI, et al. Psychedelics and psychedelic-assisted psychotherapy. American Journal of Psychiatry. 2020 May 1;177(5):391–410.
26. de Gregorio D, Aguilar-Valles A, Preller KH, Heifets BD, Hibicke M, Mitchell J, et al. Hallucinogens in mental health: Preclinical and clinical studies on LSD, psilocybin, MDMA, and ketamine. In: Journal of Neuroscience. Society for Neuroscience; 2021. p. 891–900.
27. Figueiredo IC, Corvacho M, Mota P. Psicadélicos em Saúde Mental. 2nd ed. Lisboa: LIDEL; 2023.
28. Passie T. The early use of MDMA ('Ecstasy') in psychotherapy (1977–1985). Drug Sci Policy Law. 2018 Jan;4:205032451876744.
29. DEA. United States Drug Enforcement Administration. 2018. Drug Scheduling.
30. Williams T, Phillips NJ, Stein DJ, Ipser JC. Pharmacotherapy for post traumatic stress disorder (PTSD). Vol. 2022, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2022.
31. Koek RJ, Schwartz HN, Scully S, Langevin JP, Spangler S, Korotinsky A, et al. Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future. Prog Neuropsychopharmacol Biol Psychiatry. 2016;70:170–218.
32. National Health Service - UK [Internet]. 2022. Treatment - Post-traumatic stress disorder.
33. Feduccia AA, Jerome L, Yazar-Klosinski B, Emerson A, Mithoefer MC, Doblin R. Breakthrough for trauma treatment: Safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and sertraline. Front Psychiatry. 2019 Sep 1;10(SEP).
34. Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, Hoge CW. PSYCHOTHERAPY VERSUS PHARMACOTHERAPY FOR POSTTRAUMATIC STRESS DISORDER: SYSTEMIC REVIEW AND META-ANALYSES TO DETERMINE FIRST-LINE TREATMENTS. Depress Anxiety. 2016 Sep;33(9):792–806.
35. Flory JD, Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: Alternative explanations and treatment considerations. Dialogues Clin Neurosci. 2015;17(2):141–50.
36. Lutyens D. Journey to the Centre of the Mind: Psychedelic Treatment of Mental Health in Aotearoa. [Te Herenga Waka]: University of Wellington; 2023.

37. Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, Wymer J, et al. 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. Lancet Psychiatry. 2018 Jun 1;5(6):486–97.
38. Baggott MJ, Coyle JR, Siegrist JD, Garrison KJ, Galloway GP, Mendelson JE. Effects of 3,4-methylenedioxymethamphetamine on socioemotional feelings, authenticity, and autobiographical disclosure in healthy volunteers in a controlled setting. Journal of Psychopharmacology. 2016 Apr 1;30(4):378–87.
39. Ogden P, Pain C, Fisher J. A Sensorimotor Approach to the Treatment of Trauma and Dissociation. Psychiatric Clinics of North America. 2006 Mar;29(1):263–79.
40. Lau F, Kuziemsky C. Handbook of eHealth Evaluation: An Evidence-based Approach EDITED BY. Victoria; 2016.
41. Bedi G, Hyman D, De Wit H. Is ecstasy an "empathogen"? Effects of ±3,4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. Biol Psychiatry. 2010 Dec 15;68(12):1134–40.
42. Goldman BM, Kernis MH. The role of authenticity in healthy psychological functioning and subjective well-being. 2002; Available from: https://www.researchgate.net/publication/251802973
43. Rogers CR. On Becoming a Person A Therapist's View of Psychotherapy. 1969.
44. Sheldon KM, Ryan RM, Rawsthorne LJ, Ilardi B. Trait self and true self: Cross-role variation in the big-five personality traits and its relations with psychological authenticity and subjective well-being. J Pers Soc Psychol. 1997 Dec;73(6):1380–93.
45. Wolfson PE, Andries J, Feduccia AA, Jerome L, Wang JB, Williams E, et al. MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: a randomized pilot study. Sci Rep. 2020 Dec 1;10(1).
46. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories IA and II in Psychiatric Outpatients. J Pers Assess. 1996;67(3):588–97.
47. Beck AT, Steer RA. Internal consistencies of the original and revised beck depression inventory. J Clin Psychol. 1984 Nov;40(6):1365–7.
48. Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res. 1989 May;28(2):193–2013.
49. Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining Anchor and Distribution-Based Methods to Derive Minimal Clinically Important Differences on the Functional Assessment of Cancer Therapy (FACT) Anemia and Fatigue Scales. J Pain Symptom Manage. 2002 Dec;24(6):547–61.
50. Cella D, Nowinski CJ. Measuring quality of life in chronic illness: The functional assessment of chronic illness therapy measurement system. Arch Phys Med Rehabil. 2002 Dec;83(2):S10–7.
51. Montgomery SA, Åsberg M. A New Depression Scale Designed to be Sensitive to Change. British Journal of Psychiatry. 1979 Apr 29;134(4):382–9.
52. Mitchell JM, Ot'alora G M, van der Kolk B, Shannon S, Bogenschutz M, Gelfand Y, et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. Nat Med. 2023 Oct 1;29(10):2473–80.
53. Nardou R, Lewis EM, Rothhaas R, Xu R, Yang A, Boyden E, et al. Oxytocin-dependent reopening of a social reward learning critical period with MDMA. Nature. 2019 May 3;569(7754):116–20.
54. Sharma SR, Gonda X, Dome P, Tarazi FI. What's Love Got to do with it: Role of oxytocin in trauma, attachment and resilience. Pharmacol Ther. 2020 Oct 1;214.
55. Doblin R, Greer G, Holland J, Jerome L, Mithoefer MC, Sessa B. A reconsideration and response to Parrott AC (2013) "human psychobiology of MDMA or 'Ecstasy': An overview of 25 years of empirical research." Hum Psychopharmacol. 2014 Dec 17;29(2):105–8.

56. Parrott AC. Human psychobiology of MDMA or “Ecstasy”: An overview of 25 years of empirical research. Hum Psychopharmacol. 2013 Jul;28(4):289–307.
57. Koenen KC, Ratanatharathorn A, Ng L, McLaughlin KA, Bromet EJ, Stein DJ, et al. Posttraumatic stress disorder in the World Mental Health Surveys. Psychol Med. 2017 Oct 1;47(13):2260–74.
58. Morgan L. MDMA-assisted psychotherapy for people diagnosed with treatment-resistant PTSD: What it is and what it isn’t. Ann Gen Psychiatry. 2020 May 12;19(1).

Bibliography

1.Nardou R, Lewis EM, Rothhaas R, Xu R, Yang A, Boyden E, et al. Oxytocin-dependent reopening of a social reward learning critical period with MDMA. Nature. 2019 May 3;569(7754):116–20.

2.Ogden P, Pain C, Fisher J. A Sensorimotor Approach to the Treatment of Trauma and Dissociation. Psychiatric Clinics of North America. 2006 Mar;29(1):263–79.

3.Lee DJ, Schnitzlein CW, Wolf JP, Vythilingam M, Rasmusson AM, Hoge CW. PSYCHOTHERAPY VERSUS PHARMACOTHERAPY FOR POSTTRAUMATIC STRESS DISORDER: SYSTEMIC REVIEW AND META-ANALYSES TO DETERMINE FIRST-LINE TREATMENTS. Depression and Anxiety. 2016 Sep;33(9):792–806.

4.Figueiredo IC, Corvacho M, Mota P. Psicadélicos em Saúde Mental. 2nd ed. Lisboa: LIDEL; 2023.

5.Abdallah CG, Averill LA, Collins KA, Geha P, Schwartz J, Averill C, et al. Ketamine Treatment and Global Brain Connectivity in Major Depression. Neuropsychopharmacology. 2017 May 8;42(6):1210–9.

6.Abdallah CG, Averill CL, Salas R, Averill LA, Baldwin PR, Krystal JH, et al. Prefrontal Connectivity and Glutamate Transmission: Relevance to Depression Pathophysiology and Ketamine Treatment. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2017 Oct;2(7):566–74.

7.Li N, Liu RJ, Dwyer JM, Banasr M, Lee B, Son H, et al. Glutamate N-methyl-D-aspartate Receptor Antagonists Rapidly Reverse Behavioral and Synaptic Deficits Caused by Chronic Stress Exposure. Biological Psychiatry. 2011 Apr;69(8):754–61.

8.Abdallah CG, Jackowski A, Salas R, Gupta S, Sato JR, Mao X, et al. The Nucleus Accumbens and Ketamine Treatment in Major Depressive Disorder. Neuropsychopharmacology. 2017 Jul 8;42(8):1739–46.

9.Melo A, Kokras N, Dalla C, Ferreira C, Ventura-Silva AP, Sousa N, et al. The positive effect on ketamine as a priming adjuvant in antidepressant treatment. Translational Psychiatry. 2015 May 26;5(5):e573–e573.

10.Mitchell MA, Contractor AA, Dranger P, Shea MT. Unique relations between counterfactual thinking and DSM–5 PTSD symptom clusters. Psychological Trauma: Theory, Research, Practice, and Policy. 2016 May;8(3):293–300.

11.National Health Service - UK [Internet]. 2022. Treatment - Post-traumatic stress disorder.

12.DEA. United States Drug Enforcement Administration. 2018. Drug Scheduling.

13.PTSD UK [Internet]. OCD and PTSD – and the relationship between the two.

14.American Psychiatric Association [Internet]. 2022. What is Posttraumatic Stress Disorder (PTSD)?

15.Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories IA and II in Psychiatric Outpatients. Journal of Personality Assessment. 1996;67(3):588–97.

16.Montgomery SA, Åsberg M. A New Depression Scale Designed to be Sensitive to Change. British Journal of Psychiatry. 1979 Apr 29;134(4):382–9.

17.Cella D, Nowinski CJ. Measuring quality of life in chronic illness: The functional assessment of chronic illness therapy measurement system. Archives of Physical Medicine and Rehabilitation. 2002 Dec;83(2):S10–7.

18.Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Research. 1989 May;28(2):193–2013.

19.Beck AT, Steer RA. Internal consistencies of the original and revised beck depression inventory. Journal of Clinical Psychology. 1984 Nov;40(6):1365–7.

20.Rogers CR. On Becoming a Person A Therapist's View of Psychotherapy. 1969.

21.Sheldon KM, Ryan RM, Rawsthorne LJ, Ilardi B. Trait self and true self: Cross-role variation in the big-five personality traits and its relations with psychological authenticity and subjective well-being. Journal of Personality and Social Psychology. 1997 Dec;73(6):1380–93.

22.Cella D, Eton DT, Lai JS, Peterman AH, Merkel DE. Combining Anchor and Distribution-Based Methods to Derive Minimal Clinically Important Differences on the Functional Assessment of Cancer Therapy (FACT) Anemia and Fatigue Scales. Journal of Pain and Symptom Management. 2002 Dec;24(6):547–61.

23.Goldman BM, Kernis MH. The role of authenticity in healthy psychological functioning and subjective well-being. 2002; Available from: https://www.researchgate.net/publication/251802973

24.Alfardan S, Rose J, Siddig M, Yousif A. Psychedelics for post-traumatic stress disorder: A systematic review and meta-analysis. International Journal of Emergency Mental Health and Human Resilience [Internet]. 2023 Jun;25(3):56–66. Available from: https://www.researchgate.net/publication/371733451

25.Singewald N, Sartori SB, Reif A, Holmes A. Alleviating anxiety and taming trauma: Novel pharmacotherapeutics for anxiety disorders and posttraumatic stress disorder. Neuropharmacology. 2023 Mar 15;226.

26.Saeed SA, Majarwitz DJ, Santos melody G. Treating PTSD: A review of 8 studies. Current Psychiatry. 2023 Jan;22(1).

27.van der Kolk BA, Wang JB, Yehuda R, Bedrosian L, Cooker A, Charlotte ;, et al. Self-experience in MDMA assisted therapy of PTSD [Internet]. 2022 Oct. Available from: https://doi.org/10.1101/2023.01.03.23284143

28.Tedesco S, Gajaram G, Chida S, Ahmad A, Pentak M, Kelada M, et al. The Efficacy of MDMA (3,4-Methylenedioxymethamphetamine) for Post-traumatic Stress Disorder in Humans: A Systematic Review and Meta-Analysis. Cureus. 2021 May 17;

29.Lewis C, Roberts NP, Bethell A, Robertson L, Bisson JI. Internet-based cognitive and behavioural therapies for posttraumatic stress disorder (PTSD) in adults. Cochrane Database of Systematic Reviews. 2018 Dec 14;2018(12).

30.Lewis C, Roberts NP, Andrew M, Starling E, Bisson JI. Psychological therapies for post-traumatic stress disorder in adults: systematic review and meta-analysis. European Journal of Psychotraumatology. 2020 Dec 31;11(1).

31.Varker T, Watson L, Gibson K, Forbes D, O'Donnell ML. Efficacy of Psychoactive Drugs for the Treatment of Posttraumatic Stress Disorder: A Systematic Review of MDMA, Ketamine, LSD and Psilocybin. Journal of Psychoactive Drugs. 2021;53(1):85–95.

32.Yatham S, Sivathasan S, Yoon R, da Silva TL, Ravindran A v. Depression, anxiety, and post-traumatic stress disorder among youth in low and middle income countries: A review of prevalence and treatment interventions. Asian Journal of Psychiatry. 2018 Dec 1;38:78–91.

33.Koopowitz SM, Maré KT, Zar HJ, Stein DJ, Ipser JC. The neurocognitive profile of post-traumatic stress disorder (PTSD), major depressive disorder (MDD), and PTSD with comorbid MDD. Brain and Behavior. 2021 Apr 1;11(4).

34.de Bellis MD. Developmental traumatology: The psychobiological development of maltreated children and its implications for research, treatment, and policy. Development and Psychopathology. 2001;13:539–64.

35.Yang P, Wu MT, Hsu CC, Ker JH. Evidence of early neurobiological alternations in adolescents with posttraumatic stress disorder: A functional MRI study. Neuroscience Letters. 2004 Nov 3;370(1):13–8.

36.American Psychological Association. Using the APA Clinical Practice Guideline for the Treatment
of Posttraumatic Stress Disorder (PTSD) in Adults. American Psychological Association; 2021.

37.Martin A, Naunton M, Kosari S, Peterson G, Thomas J, Christenson JK. Treatment guidelines for PTSD: A systematic review. Journal of Clinical Medicine. 2021 Sep 1;10(18).

38.The Little Book Psychedelic Substances. Psychedelic Support; 2022.

39.American Psychiatric Association., American Psychiatric Association. DSM-5 Task Force. Diagnostic and statistical manual of mental disorders : DSM-5. 5th ed. American Psychiatric Association, editor. American Psychiatric Association; 2013. 271–273.

40.Bryant RA. A critical review of mechanisms of adaptation to trauma: Implications for early interventions for posttraumatic stress disorder. Clinical Psychology Review. 2021 Apr 1;85.

41.Sharma SR, Gonda X, Dome P, Tarazi FI. What's Love Got to do with it: Role of oxytocin in trauma, attachment and resilience. Pharmacology and Therapeutics. 2020 Oct 1;214.

42.Pierce ZP, Black JM. The Neurophysiology Behind Trauma-Focused Therapy Modalities Used to Treat Post-Traumatic Stress Disorder Across the Life Course: A Systematic Review. Trauma, Violence, and Abuse. 2023 Apr 1;24(2):1106–23.

43.Cusack K, Jonas DE, Forneris CA, Wines C, Sonis J, Middleton JC, et al. Psychological treatments for adults with posttraumatic stress disorder: A systematic review and meta-analysis. Clinical Psychology Review. 2016 Feb 1;43:128–41.

44.Koek RJ, Schwartz HN, Scully S, Langevin JP, Spangler S, Korotinsky A, et al. Treatment-refractory posttraumatic stress disorder (TRPTSD): a review and framework for the future. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2016;70:170–218.

45.Williams T, Phillips NJ, Stein DJ, Ipser JC. Pharmacotherapy for post traumatic stress disorder (PTSD). Vol. 2022, Cochrane Database of Systematic Reviews. John Wiley and Sons Ltd; 2022.

46.Mitchell JM, Ot'alora G M, van der Kolk B, Shannon S, Bogenschutz M, Gelfand Y, et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. Nature Medicine. 2023 Oct 1;29(10):2473–80.

47.Lau F, Kuziemsky C. Handbook of eHealth Evaluation: An Evidence-based Approach EDITED BY. Victoria; 2016.

48.Koenen KC, Ratanatharathorn A, Ng L, McLaughlin KA, Bromet EJ, Stein DJ, et al. Posttraumatic stress disorder in the World Mental Health Surveys. Psychological Medicine. 2017 Oct 1;47(13):2260–74.

49.Marseille E, Mitchell JM, Kahn JG. Updated cost-effectiveness of MDMA-assisted therapy for the treatment of posttraumatic stress disorder in the United States: Findings from a phase 3 trial. PLoS ONE. 2022 Feb 1;17(2 February).

50.Hills J. Phenomenology of MDMA Solo Sessions. [Santa Barbara]; 2023.

51.Marchetta E, Mancini GF, Morena M, Campolongo P. Enhancing Psychological Interventions for Post-Traumatic Stress Disorder (PTSD) Treatment with Memory Influencing Drugs. Current Neuropharmacology. 2022 Dec 12;21(3):687–707.

52.Bhatt MP, Guryan J, Pollack HA, Castrejon JC, Clark M, Delgado-Sanchez L, et al. Randomized evaluation of a school-based, trauma-informed group intervention for young women in Chicago. Science Advances [Internet]. 2023 Jun;9(23). Available from: https://www.science.org

53.Barber GS, Aaronson ST. The Emerging Field of Psychedelic Psychotherapy. Current Psychiatry Reports. 2022 Oct 1;24(10):583–90.

54.Lewis CR, Tafur J, Spencer S, Green JM, Harrison C, Kelmendi B, et al. Pilot study suggests DNA methylation of the glucocorticoid receptor gene (NR3C1) is associated with MDMA-assisted therapy treatment response for severe PTSD. Frontiers in Psychiatry. 2023 Feb 6;14.

55.Lutyens D. Journey to the Centre of the Mind: Psychedelic Treatment of Mental Health in Aotearoa. [Te Herenga Waka]; 2023.

56.Lamarco N. Psychedelic Support. 2023. MDMA Therapy for PTSD: MDMA therapy for PTSD could become a new treatment option for millions of people living with trauma. The

clinical evidence is growing. Available from: https://psychedelic.support/resources/mdma-therapy-for-ptsd/

57.Mulumba P. Longevity. Is Ecstasy (MDMA) The Future of Mental Health Treatments?

58.Mithoefer MC, Feduccia AA, Jerome L, Mithoefer A, Wagner M, Walsh Z, et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. Psychopharmacology. 2019 Sep 1;236(9):2735–45.

59.Clancy ME, Francisco S. Creating Greater Safety in Psychedelic-Assisted Therapy Spaces. [San Francisco]; 2023.

60.Herringa RJ. Trauma, PTSD, and the Developing Brain. Current Psychiatry Reports. 2017 Oct 1;19(10).

61.Štefánik T. Prospects of PTSD Treatment in War Veterans with Psychedelic-Assisted Psychotherapy. [Prague]; 2023.

62.de Bellis MD. Developmental traumatology: The psychobiological development of maltreated children and its implications for research, treatment, and policy. Development and Psychopathology. 2001;13:539–64.

63.Cisler JM, Herringa RJ. Posttraumatic Stress Disorder and the Developing Adolescent Brain. Biological Psychiatry. 2021 Jan 15;89(2):144–51.

64.American Psychiatric Association. Treating Patients with Acute Stress Disorder and Post Stress Disorder - A Quick Reference Guide [Internet]. Available from: http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm.

65.Kline AC, Cooper AA, Rytwinksi NK, Feeny NC. Long-term efficacy of psychotherapy for posttraumatic stress disorder: A meta-analysis of randomized controlled trials. Clinical Psychology Review. 2018 Feb 1;59:30–40.

66.Parrott AC. Human psychobiology of MDMA or “Ecstasy”: An overview of 25 years of empirical research. Human Psychopharmacology. 2013 Jul;28(4):289–307.

67.Los Santos S de. MDMA Statistics: Common Doses, Safety, & A Look At the Trends Worldwide (2022). 2023.

68.Ordem dos Médicos. Resolução sobre o uso de Psicadélicos [Internet]. 2023 Aug. Available from: https://ordemdosmedicos.pt/colegio-da-especialidade-de-psiquiatria/

69.van Vugt AS, Zijlmans J, Lindauer R, van Dam L. MDMA-assisted psychotherapy with adolescents suffering from PTSD: Do or don't? a qualitative study with youth, parents, and clinicians. Drug Science, Policy and Law. 2023 Jan;9:1–15.

70.Kangaslampi S, Zijlmans J. MDMA-assisted psychotherapy for PTSD in adolescents-rationale, potential, risks, and considerations [Internet]. 2023. Available from: https://orcid.org/0000-0002-0480-9806

71.Gorman I, Belser AB, Jerome L, Hennigan C, Shechet B, Hamilton S, et al. Posttraumatic Growth After MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder. Journal of Traumatic Stress. 2020 Apr 1;33(2):161–70.

72.Elsouri KN, Kalhori S, Colunge D, Grabarczyk G, Hanna G, Carrasco C, et al. Psychoactive Drugs in the Management of Post Traumatic Stress Disorder: A Promising New Horizon. Cureus. 2022 May 23;14(5).

73.Bedi G, Cotton SM, Guerin AA, Jackson HJ. MDMA-assisted psychotherapy for post-traumatic stress disorder: The devil is in the detail. Australian and New Zealand Journal of Psychiatry. 2023 Apr 1;57(4):476–81.

74.Wolfson PE, Andries J, Feduccia AA, Jerome L, Wang JB, Williams E, et al. MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: a randomized pilot study. Scientific Reports. 2020 Dec 1;10(1).

75.Morgan L. MDMA-assisted psychotherapy for people diagnosed with treatment-resistant PTSD: What it is and what it isn't. Annals of General Psychiatry. 2020 May 12;19(1).

76.Reiff CM, Richman EE, Nemeroff CB, Carpenter LL, Widge AS, Rodriguez CI, et al. Psychedelics and psychedelic-assisted psychotherapy. American Journal of Psychiatry. 2020 May 1;177(5):391–410.

77.Flory JD, Yehuda R. Comorbidity between post-traumatic stress disorder and major depressive disorder: Alternative explanations and treatment considerations. Dialogues in Clinical Neuroscience. 2015;17(2):141–50.

78.Abdallah CG, Averill LA, Akiki TJ, Raza M, Averill CL, Gomaa H, et al. The Neurobiology and Pharmacotherapy of Posttraumatic Stress Disorder (PTSD). Annual Review of Pharmacology and Toxicology. 2019 Jan 19;59:171–89.

79.Wagner MT, Mithoefer MC, Mithoefer AT, MacAulay RK, Jerome L, Yazar-Klosinski B, et al. Therapeutic effect of increased openness: Investigating mechanism of action in MDMA-assisted psychotherapy. Journal of Psychopharmacology. 2017 Aug 1;31(8):967–74.

80.Haycraft AL. The Future for Psychedelic Agents in the Treatment of Posttraumatic Stress Disorder. Journal for Nurse Practitioners. 2023 May 1;19(5).

81.Higgins MN. Physical Activity and Posttraumatic Outcomes Among Sexual Assault Survivors: Examining Relations Between Activity Type, PTSD, and Related Resilience-Recovery Factors Following Sexual Trauma. [Colorado Springs]; 2022.

82.Jerome L, Feduccia AA, Wang JB, Hamilton S, Yazar-Klosinski B, Emerson A, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. Psychopharmacology. 2020 Aug 1;237(8):2485–97.

83.Spann K. Efficacy and Safety Efficacy and Safety of MDMA-Assisted of MDMA-Assisted Psychotherapy Psychotherapy. 2021.

84.Hasler G. Psychotherapy and psychedelic drugs. Vol. 10, The Lancet Psychiatry. Elsevier Ltd; 2023. p. 167–8.

85.Krediet E, Bostoen T, Breeksema J, van Schagen A, Passie T, Vermetten E. Reviewing the Potential of Psychedelics for the Treatment of PTSD. International Journal of Neuropsychopharmacology. 2020 Mar 14;23(6):385–400.

86.Latimer D, Stocker MD, Sayers K, Green J, Kaye AM, Abd-Elsayed A, et al. MDMA to Treat PTSD in Adults. PsychoPharmacology Bulletin. 51(3):125.

87.Krystal JH, Davis LL, Neylan TC, A. Raskind M, Schnurr PP, Stein MB, et al. It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group. Biological Psychiatry. 2017 Oct 1;82(7):e51–9.

88.Passie T. The early use of MDMA ('Ecstasy') in psychotherapy (1977–1985). Drug Science, Policy and Law. 2018 Jan;4:205032451876744.

89.LoSavio ST, Dillon KH, Resick PA. Cognitive factors in the development, maintenance, and treatment of post-traumatic stress disorder. Current Opinion in Psychology. 2017 Apr 1;14:18–22.

90.Doblin R. A Clinical plan for MDMA (Ecstasy) in the treatment of posttraumatic stress disorder (PTSD): Partnering with the FDA. Journal of Psychoactive Drugs. 2002 Jun;34(2):185–94.

91.Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, Wymer J, et al. 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. 2018 Jun 1;5(6):486–97.

92.Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nature Medicine. 2021 Jun 1;27(6):1025–33.

93.Sessa B. MDMA and PTSD treatment: "PTSD: From novel pathophysiology to innovative therapeutics." Neuroscience Letters. 2017 May 10;649:176–80.

94.de Gregorio D, Aguilar-Valles A, Preller KH, Heifets BD, Hibicke M, Mitchell J, et al. Hallucinogens in mental health: Preclinical and clinical studies on LSD, psilocybin, MDMA, and ketamine. In: Journal of Neuroscience. Society for Neuroscience; 2021. p. 891–900.

95.Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (±3,4- Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). Journal of Psychopharmacology. 2013 Jan;27(1):40–52.

96.Feduccia AA, Jerome L, Yazar-Klosinski B, Emerson A, Mithoefer MC, Doblin R. Breakthrough for trauma treatment: Safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and sertraline. Frontiers in Psychiatry. 2019 Sep 1;10(SEP).

97.Doblin R, Greer G, Holland J, Jerome L, Mithoefer MC, Sessa B. A reconsideration and response to Parrott AC (2013) "human psychobiology of MDMA or 'Ecstasy': An overview of 25 years of empirical research." Human Psychopharmacology. 2014 Dec 17;29(2):105–8.

98.Bedi G, Hyman D, de Wit H. Is ecstasy an "empathogen"? Effects of ±3,4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. Biological Psychiatry. 2010 Dec 15;68(12):1134–40.

99.Baggott MJ, Coyle JR, Siegrist JD, Garrison KJ, Galloway GP, Mendelson JE. Effects of 3,4-methylenedioxymethamphetamine on socioemotional feelings, authenticity, and autobiographical disclosure in healthy volunteers in a controlled setting. Journal of Psychopharmacology. 2016 Apr 1;30(4):378–87.

100.Feduccia AA, Mithoefer MC. MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms? Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2018 Jun 8;84:221–8.

101.Mithoefer MC, Grob CS, Brewerton TD. Novel psychopharmacological therapies for psychiatric disorders: Psilocybin and MDMA. The Lancet Psychiatry. 2016 May 1;3(5):481–8.