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3,4-methylenedioxymethamphetamine-assisted psychotherapy for the treatment of posttraumatic stress disorder

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Thesis

3,4-METHYLENEDIOXYMETHAMPHETAMINE-ASSISTED PSYCHOTHERAPY FOR THE TREATMENT OF POSTTRAUMATIC STRESS DISORDER

by

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a debilitating and prevalent psychiatric pathology across the world and highly effective treatments for it are lacking. PTSD is characterized by frequent and intrusive memories of trauma that arise several months after experiencing or witnessing a traumatic event. These memories elicit strong emotional responses in PTSD patients and initiate many somatic and psychiatric comorbidities. Treatments for PTSD exist, but the clinical trials evaluating them have produced inconsistent results including highly variable data on effect sizes and tolerability. Recent meta-analyses on these randomized clinical studies, comparing the effects of the approved treatments on PTSD symptom severity with control groups (employing inactive placebos or intent-to-treat groups), have shown similar safety profiles and low-to-medium effects sizes. Treatments currently approved for use in PTSD include manualized, trauma-focused psychotherapies (cognitive processing therapy (CPT) and prolonged exposure therapy) and pharmacotherapies that employ selective serotonin reuptake inhibitors (SSRIs). Conclusive data comparing the efficacy and tolerability of these therapies must be derived from head-to-head comparisons in randomized clinical trials. These studies are not yet available for 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for the treatment of

PTSD; the first phase 3 clinical trial of this treatment was published in early 2021. The development, and history of the treatment is also discussed.

MDMA is a commonly used drug of abuse. In the context of its illicit use, it is often referred to as ecstasy or molly, where it is used in dance-party and music festival settings. It is a Drug Enforcement Agency (DEA) schedule I substance. The DEA scheduling of drugs under the controlled substance act is discussed to explain MDMA's legal status relative to other drugs of abuse. MDMA's legal designation has slowed research on this treatment and is therefore an important aspect of the history and development of the treatment.

In MDMA-assisted psychotherapy, MDMA is administered to the participant prior to an eight-hour manualized therapy session. In this context, "manualized" refers to the strict adherence to a protocol and methodology of psychotherapeutic treatment by the therapist. Consistent with phase 2 clinical trials, the first and only published phase 3 trial for MDMA-assisted psychotherapy has shown it to be a highly efficacious and safe treatment for PTSD. There are many common subjective psychological effects of MDMA that have been reported in the literature, but its ability to enhance sociability, self-esteem, trust in others (especially the therapist), and reduce anxiety and defensiveness during the therapy session have long been thought to be the primary benefit in therapy. These behavioral traits are characteristically impaired in trauma-related disease states, which adversely affects the therapeutic processes. Acute cessation of some PTSD symptoms due to the subjective effects of MDMA may provide a "window of tolerance", in which the patient can discuss traumatic memories without shutting down socially and mentally,

which is common in psychotherapeutic treatment for PTSD.

This thesis will also discuss MDMA pharmacology, chemistry, its role as a drug of abuse, and some of its molecular mechanisms of action that may confer its psychiatric subjective effects that have been reported in humans. Early studies on the toxicity of MDMA indicated adverse public health implications due to safety concerns and largely led to this designation of the molecule as a schedule I material. Further research has brought the validity of this early research into question, although serotonergic neurotoxicity seems to be the most prevalent. In short, single-dose MDMA administration in normal dosing ranges of MDMA used in illicit contexts has been shown to elicit some of the same histological and cellular changes produced by long-term SSRI use, further calling the toxicity of MDMA into question.

An overview of PTSD will follow this discussion on MDMA. Specifically, this section will discuss the pathology, symptoms, diagnosis, comorbidities, risk factors, and the underlying neurobiology of PTSD and stress-related disease states. Resilience is an important feature of PTSD risk; more resilient people tend to develop PTSD less frequently upon exposure to trauma. Resilience is correlated with one's capacity for regulating his or her own emotions, which is characteristically impaired in stress-related disease states and strongly contributes to many of the symptoms involved in this pathology. Understanding resilience and emotional regulation, their neurological basis, and role in PTSD pathology is therefore important for understanding these aspects of the disease state and are discussed thoroughly. The information presented in the MDMA and PTSD sections will then be discussed together in the following section on MDMA-

assisted psychotherapy as it relates to the treatment and its proposed therapeutic mechanisms of action.

The treatment methods in the stage 2 and 3 clinical trials of MDMA-assisted psychotherapy for PTSD are discussed and compared, the major focus of this section, however, will be the methods used in the first phase 3 clinical trial, as well as the results and limitations of this study. In short, the first stage 3 trial for the treatment showed a significantly improved efficacy in treating PTSD and its comorbid psychiatric pathologies as compared to both the current FDA-approved pharmaceutical and psychotherapeutic treatments for PTSD.

Three main mechanisms of action that may account for the efficacy of MDMA-assisted psychotherapy for PTSD treatment have been discussed in the literature. These are not necessarily mutually exclusive and may all partly explain the treatment effects. These include the "window of tolerance" mechanism discussed above, the critical-period reopening mechanism, and the fear extinction facilitation mechanism.

MDMA-assisted psychotherapy is a novel and creative approach to treating psychiatric pathologies. It is also the first treatment regime approved for investigation by the US Food and Drug Administration (FDA) in which a psychedelic or psychedelic-like agent is employed therapeutically or in which a psychoactive agent is employed alongside psychotherapeutic treatments. Other clinical trials of drug-assisted psychotherapy treatments using similar methods while employing different psychoactive drugs for the treatment of many psychiatric diseases are currently ongoing, MDMA-assisted psychotherapy has been the first of this novel method of therapy to be stringently

studied under modern scientific randomized, placebo-controlled clinical is now being investigated for applications in other psychiatric pathologies. Further research into this treatment is critical for finding new ways for improving the treatment protocol, therefore improving treatment efficacy and safety. Such research will include addressing the limitations of the first published phase 3 clinical trial, investigating the mechanisms of action by which the treatment works, and conducting clinical trials in larger or more specific populations.

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LIST OF ABBREVIATIONS

ACC ..... Anterior Cingulate Cortex

BDI-II ..... Beck Depression Inventory II

CAPS-5 ..... Clinician-Administered PTSD Scale for DSM-V

CNS ..... Central Nervous System

CPT ..... Cognitive Processing Therapy

CYP ..... Cytochrome P450

DEA ..... Drug Enforcement Agency

DSM-V ..... *Diagnostic and Statistical Manual of Mental Disorders*-fifth edition

FDA ..... Food and Drug Administration

fMRI ..... Functional Magnetic Resonance Imaging

HHMA 3,4-Dihydroxymethamphetamine

HMMA 4-Hydroxy-3-Methoxymethamphetamine

LSD ..... Lysergic Acid Diethylamide

MAO ..... Monoamine Oxidase

MAPS ..... Multidisciplinary Association for Psychedelic Studies

MAT ..... Monoamine Transporter

MDA 3,4-Methylenedioxyamphetamine

MDMA 3,4-Methylenedioxymethamphetamine

NE ..... Norepinephrine

PFC ..... Prefrontal Cortex

PTSD ..... Posttraumatic Stress Disorder

SD ..... Standard Deviation

SDS ..... Sheehan Disability Scale

SEM ..... Standard Error of the Mean

SMD ..... Standardized Mean Deviation

SSRI ..... Selective Serotonin Reuptake Inhibitor

VMAT ..... Vesicular Monoamine Transporter

INTRODUCTION

PTSD affects about 8% of the US population and 4% of the global population across their lifetime; women develop PTSD at rates twice that of men (Koenen et al. 2017). Moreover, 10-13% of US veterans that have seen combat develop PTSD and as many as 4.7 million US armed forces veterans report service-related disabilities that cost the government an estimated $73 billion each year (Mitchell et al. 2021). The *Diagnostic and Statistical Manual of Mental Disorders*-fifth edition (DSM-V) characterizes the disease as a trauma- or stress-related disorder with symptoms that arise following exposure to or experiencing a traumatic event or events. Such events may include physical- or noncontact-sexual assault, natural disasters, physical assault, exposure to combat as a civilian or combatant, childhood neglect, and acute medical catastrophes or injuries including severe hemorrhage or anaphylactic shock (APA 2013). Many psychiatric and somatic comorbidities arise due to PTSD, and effective treatments for it are lacking. It follows that PTSD is an economic and social burden for which novel treatments are desperately needed (Steenkamp et al. 2015). As indicated by phase 3 clinical trials, MDMA-assisted psychotherapy, in which MDMA is administered prior to a trauma-focused psychotherapy session, appears to be a strong candidate as a novel and effective treatment for PTSD (Mitchell et al. 2021, MAPS 2023).

This thesis will cover the unique history of MDMA- and drug-assisted psychotherapy, the pathology of PTSD, the chemistry and pharmacology of MDMA, various aspects of MDMA-assisted psychotherapy for the treatment of PTSD including its efficacy, methodology, and hypotheses on the mechanism of action for its success in

treating PTSD. Importantly, this review will also include a discussion on the current state of this therapeutic and on the only published phase 3 trial for it. This introductory section will compare MDMA with hallucinogenic drugs and discuss their history, legal status, development, and use as it relates to the practice of MDMA-assisted psychotherapy and its development. Moreover, it will discuss the progress and current state of clinical trials on the application of MDMA-assisted psychotherapy for the treatment of PTSD as well as driving forces and funding for this research.

MDMA is a Drug Enforcement Agency (DEA) schedule I substance and widely used drug of abuse. It is used illicitly in nightlife, rave, dance festival, or party settings where it is commonly referred to as "ecstasy" or "molly". Older literature on MDMA has referred to it as a psychedelic or hallucinogen. While it produces alterations in perception, these are different from the mental states induced by the "classic hallucinogens": lysergic acid diethylamide (LSD), mescaline, and psilocybin. Therefore, MDMA is better classified as an empathogen or entactogen, particularly due to its unique subjective effect of acutely enhancing the user's capacity to feel empathy or experience emotions (Nichols 1986).

Legal Status of MDMA and the Controlled Substances Act

To better understand the legal status of MDMA and obstacles that have hampered research on it and its medical applications, a brief discussion of the Controlled Substances Act of 1970 is warranted. The DEA classifies controlled molecules into 5 categories based on their use in medicine, abuse potential, and potential dangers to users.

Schedule I controlled substances are those that are said to have no accepted medical application, pose a high degree of danger to users, and have a high abuse potential. Examples include heroin, marijuana, and the hallucinogens such as LSD and psilocybin. Schedule II controlled substances have a high potential for abuse and dependence but have currently accepted use in medicine; such substances include amphetamines (marketed under the proprietary pharmaceutical names of Adderall and Dexedrine), oxycodone (Percocet and Oxycontin), and cocaine (used sparingly as a local anesthetic, Brain and Coward 1989). Schedule III substances have accepted medical application and potential for abuse that is lower than that of schedule I and II substances. Examples include ketamine and anabolic steroids such as testosterone. Schedule IV substances are said to have medical application and lower potential for abuse than that of schedule III substances. Such substances include muscle relaxants such as carisoprodol (Soma) and benzodiazepines such as alprazolam (Xanax) and diazepam (Valium). This designation of benzodiazepines as schedule IV substances, however, is a topic of debate among experts due to their high abuse potential and dangers to users (Ogbonna and Lembke 2017). Finally, schedule V substances are said to have the lowest potential for abuse and generally exclusively include prescription pharmaceutical preparations containing a defined and low concentration of more tightly controlled substances. Examples include cough medications with codeine including Robitussin AC (guaifenesin with codeine). The DEA monitors the lower number-scheduled drugs (i.e., schedule I and II substances) more closely and applies the most restrictions to them regarding their use in medicine and

research, so these agents tend to be more difficult for investigators to obtain for their research (DEA).

History of Drug- and Psychedelic-Assisted Psychotherapy

The story of MDMA- and drug-assisted psychotherapy begins in antiquity where indigenous and religious groups have used psychoactive drugs as a religious sacrament or for the treatment of various psychological and somatic symptoms. In this context, the drug is administered by a shaman or trained professional in the relevant religious or cultural practice. These drugs fall under the classification of psychedelics (also known as hallucinogens), psychoactive substances that produce subjective changes in perception and sensation. In these contexts, the psychedelic drugs were obtained from natural sources and generally consumed orally. Examples include mescaline, found in the peyote cactus; dimethyltryptamine (DMT), found in various plants in South America; salvinorin from the *Salvia divinorum* plant; and psilocybin from mushrooms in the Psilocybe genus (Grinspoon and Bakalar 1980).

In 1943 the psychedelic substance, LSD, was synthesized and its psychoactive effects were serendipitously characterized. While investigating alkaloids found in the ergot fungus for the purpose of discovering a circulatory system stimulant in his lab at Sandoz Pharmaceuticals in Switzerland, chemist Albert Hoffman synthesized LSD. Hoffman accidentally was exposed to a low dose of LSD cutaneously through his fingertips while handling the substance. He noted minor changes in perception that resolved within a few hours, then sought to further investigate the psychoactive effects of

the substance by intentionally orally ingesting it a few days later. Under the influence of the drug, he experienced significant sensory aberrations including synaesthesia and visual distortions for several hours. Despite the strong anxiety and fear that the drug also elicited in this experience, Hoffman believed the drug could be an important tool for researching the mind and sensory perception. He was right, as LSD contributed to the discovery of a major neurotransmitter, serotonin (Doblin et al. 2019). Hoffman disseminated this information and researchers from various fields began investigating the drug, its effects, and its potential therapeutic applications (Lee and Shlain 1994).

Within 15 years of the discovery of LSD, psilocybin and mescaline were also isolated and researched. These substances are also psychedelics and elicit subjective psychological effects that are nearly identical to that of LSD. Despite this early research on LSD showing its potential as a therapeutic for a wide variety of psychological pathologies, research was largely paused by the mid 1960s due to the drug's illegalization by the US government, which was primarily a result of it being used illicitly, outside the context of research and therapeutics (Lee and Shlain 1994).

This discussion on psychedelic-assisted psychotherapy pertains strongly to the discussion of MDMA-assisted psychotherapy and its history because the protocols that therapists adhere to in administering this treatment regimen are based on this early research from the 50s and 60s on using drugs (particularly psychedelics) in conjunction with psychotherapy for treating psychiatric diseases (Mitchell et al. 2021). Research on clinical applications of hallucinogenic and similar psychoactive substances resumed sparingly in the mid-2000s. Their status as controlled substances has made it an obstacle

for researchers and has been the primary factor for the slow progress in this area of research. At present, many FDA-approved clinical trials are being conducted to investigate the application of various psychedelics or psychedelic-like substances for the treatment of many different psychological pathologies including chronic pain, depression, PTSD, and eating disorders (Stein and Simon 2021). This surge of research has led many to refer to the present era as the psychedelic renaissance (Reiff et al. 2020).

History of MDMA-Assisted Psychotherapy and the Current State of Research on its Application for Treating PTSD

The first record of MDMA in the literature was a patent submitted by Merck Pharmaceuticals in Germany in 1912. This literature described its synthesis and chemical properties but did not discuss its pharmacology. It did, however, state that it could be used as an intermediate for the synthesis of therapeutically active substances. Although it was not mentioned in this document, nor was it discussed in any literature, many believe that it was developed for use as an appetite suppressant (Shulgin 1990). Its psychoactive properties were not characterized in the literature until 1978 by the organic chemist Alexander Shulgin, who also developed a new synthesis for it, which has been referred to as its "rediscovery". Prior to Shulgin's research on the molecule, little was known about MDMA, and it was not known to be a drug of abuse. Shulgin's initial interest and motives in researching this molecule are not explained in his publications, but reflect an interesting aspect in the history and rediscovery of the molecule. In his autobiography, *PiHKAL: A Chemical Love Story*, Shulgin states that his interest in the molecule arose

when he met a student at a pharmacology conference who claimed that his speech impediment was cured after taking a single dose of MDMA. Following this encounter, Shulgin synthesized the drug, tried it himself, then administered it to friends. He also gave it to investigators and clinicians that incorporated it into their research and psychotherapeutic practices. Results of this research were communicated amongst the few investigators and clinicians whom Shulgin selected via unpublished manuscripts prior to publishing his first paper on the pharmacological properties of MDMA in 1978. The ethics of this process that Shulgin chose in his rediscovery of the molecule may be a topic for debate, as this essentially circumvented the processes of FDA approval and institutional review boards that would normally be required for such pilot studies for various potential therapeutic applications of MDMA. As a relevant aside and critical piece of the history of drug-assisted psychotherapy, *PiHKAL* is widely considered to be a prolific work that has piqued the interest of many in psychoactive and psychedelic compounds. (Note that PiKHAL is an acronym for Phenethylamines I have Known and Loved.) It was coauthored by his wife, Ann, who is considered to be the mother of MDMA-assisted psychotherapy, especially for treating PTSD. She consumed some of the compounds that Shulgin was synthesizing including MDMA, was working as an unlicensed therapist, and hypothesized that some patients that are difficult to get to open up emotionally may do so under the influence of some of these drugs, primarily MDMA (Shulgin and Shulgin 1990, Benzenhofer and Passie 2010).

Shulgin was initially trained in organic chemistry, spent a few years in the US navy, then went to medical school for 2 years, and eventually resumed work as a

synthetic organic chemist at Dow Chemicals in San Francisco, CA, where he developed a novel pesticide called Zectran. Dow patented this material and greatly profited off it, so they ultimately gave Shulgin the freedom to work on whatever he wanted at Dow. He became interested in psychoactive drugs after receiving a placebo dose of opiate analgesic during a minor procedure on an infected wound while on a boat in the navy. He eventually became a prolific researcher in his field and became friends with the heads of the DEA and other researchers and was able to leave Dow and move his lab to his farm in the ‘50s. During this time, he also became a professor of chemistry at University of California Berkeley. He had recently tried mescaline. As he entered the field of synthetic chemistry of psychoactive drugs, he first used mescaline as the core structure that he modified, synthesizing novel psychoactive drugs. In his research, he would come up with a similar molecular structure, hypothesize on the subjective effects of it, then consume the drug (i.e., structure-function relationships followed by self-experimentation). If he thought it was worth further research and it "felt safe," he would give it to his wife. He did this for a few years, then made friends that were clinicians and professors in the San Francisco area that were also interested in trying these molecules. These friends would take in group settings with Shulgin and record their experience and the subjective effects of the drugs. Further, in his autobiographies (he also published another book called *TiHKAL: The Continuation*, Tryptamines I have Known and Loved), he claims that they are works of fiction and changes the names of all characters who represented real people to retain their anonymity, some of whom have claimed membership of Shulgin’s club (Shulgin and Shulgin 1990, Benzenhofer and Passie 2010).

Despite Shulgin's choice of not publishing much of his research on therapeutic applications of MDMA while he was working at his lab on his private farm, he conducted research that was published in peer-reviewed journals. Much of this research was conducted in conjunction with and funded by the DEA and included the identification of drugs of abuse. The chief administrator of the DEA at this time was a friend of Shulgin's, and the DEA would mail him samples of drugs. This research would unveil important information on the drug samples that would aid the agency in their goals of controlling the illicit synthesis, distribution, and use of drugs of abuse. For example, in a seized drug sample, Shulgin could identify chemical impurities that could indicate the synthetic route used by clandestine chemists. This information can guide the DEA in making legal decisions to accomplish their goals, such as limiting the legal sales and improving the tracking of precursor chemicals. In addition to providing an autobiography of his life, *PiHKAL* also included a section on the synthesis of these novel drugs and their structures, which was notably used by clandestine chemists that sought to profit off the sale of these drugs. A new DEA administration whom Shulgin did not have a professional or personal relationship with was appointed around the time that *PiHKAL* was published, which resulted in the DEA raiding his lab (Shulgin and Shulgin 1990, Benzenhofer and Passie 2010).

Anti-psychoactive drug sentiment arose in the US following the illegalization of LSD in the mid-1960s (Lee and Shlain 1994). Consistent with this, the DEA designated MDMA as a schedule I substance in 1986, effectively halting research on therapeutic applications of the drug (Shulgin 1990). Research on therapeutic applications of MDMA,

published between 1978 and 1986, had shown promise for therapeutic applications of MDMA (Greer and Tolbert 1986). However, reports on the illicit use of substituted phenethylamines including MDMA were reported in the literature as early as 1970 (Sreenivasan 1972). This information substantiates the claim that Shulgin had rediscovered MDMA and provided it to his colleagues well before he published his paper on it in 1978 (Benzenhofer and Passie 2010).

Given the promise of MDMA as a therapeutic agent, research on it resumed sparingly. Phase 1 toxicology studies on MDMA in humans were completed in 1996, and six phase 2 randomized trials of MDMA-assisted psychotherapy for the treatment of PTSD were conducted between 2004 and 2017. Four of these studies were published and all demonstrated acceptable safety and efficacy for treating PTSD relative to other FDA-approved treatments (MAPS, 2023).

Phase 1, 2, and 3 trials of MDMA-assisted psychotherapy for treating PTSD were all sponsored and coordinated by the Multidisciplinary Association for Psychedelic Studies (MAPS). MAPS is a non-profit organization that was founded in 1986 following the criminalization of MDMA. The organization funds and coordinates research on therapeutic applications of psychedelics, MDMA, and marijuana, and is also committed to educating the public on this research. MAPS has received over $140 million from philanthropic donors and grantors since its advent and its most significant endeavor has been funding research on MDMA-assisted psychotherapy for the treatment of PTSD (MAPS, n.d.).

In 2017 the FDA designated the treatment regimen as a breakthrough therapy and

approved two phase 3 trials, both of which began in 2018 (Mithoefer et al. 2019). This designation is a process that intends to expedite the development and review of new drugs and therapies that demonstrate significant advantages over currently approved therapies for prevalent and life-threatening conditions. One of these trials concluded and the results were published in 2021, again demonstrating safety and efficacy of the treatment (Mitchell et al. 2021). The other has completed data collection and is expected to be published in early 2023. The first stage 3 trial only had about 100 participants, while stage 3 clinical trials for other pharmaceuticals typically have hundreds or several thousand participants (Koenen et al. 2017, Leichsenring et al. 2022). Given the time and resource (for example, funding and trained staff) requirements for this treatment, it is not surprising that this number of participants in this study is relatively low. A new drug application is expected to be submitted to the FDA in late 2023 by MAPS, who is also funding this process. Currently, phase 2 trials for the application of MDMA-assisted psychotherapy in treating opiate-use disorder and eating disorders have been approved (MAPS, 2023).

Specific Aims

Specific aims of the following thesis include:

1. Review of literature to characterize the history, pharmacology, toxicity, and safety of the drug MDMA, as well as the pathology, treatments, and underlying neurobiological mechanisms of PTSD as it relates to MDMA-assisted psychotherapy for treating PTSD.

2. Discussion of the history, methodology, efficacy, and current state of research on the practice of MDMA-assisted psychotherapy for the treatment of PTSD.

3. Investigation into the proposed mechanisms of action by which MDMA-assisted psychotherapy is effective for treatment of PTSD.

CHEMISTRY, PHARMACOLOGY, TOXICITY, AND NON-CLINICAL USE OF MDMA

MDMA belongs to the phenethylamine class of molecules and is a substituted structural analogue of methamphetamine but produces different and unique subjective psychoactive effects. MDMA bears structural similarities to the phenylethylamine dopamine, an endogenous neurotransmitter. The structures of MDMA, dopamine, amphetamine, and other relevant phenethylamines are shown in Figure 1. Unlike methamphetamine, in which the psychoactive effects of central nervous system (CNS) stimulation are nearly exclusively mediated by the S-stereoisomer, both enantiomers of MDMA are psychoactive, but differ in their affinities for their protein targets that are discussed in the next section (Baumann et al. 2007). The S-isomer of MDMA is believed to be responsible for its CNS stimulatory and empathogenic effects, while the R-isomer is believed to be responsible for the effects on sensory perception, which many refer to as the hallucinogenic effects (De la Torre et al. 2004). The subjective psychoactive effects of MDMA contribute to its abuse potential and include euphoria, stimulation, changes in auditory and visual perception, synaesthesia, and increased self-esteem, extroversion, emotion, and empathy (De la Torre et al. 2004). Moreover, the drug is reported to induce a state of reduced anxiety and defensiveness (Nichols 1986).

Pharmacology and Metabolism of MDMA

On the cellular level, within hours of administration MDMA increases serotonin, dopamine, and norepinephrine concentrations in the synapse. MDMA is more selective for increasing serotonin than R- or (+)-methamphetamine and amphetamines, which probably accounts for the difference in the subjective psychoactive effects between these drugs (Papaseit et al. 2020). The mechanism by which MDMA increases synaptic concentrations of each of these monoamines is the same. Presynaptic monoamine transporter proteins (MATs) normally facilitate flux of excess neurotransmitters (e.g., norepinephrine (NE) back into the presynaptic cell such that the neurotransmitter can be reused. MDMA inhibits the reuptake of these neurotransmitters by binding the presynaptic transporter proteins such that their function is essentially reversed and the neurotransmitters in the cytoplasm flow out of the cell, down their concentration gradient through the transporter proteins (de la Torre et al. 2004). Moreover, MDMA inhibits the vesicular monoamine transporter (VMAT) protein that normally packs the neurotransmitter into vesicles that fuse with the presynaptic membrane and release the molecules upon stimulation. Specifically, these transporters pack MDMA into the vesicles in the place of the neurotransmitter, such that less of the normal neurotransmitter is stored in the vesicles, further increasing presynaptic intracellular concentrations of the neurotransmitter (Baumann et al. 2007). Furthermore, MDMA also inhibits monoamine oxidase (MAO), a presynaptic cytoplasmic protein that breaks down neurotransmitters. Two isoforms of MAO are expressed in the CNS differ in their affinities for monoamine substrates. One isoform is primarily expressed by serotonergic neurons, while the other is

primarily expressed by dopamine- and norepinephrine-releasing neurons (Wang et al. 2013). Similarly, different isoforms of VMAT and MAT are expressed depending on the type of neuron that produces them and functionally differ in their affinities for their endogenous substrate. For example, the MAT expressed by serotonergic cells (i.e., the serotonin transporter) shows the highest affinity for serotonin compared to the other endogenous monoamine neurotransmitters (Fei et al. 2008).

These proteins (MAO, VMAT, and MAT) regulate neurotransmitter concentrations in the synapses where they are expressed (Biaggioni and Robertson 2017). A schematic for these mechanisms is shown in Figure 2. This figure uses amphetamines and norepinephrine-releasing neurons as an example, but the mechanism by which MDMA increases synaptic serotonin, dopamine, and norepinephrine concentrations is the same (Baumann et al. 2007).

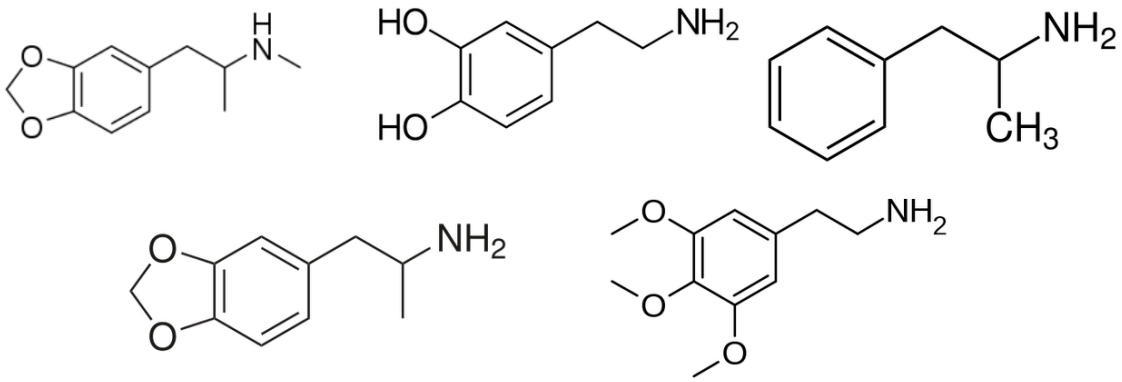

Figure 1. Molecular structures of MDMA and structurally similar phenethylamine analogues. From left to right, the names of the structures are as follows: MDMA, dopamine, an unsubstituted phenethylamine, 3,4-methylenedioxyamphetamine (MDA), mescaline.

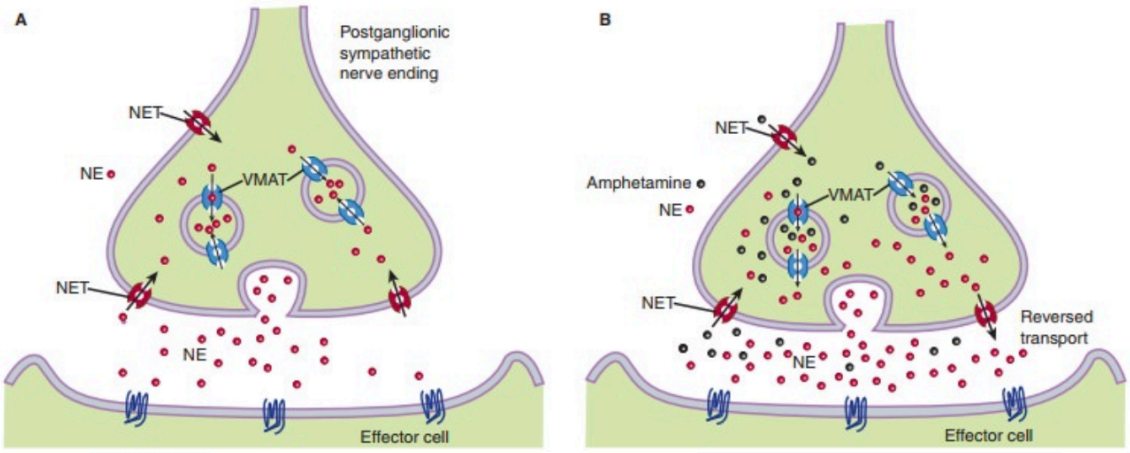

Figure 2. Schematic diagram of the mechanism by which amphetamines increase norepinephrine concentrations in the synapse. A shows a normally functioning norepinephrine synapse in the absence of amphetamine, while B graphically shows the resulting synaptic effects in the presence of amphetamine. NE, norepinephrine; NET, norepinephrine transporter; VMAT, vesicular monoamine transporter. From Biaggioni and Robertson 2017.

In addition to these effects on the principal monoamines in the brain, MDMA also induces the secretion of the neuropeptide and hormone oxytocin, which probably mediates much of the prosocial subjective effects of the drug (Nardou et al. 2019). This peptide is involved in uterine contraction and milk ejection on the hormonal level, and on the cognitive level, oxytocin mediates social behaviors including sexual activity, partner preference, parental nurture of children, and enhanced bonding (Love 2013). MDMA-induced increased serotonin, released by nucleus accumbens axons projecting to the hypothalamus, stimulates the postsynaptic serotonin 4A receptors on the oxytocin-secreting hypothalamic cells, leading to their production and secretion of oxytocin (Nardou et al. 2019).

In humans, the elimination half-life of a typical MDMA dose of 50-125 mg in humans is 8-9 hours, with peak plasma concentrations reached 1-2 hours after oral administration. The time-course of MDMA plasma concentration magnitude mirrors that of its physiological effects, and these effects return to baseline 4-6 hours after oral administration (de la Torre et al. 2004, Papaseit et al. 2018). MDMA is primarily broken down by the liver and its metabolic pathways and intermediates are conserved across animals, with differences lying in the concentrations of intermediate metabolites and the time courses of their formation. This is a result of the different isoforms and concentrations of the relevant metabolic proteins, particularly hepatic cytochrome P450 (CYP) proteins between species. These enzymes mediate O-demethylation, the first step of the major metabolic pathway in which 3,4-dihydroxymethamphetamine (HHMA) is formed. The two metabolic pathways are summarized in Figure 3 (De La Torre et al.

2004). In the major pathway in humans, HHMA is formed by CYP2D6, which is O-methylated by the enzyme catechol-O-methyltransferase, yielding 4-hydroxy-3-methoxymethamphetamine (HMMA). HHMA and HMMA are then conjugated with glucuronide or sulfate and excreted in urine. These major products of MDMA metabolism account for 40% of a 100 mg MDMA dose, 24 hours after administration. It is interesting to note that these metabolites are both psychoactive and produce effects that are similar to that of MDMA when administered individually in rats (Baumann et al. 2009).

In the minor metabolic pathway, MDMA is N-demethylated by CYP1A to form 3,4-methylenedioxyamphetamine (MDA). The formation of this molecule accounts for 8-9% of MDMA elimination in a 100 mg dose of MDMA. Moreover, with the same dose, 24-hour urinary excretion recovery of MDMA is 15.0%. This figure increases with higher doses of MDMA, indicating nonlinear pharmacokinetics due to MDMA inhibition of its own metabolism (de la Torre et al. 2004). Three other studies evaluating MDMA and HMMA concentrations across time after a second dose (50-100 mg) of MDMA administered 2-24 hours after the first dose (50-100 mg) have demonstrated the same conclusion. In these studies, higher maximum MDMA and MDA plasma concentrations and lower maximum HMMA plasma concentrations than expected (given the pharmacokinetic parameters of the first dose) were observed after the second dose. This is probably a result of the methylenedioxy substituent on the aromatic ring of MDMA, which is known to irreversibly inhibit CYP proteins (Papaseit et al. 2018).

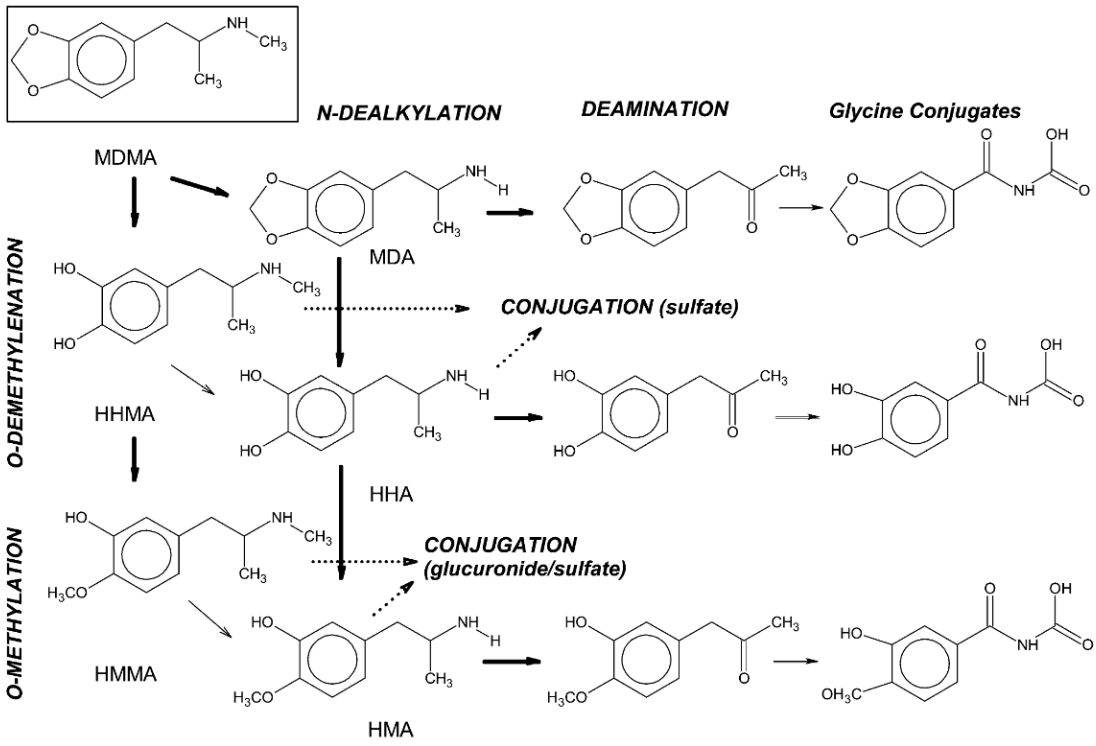

Figure 3. The metabolic pathways of MDMA in humans. HHMA = 3,4–dihydroxymethamphetamine, HHA = 3,4-dihydroxyamphetamine, HMA = 4-hydroxy-3methoxymethamphetamine, MDA = 3,4-methylenedioxyamphetamine, HMMA = 4-hydroxy-3-methoxymethamphetamine (De La Torre et al. 2004).

It is noteworthy that the minor metabolic byproduct, MDA, is a DEA schedule I substance that also produces effects similar to those of MDMA and is another commonly used illicit drug (Baumann et al. 2009). Relative to MDMA, MDA produces less stimulatory effects and more hallucinogenic effects (Nichols 1986). Moreover, despite their similar psychoactive effects and abuse potential to that of MDMA, HHMA and HMMA are not scheduled by the DEA, nor are they commonly used illicitly. However, they may be treated as schedule I substances under the DEA Federal Analogue Act for criminal prosecution, which allows prosecutors to treat such molecules as schedule I substances. The DEA defines analogues of controlled substances as those that are

intended for human consumption and are structurally similar to and produce pharmacological effects similar to schedule I or II substances (DEA).

Illicit Use, Subjective Effects, and Safety of MDMA

It is estimated that 0.9% of the North American population aged 15-64 have used MDMA at least once in the last 12 months (Papaseit et al. 2020). Pure MDMA can be insufflated, consumed orally, or injected intravenously, but the former two routes of administration are most commonly observed in its illicit use. It is usually consumed in a single dose of 100-200 mg, or less commonly, in sequential small doses referred to as "bumping". In illicit settings, MDMA can be sold as pressed tablets or in its purer crystal form (DEA 2020). The pressed tablets are notoriously impure and often contain other stimulants including amphetamines and cathinones instead of MDMA or in combination with MDMA. Moreover, unknown quantities of the drugs are contained in the tablets, and this contributes to their danger to recreational users. It is noteworthy that these impurities confound research on recreational ecstasy use (Danforth et al. 2016). One study conducted in 2007 found that as few as 3% of seized ecstasy tablets in Canada contained MDMA (Hudson et al. 2014).

It follows that MDMA is much less safe in non-clinical settings. Aside from the dangers of administering the drug via pressed tablets, there are many other safety concerns involving the use of pure MDMA in non-clinical settings. The sensory changes and central nervous system stimulation elicited by MDMA in these contexts may make a user sweat and want to dance or move around more than they normally would, and they

may not recognize or be receptive to signs of elevated body temperature and significant water loss. The settings in which MDMA is most commonly used illicitly, as discussed above, often include dancing, crowds, and high ambient temperatures. These all contribute to the possibility of users developing dehydration and heatstroke, which appear to be the primary danger of illicit MDMA use and can lead to renal failure and death (De La Torre et al. 2004, Papaseit et al. 2020). Symptoms of acute overdoses include hypertension, hyperthermia, serotonin syndrome, and seizures. The primary adverse effects observed in both illicit and controlled clinical settings include elevated body temperature, sweating, and vasoconstriction and elevated heart rate which lead to hypertension, a specific concern for hypertensive patients. These effects have led many to label the drug as cardiotoxic, but as will be discussed later in the context of neurotoxicity, drug toxicity is not always well defined and warrants a more thorough discussion. The cardiac effects of MDMA are believed to be a result of increased release of peripheral norepinephrine, and the effects on body temperature are believed to be mediated by the increased release of serotonin and dopamine (Baumann et al. 2007). Other short-term side effects observed within 24 hours of administration include lack of appetite, bruxism (grinding and/or clenching of the teeth), mydriasis (pupil dilation), muscle tension and tremors, nausea and vomiting, thirst, dry mouth, nystagmus (uncontrolled, twitching-like eye movement), heart palpitations, and dry mouth. MDMA can also produce transient adverse psychological effects including panic attacks, anxiety, delirium, and brief psychosis; other CNS stimulants including caffeine, cocaine, and amphetamines are also known to produce these effects in higher doses. Late short-term side effects, defined as

those whose onset occurs after the drug is nearly completely excreted from the body and the short-term acute effects have subsided, i.e., effects that appear in users 1-7 days after consumption, include fatigue, irritability, anxiety, insomnia, and depressed mood. The adverse- and side-effects of MDMA are reportedly observed less frequently under controlled clinical and research settings as compared with such settings in which it is commonly used illicitly (de la Torre et al. 2004).

The safety of chronic, repeated abuse of MDMA is not clinically relevant in the context of its therapeutic applications, with the exception of a second dose of MDMA administered within the time in which the psychoactive effects of the first dose are still present, that is, about 2-4 hours after the first dose. The dosing regimen of this exception is discussed in a later section on methodology used in clinical trials for the treatment of PTSD with MDMA. Chronic abuse patterns cause long-term cognitive impairment and negative alterations in mood and attention (Papaseit et al. 2020). Moreover, studies on MDMA in rats conducted by the US Army in the 1950s found high degrees of toxicity, but upon further evaluation, it was noted that these studies used much higher, non-equivalent doses (evaluated in mg MDMA per kg animal mass) than that which humans would normally consume. This research was cited in the discussions on the DEA scheduling of the drug in 1985, which resulted in MDMA being classified as a schedule I substance. When these studies were repeated with more relevant dosing, less toxicity was observed (Shulgin 1990, Danforth et al. 2016).

Toxicity and Serotonergic Neurotoxicity of MDMA in Mammals

In the context of pharmaceuticals, labeling a compound as toxic warrants a more nuanced discussion as nearly all chemical compounds can be toxic at sufficiently high enough doses. Compounds labeled as toxic may even elicit the same physiological changes as FDA-approved drugs that are not typically considered toxic. The neurotoxicity of MDMA has been a subject of controversy and research in the literature. Many animal studies have found that single-dose administration of MDMA and MDA produce long-term changes in serotonergic neurons and neurotransmission and long-term deficits in serotonergic neurotransmission serves as the definition of neurotoxicity in this context (Shulgin 1990). Some investigators have grouped the effects of single-dose administration of MDMA on serotonin levels into 2 phases. The acute phase begins upon drug administration and lasts for a few hours. In this phase, there is an initial intracellular depletion of serotonin and inhibition of tryptophan hydroxylase, the enzyme that catalyzes the first step in the synthesis of serotonin from tryptophan. Twenty-four hours later, serotonin levels return to normal, but tryptophan hydroxylase activity remains reduced. The long-term phase begins a week after drug administration and lasts for months. In this phase, there is a marked reduction in serotonin levels, sustained reduction in tryptophan hydroxylase activity, and reduced serotonin transporter activity. Moreover, in this phase, histological data has shown synaptic uncoupling and rearranging in the axon terminals of serotonin-releasing neurons, and no effects of single-dose MDMA administration on serotonin cell bodies in the dorsal raphe nucleus despite marked reduction of serotonin levels in the forebrain regions that these neurons project to. This

phase eventually resolves as serotonin levels and serotonin transporter activity return to normal. This evidence suggests that in the long-term phase, serotonin-releasing neuron axon terminals are acutely damaged, but not destroyed (Baumann et al. 2007). Furthermore, other studies have found lower concentrations of 5-hydroxyindoleacetic acid (the product of serotonin breakdown) and reduced serotonin transporter binding sites in human MDMA users as compared with non-MDMA users, and the magnitude of these effects correlates with the extent of reported MDMA use. This was determined using positron emission tomography in which radiolabeled MDMA was administered in-vivo to MDMA users and non-users (McCann et al. 1998). These findings are not conclusive as the impurity of ecstasy tablets and their frequent inclusion of other drugs confounds these studies. Moreover, the directionality of these effects is brought into question; that is, does frequent MDMA use elicit these differences or are they a result of physiological and psychological differences that predispose some to drug abuse (Steinkellner et al. 2011)?

In mice, chronic MDMA use has been shown to impair learning and memory, and in both chronic and acute administration contexts MDMA increases the phosphorylation of tau proteins in the mouse hippocampus. Increased phosphorylation of these proteins is associated with Alzheimer's and other neurodegenerative diseases. These studies have found that MDMA-associated tau protein phosphorylation correlates with impaired hippocampus-dependent spatial learning, which outlasted the changes in tau protein phosphorylation (Busceti et al. 2008).

Some FDA-approved drugs elicit similar effects and are not considered to be neurotoxic in therapeutic doses and dosing regimens. Chronic administration of SSRIs

(namely paroxetine and sertraline) has been shown to reduce serotonin transporter activity and elicit the same changes in serotonergic nerve terminals shown in the long-term phase following single-dose MDMA administration in rats (Baumann et al. 2007).

PTSD PATHOLOGY, TREATMENTS, RISK FACTORS, AND UNDERLYING BIOLOGY

In the DSM-IV, PTSD was characterized as an anxiety-disorder and 14 years later, with the release of the DSM-V in 2013, it was regrouped into a new category as a trauma- or stressor-related disorder. This decision was based on newer research that unveiled a wider range of similar but different diseases than PTSD which demonstrate the existence of a spectrum of severity of PTSD (as opposed to an all-or none PTSD diagnosis), and ultimately showed that the diagnostic criteria for these disorders and their symptoms are different than that of anxiety-related disorders. Moreover, PTSD manifests differently across patients and anxiety- or fear-based symptoms are not a diagnostic requirement for PTSD. PTSD patients can present with primarily anhedonic and dysphoric symptoms and less anxiety symptoms, or vice versa (APA 2013). Broadly speaking, these disorders are marked by the presence of intrusive symptoms following the initial traumatic event or events. These are generally chronically recurrent and stress-inducing memories relating to the traumatic event (DSM V).

A dissociative subtype of PTSD exists. The diagnostic criteria for this subtype meet that of PTSD and also include symptoms of dissociation – depersonalization or derealization or both. These symptoms typically occur when the patient revisits traumatic memories, and dissociative states may last anywhere from a few seconds to several days. Moreover, in such states, the patient behaves as if the past traumatic events are currently happening. Depersonalization is characterized by feelings of detachment from one's current experience and mental processes, as if the patient was another person observing

such phenomena. Derealization is characterized by experiencing feelings of unreality upon recalling traumatic memories. A representative example may include the patient experiencing their present environment as if it is distant, distorted, or not real (DSM V).

PTSD Pathology: Symptoms, Diagnosis, and Comorbidities

The full diagnostic criteria for PTSD are shown in Figure 4. It is important to note that these symptoms must arise or worsen after the trauma, cause functional impairment in everyday activities including inability to fulfill social and occupational responsibilities, and be present for at least a month to be considered indicative of PTSD. All symptoms of one's PTSD may not arise until several months after the trauma, though some arise immediately. This section will highlight some of the hallmark symptoms of PTSD.

One hallmark is the persistent avoidance of stimuli associated with the trauma. Moreover, PTSD patients often overgeneralize the relevant fear cues, such that otherwise non-threatening stimuli may elicit a fear response, which exacerbates this symptom and its effects (Horn and Feder 2018).

Declined cognition after the occurrence of the traumatic event, which may or may not relate to it, is a necessary diagnostic criterion for PTSD. This may include persistent declined mood (dysphoria); feelings of helplessness in relation to these symptoms and mental health; feelings of guilt and blaming oneself for causing the trauma and the events leading up to it; amnesia, that is, the patient may not be able to recall the trauma or important aspects of it; concentration disturbances marked by impaired short-term memory and focus; and impaired social cognition and decreased sensitivity to positive

social stimuli (Horn and Fever 2018). This latter symptom may be marked and partly caused by distrust of others and social hypervigilance and include social withdrawal, especially as it relates to social activities that the patient previously enjoyed; impaired ability to form relationships and constructively socialize; and a short temper and increased aggression, especially without provocation (DSM V).

As stated, the presence of intrusion symptoms is a critical diagnostic criterion. These memory-related symptoms can take the form of nightmares whose content relates to the trauma (which contributes to sleep disturbances), dissociative symptoms as described above, recurrent and involuntary recall of stress-inducing memories, and acute physiological and intense negative psychological responses to stimuli that resemble or are interpreted as resembling components of the traumatic event. The physiological responses to traumatic memories in lucid states or memories are autonomic in nature and may take the form of shortness of breath, high heart rates or palpitations, as well as increased body temperature and sweating.

The last key diagnostic criterion for PTSD is altered reactivity and arousal responses relating to the trauma. The anxiety component of PTSD is particularly relevant to this criterion. This criterion may manifest as hypervigilance (high exertion of focus and attention on the present environment as it may be perceived consciously or subconsciously as potentially posing a threat), irritable behavior, sleep disturbances (due to hyperarousal), difficulty concentrating, and exaggerated startle responses (DSM V). At least 80% of PTSD patients have at least one comorbid disorder, the most common being suicidality, hypertension, obesity, and mental health conditions including substance use

disorders, anxiety, and depression. The comorbid substance use disorders may arise from patients' attempts at self-treatment, specifically the administration of psychoactive substances for the purpose of dulling the negative emotional aspects of the disorder (Mithoefer et al. 2019).

Diagnostic Criteria **309.81 (F43.10)**

Posttraumatic Stress Disorder

Note: 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:

1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
2. 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:

1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
2. 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").
3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
5. Markedly diminished interest or participation in significant activities.
6. Feelings of detachment or estrangement from others.
7. 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:

1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
2. Reckless or self-destructive behavior.
3. Hypervigilance.
4. Exaggerated startle response.
5. Problems with concentration.
6. 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).

Figure 4. Full diagnostic criteria of PTSD from the DSM-V (2013).

FDA-Approved PTSD Treatments

Treatment seeking is low among PTSD patients, even in the US, where treatments are more available relative to other countries. Moreover, treatment-seeking declines in lower-income areas. In the US, only about half of PTSD patients seek treatment, and half of those receive care from a licensed mental health professional. Little is known about this trend in treatment seeking (Koenen et al. 2017), but a possible explanation for this is that trauma-focused therapy. This therapy involves revisiting traumatic memories, which can trigger stress, anxiety, and avoidance in the patient, all of which are hallmarks of PTSD as discussed above (Stein and Simon 2021). Other possible explanations include perceived treatment inefficacy, discomfort with the therapist, stigma, and time demands (Steenkamp et al. 2015).

The current FDA-approved treatments for PTSD include trauma-focused psychotherapy and the SSRIs, sertraline and paroxetine. The most well-studied trauma-focused psychotherapies for treating PTSD include cognitive processing therapy (CPT) and prolonged exposure therapy. These are both manualized therapies, meaning that they are conducted by a therapist according to a protocol in a session-by-session manner. CPT is a type of cognitive-behavioral therapy that is specialized for the treatment of trauma-related diseases. The treatment seeks to notice negative and detrimental thought processes and emotions and replace them with constructive thought processes and positive perspectives. Prolonged exposure involves having the patient repeatedly recount the traumatic experience in a controlled environment with the support of the therapist in an effort to facilitate fear extinction, that is, diminishing the fear-responses elicited by

recalling these memories (Steenkamp et al. 2015). This treatment has been shown to have a relatively high short-term efficacy and low long-term efficacy in extinguishing fear responses (Hake et al. 2018). Trauma-focused psychotherapies tend to be difficult to access and ineffective for many (Mithoefer et al. 2019); the efficacies of these treatments and that of the approved pharmaceutical therapies are discussed in greater detail, and in comparison with MDMA-assisted psychotherapy in a later section on MDMA-assisted psychotherapy. Moreover, trauma-focused psychotherapy tends to be highly emotionally demanding and requires patients to remain engaged to attain therapeutic goals (Steenkamp et al. 2015). The latter aspect may account for the observation that the dissociative subtypes of PTSD are particularly difficult to treat (Cloitre et al. 2012), as recalling the traumatic memories elicits the dissociative symptoms that derail focus and disengage the patient from the therapy. It follows from this challenging aspect of these therapies, that they have low retention rates and their clinical studies show high dropout rates. Most patients respond to these treatments, but sparingly, and given the emotional labor required for any significant improvements in PTSD symptoms, their place as PTSD treatments is not well-earned and may cause more harm (especially acutely in the therapy sessions) than benefit in many patients (Steenkamp et al. 2015).

Phase 3 randomized clinical trials have found few significant differences across the SSRIs in their efficacy for treating PTSD (Hoskins et al. 2010). Moreover, these agents often induce side effects before therapeutic effects are elicited, which contributes to the early discontinuation of the treatment (Stein and Simon 2021). Common side effects of sertraline and paroxetine include sexual dysfunction and decreased libido,

nausea and diarrhea, and nightmares (Sartori and Singewald 2019). They also carry a low risk of QT interval prolongation, a potentially fatal cardiac complication that necessitates medical intervention (Mitchell et al. 2021). The SSRIs show a similar low efficacy to that of the psychotherapies for treating PTSD (Steenkamp et al. 2015).

Risk Factors for PTSD, Resilience, and Emotional Regulation

Resilience is a trait relevant to the risk for developing PTSD given exposure to trauma; that is, it is one's ability to adapt effectively in the face of adversity, trauma, or threatening stimuli. This section will cover some of the key factors mediating resilience. This discussion will further characterize the PTSD disease state and shed light on some of the factors that confer the chronic nature of the illness. 30% - 40% of resilience is thought to be attributable to genetics and the rest to environmental and personality factors. Resilience decreases with higher severity and frequency of the trauma. Development in childhood is also an important factor in assessing PTSD risk. The timing in which trauma is experienced is a significant predictor; trauma experienced at younger ages is associated with decreased resilience. This is probably a result of heightened brain plasticity during childhood. Thought processes have corresponding neural signaling patterns that ultimately produce the thoughts and behaviors, so heightened neuroplasticity provides an opportunity for detrimental thought processes that are typically elicited by traumatic experiences to become ingrained, especially when left unattended. It follows that the quality of care received by the child from their parents and family stability are positively correlated with resilience. Similarly, higher quality and levels of social support

throughout life promote resilience; talking to a friend or therapist in stressful situations acts as a safety net through which one can mentally work through such situations or be encouraged to foster adaptive behaviors in times of adversity instead of reinforcing maladaptive thoughts and behaviors (Horn and Feder 2018).

One's capacity for emotional regulation is associated with higher resilience. Emotional regulation refers to one's ability to control internal feelings and correlates with executive function - the ability to plan and execute tasks. Evidence of two types of emotional regulation mechanisms exists in the literature, automatic (implicit) and conscious (explicit) emotional regulation. In both these processes, higher brain regions regulate the activity of the more primitive, subcortical, feeling-producing brain regions. Cognitive reappraisal is a conscious emotion-regulation strategy in which one recognizes undesirable thoughts and emotions and replaces them with more practical thought processes and positive emotions (Ledoux 2012). The capacity for cognitively reappraising one's internal environment is typically impaired in stress-related disease states and is linked to resilience. This ability is also linked to decreased anxiety and hypervigilance symptoms in patients with PTSD, which may be partly explained by the observation that positive emotions decrease autonomic arousal and increase resilience. Positive affect and emotional reward are key players in increasing cognitive control and supporting executive function, both of which are impaired in PTSD (Pechtel and Pizzagalli 2010). Moreover, the goal of cognitive-behavioral therapy and CPT is increasing the patient's capacity for cognitive reappraisal. Similarly, one's capacity for coping self-efficacy is linked to increased resilience and lower magnitudes of PTSD

symptom severity. Coping self-efficacy refers to one's perception or belief that he or she is able to mentally deal with or recover from trauma (Horn and Feder 2018). This trend is not surprising given that coping self-efficacy is characteristically impaired in PTSD (DSM-V).

Neurobiological Basis of PTSD and Neuroanatomical Correlates of Resilience

The next discussion will focus on the neurobiological basis and correlates of PTSD. It will begin with a review of the key brain regions and their functions involved in the PTSD disease state and will be referenced throughout the section. The hippocampus is the key brain region concerning memory. More specifically, it is involved in memory recall and the consolidation of short-term memories into long-term memories. The amygdala regulates emotional expression and the implicit aspect of emotion. Its projections to the hypothalamus and the brain stem elicit the visceral aspects of emotion, including changes in heart rate, breathing, blood pressure, body temperature, and sweating. The prefrontal cortex (PFC) mediates executive function and is thought to be the mental drawing board of thought and the center of consciousness (Patestas and Gartner 2006). The anterior cingulate cortex (ACC) primarily mediates learning about the outcome of actions, that is, reward or punishment, which are coded by the brain as emotions. The ACC also serves as a bridge between the amygdala and hippocampus and functions in storing the emotional aspects of episodic memories. Further, the ACC connects the hippocampus to the neocortex, which includes the PFC (Rolls 2019).

As alluded to previously in this section, the recall of traumatic memories, the emotional affect of them, and the patient's ability to regulate these emotions are key dysfunctions in stress-related disease states. A brief discussion of the neurobiology of memory as it relates to PTSD follows. As stated, patients with PTSD often overgeneralize stimuli relating to their trauma, such that non-threatening cues in the patient's environment that do not immediately relate to their traumatic experience evoke memories of their initial trauma (Horn and Feder 2018). Memory, or the recall of experiences, feelings, and facts is a dynamic process and not a static one. That is, when memories are accessed, the hypothalamic storage space sends the memories to the PFC, the "drawing board" of thought, where the memory can be reconsolidated or reappraised, and innate behavioral or emotional responses to their recall (for example, a fear response) can be changed. In other words, the memory and its associated emotional affect can be strengthened, weakened, manipulated, altered, or updated with new information (Delorenzi et al. 2014).

That said, in such disease states, outside of therapeutic contexts, when traumatic memories are recalled, they are not reappraised in a constructive manner, if at all. Upon recognizing a cue that the patient associates with the trauma, a fear- or dysphoric-emotional response is elicited. Moreover, upon exposure to traumatic reminders, such disease states are associated with decreased PFC activity and branching (that is, the number of axonal projections of neurons whose cell bodies originate in the PFC) and increased amygdalar activity as compared with controls. Changes in neurocircuitry from relevant investigations was determined using immunohistochemistry, that is, brains of

rodent models were stained to label the PFC axons and this number was counted and compared between treatment groups (Radley et al. 2004). Such conditions and disease states are also associated with impaired hippocampal function. Specifically, they are associated with less hippocampal activation during memory tasks relative to controls, which may partly account for some of the memory symptoms associated with PTSD. Fear extinction, or the decreased magnitude of conditioned fear-responses to unconditioned stimuli (such as those produced as a result of overgeneralization of reminders of trauma) as shown in prolonged exposure therapy, appears to be mediated by increased PFC-mediated inhibition of amygdalar activity (Bremner 2006). Increased amygdalar activation produces a more intense emotional response and is also associated with PTSD upon exposure to stimuli that serve as traumatic reminders (Horn and Feder 2018). This leads to our discussion of the circuitry of emotional regulation in PTSD.

In implicit emotional regulation, amygdalar activity is regulated by the ACC. This process is characteristically impaired in patients with PTSD (Horn and Feder 2018) and may relate to the smaller ACC volumes associated with PTSD (Bremner 2006). Consistent with this ACC dysfunction in such disease states, higher resilience is associated with increased ACC activation during emotional conflict. In explicit emotional regulation, amygdalar activity is regulated by the PFC, and upon exposure to stress-inducing stimuli, increased PFC activity is associated with higher resilience. Similarly, the ability to positively reappraise traumatic memories (or as some may put it, “finding meaning in negative experiences”) is associated with increased connectivity between the PFC and amygdala. Further, one’s capacity for cognitive reappraisal of their present

internal environment is associated with increased PFC activation and decreased amygdalar activity in response to stress-inducing stimuli. Functional magnetic resonance imaging (fMRI) in humans has been used to collect data on neurocircuitry dysfunctions and neuroanatomical correlates of emotional regulation in stress-related disease states. Such studies provide a temporally precise picture of the brain and its function under different conditions and in response to specific stimuli. One example of such human studies used this technique to collect neuroanatomically accurate data on brain region activity when participants were exposed to stress related images and were instructed to try to control the emotions that these images produced. The fMRI data from resilient, trauma-exposed individuals without PTSD were compared with participants with PTSD and controls without PTSD (New et al. 2009, Horn and Feder 2018).

Further, another similar randomized, placebo-controlled fMRI study with 17 participants elucidated the effects of MDMA on emotional valence and neurocircuitry in healthy human subjects. In this study, participants were given either a placebo or a 100 mg dose of MDMA, then 80-85 minutes later (the time in which MDMA elicits peak psychological effects), were instructed to think of a favorable or adverse autobiographical experience for 13 seconds after being shown the cue for 5 seconds, for example “think about the moment you heard of your father’s death,” or “recall the experience of first holding your newborn child.” A distraction task was then performed for 13 seconds in which the participants were instructed to listen to auditory tones of three distinct pitches, then recall which tone was presented most frequently. The patient was instructed to relax for five seconds, then this procedure was repeated 18 times total. The fMRI data was

recorded and compared between the cohorts. This study showed that in both study arms, the hippocampus was activated to a greater extent upon recall of favorable memories than it was to unfavorable memories, while the PFC (neocortical or executive region) was activated to a greater extent upon recall of unfavorable memories as compared to favorable memories. The MDMA group showed increased activation of different neocortical regions associated with the recall of favorable memories and decreased activation of the left anterior temporal cortex and the bilateral fusiform gyri (known to be involved in processing high-level visual stimuli such as faces). This latter finding may account for some of the visual subjective effects of MDMA including the enhanced vividness of visual stimuli. The emotional valence of the memories was also reported by subjects before MDMA or placebo administration and after each memory cue was presented and found that in the MDMA group, the subjective negative emotional affect of unfavorable memories was reduced, and the favorable memories were reported to be more emotionally positive. These findings ultimately reflect an MDMA-elicited positive shift in the perception of the emotional affect of recalling favorable and unfavorable memories (Carhartt-Harris et al. 2014).

MDMA-ASSISTED PSYCHOTHERAPY

The following section will discuss the methodology of MDMA-assisted psychotherapy for treating PTSD as it was conducted in the first phase 3 clinical trial as well as the results and limitations of this trial. The proposed mechanisms of action that are thought to account for the apparent success of the therapy will be considered, and the section will conclude with a discussion comparing the treatment efficacy with those of other PTSD therapies.

Procedures and Methodology of MDMA-Assisted Psychotherapy for Treating PTSD

The statistical analysis plan and study design of the first phase 3 trial was developed in conjunction with the FDA given its breakthrough therapy designation, discussed in the introduction section. The study design is as follows. A total of 105 participants were randomized into control and experimental groups, a number that the research team and FDA agreed would produce a sufficiently high effect size. This study evaluated all severe PTSD diagnoses resulting from different traumatic history, which did not vary significantly across treatment groups. Specifically, the traumatic experiences included in the study included developmental trauma, combat exposure, and multiple trauma (which included 84.4 %, 12.2%, and 87.8% of total participants respectively), the participant demographics are discussed in more detail below. The difference between the treatment groups was the amount of MDMA administered to the participants immediately prior to an eight-hour therapy session (beginning at 10:00 to be consistent with most participants' circadian rhythms,) referred to as the experimental session. The control

group received inactive placebos, while the experimental group received what are considered to be psychoactive doses of MDMA. Some of these treatments were terminated early due to the COVID-19 pandemic, in which these participants could no longer attend in-person treatment. A total of 90 participants began the treatment regimen (44 in the placebo group, and 46 in the MDMA group), which researchers believed still would produce an acceptable effect size (Mitchell et al. 2021).

Participants attended two-to-three experimental sessions spaced approximately four weeks apart, as well as nine 90-minute integration sessions following the experimental one, the first conducted the day following the first experimental session and the rest one week apart from each other. The purpose of the integration sessions was to facilitate the participants' understanding and mental processing of the previous experimental sessions as well as their incorporation of insights gained in the experimental sessions into their everyday lives. The first experimental session was preceded by three preparatory sessions for the purpose of establishing bonding and trust between the therapist and participants, administering scales for measuring baseline parameters of interest, explaining some of the subjective effects of MDMA to the participant, and providing instruction on mentally navigating the experiences, memories, and feelings that might arise in the treatment. For example, the patient might be instructed to react in particular ways when certain memories or thoughts are experienced, as these might be experienced differently in the mental states elicited by MDMA. These sessions also served to verify participant eligibility based on criteria discussed below. For example, qualitative urine drug screens were administered to verify that the patients were adhering

to the guidelines on drug use throughout the study. Subsequent experimental sessions were preceded by administration of a qualitative urine screen and pregnancy test as well as baseline measurements of blood pressure, heart rate, and body temperature. The manualized therapy was conducted by the therapists in accordance with MAPS' MDMA-assisted therapy treatment manual. This manual contains more information on the treatment protocol, sessions and their purposes, and guidelines for the therapist and staff. This manual was developed in an iterative process throughout the phase 2 trials. The first version was published in 2005 and the current version was finalized in 2017 for use in the phase 3 trials (Mithoefer et al. 2017, Mitchell et al. 2021).

Neither the treatment manual nor the phase 3 trial discusses the specific timing of scale administration, protocol adherence assessment during the preparatory session, or MDMA administration after the preparatory session. The manual emphasizes that during the preparatory session, the therapist should prioritize conducting psychotherapy and facilitating participants' trust in the therapist and treatment and bolster their feeling of comfort over completing measures and other preparatory tasks at precise times. This emphasis may introduce temporal variability in the treatment protocol, but probably improves treatment efficacy. For example, some of the instruments for measuring treatment outcomes are administered in an interview format by the attending clinician but are video-recorded and sent to and evaluated by an off-site, independent rater; the proper use of these instruments is crucial for accurate and complete data collection. For example, one of such instruments (which is discussed in greater depth later) evaluates PTSD symptom severity and diagnosis. Answering the questions in this scale can be

challenging for the patient because it requires them to recall their trauma and reflect on their PTSD diagnosis. Such processes, as discussed in the PTSD section, are characteristically impaired in such disease states, so given the nature of the questions in this scale and the pathology of PTSD, it is not surprising that the time needed by patients to respond to these questions is highly variable. Moreover, since the therapists seek to build trust with these patients, a patient-focused protocol is more appropriate than one that is more focused on mitigating minor protocol deviations. The absence of strict time constraints in the treatment protocol supports the therapists' duty of fostering the patients' trust of them and creating a calm environment in which the treatment takes place, and these components are believed to improve treatment outcomes (Mithoefer 2017). The published journal articles of the phase 2 (Jerome et al. 2020) and 3 (Mitchell et al. 2021) clinical trials of this treatment fail to discuss this variability and do not report the precise timing in which the drug or placebo was administered nor that of the start of the experimental session relative to completing the preparatory session. It is possible that these authors made this choice because the time variations were sufficiently small (probably on the order of one to ten minutes) relative to the other timing information provided, such that they did not significantly affect the treatment results, and could reasonably be omitted from the texts of these articles. Such information provided includes the length of the experimental session, timing of administering the supplemental dose, and timing of sessions. These lengths are on the order of hours to weeks. It is also possible that these loose time constraints were thought to be more than enough time to accomplish the goals of these sessions, so this may have given these therapists the

opportunity to have extra time that they could use to build their relationship with the patient and spend more time discussing different aspects of the treatment, subjective effects of the drug, and importantly, answering patient questions.

In the first experimental session, the experimental group received an initial dose of 80 mg MDMA, followed by a 40 mg supplemental dose that was administered 1.5 – 2.5 hours after the initial dose at the discretion of the participants and clinicians. The second and third experimental sessions utilized a 120 mg initial dose and 60 mg supplemental dose. (In some of the six phase 2 trials, "inactive" ranges of low MDMA doses as controls were used to improve patient blinding. This caused a reduced effect size in the experimental treatment groups as compared to control groups using doses of 0 mg MDMA.

In the planning of the first phase 3 trial, it was decided that a study design that produces the largest effect size was necessitated to demonstrate the effectiveness of the treatment and secure funding for future research. Moreover, this choice allowed for a better comparison of the safety profile of the MDMA group with a 0 mg control dose (Mithoefer et al. 2019). The supplemental dose in the phase 3 trial prolonged the subjective mental effects of the MDMA, increased their magnitude over time, and produced more consistent MDMA plasma concentrations throughout the experimental session. Physiological parameters including blood pressure, heart rate, and body temperature were measured prior to administration of the initial dose during the preparatory sessions, and immediately before administration of the supplemental dose. The latter dose was withheld by the research team as a safety measure if these parameters

were elevated beyond physiologically safe ranges with respect to their baseline values. Moreover, the participants may have opted to forego the supplemental dose if they did not psychologically tolerate the initial dose (Mitchell et al. 2021). As discussed in the MDMA pharmacology section, high doses of CNS stimulatory drugs are known to induce anxiety symptoms (de la Torre et al. 2004). The lower dose in the first session was chosen to promote tolerance to the adverse side effects of MDMA and familiarity to the mental states elicited by it. The treatment manual authors theorize that this tolerance reduces adverse effects of CNS stimulation such as fear and anxiety upon receiving larger, more therapeutically relevant dose ranges in the subsequent experimental sessions (Mithoefer 2017).

Four important measures were tracked across this phase 3 trial. Consistent with the blinding in the phase 3 trial, scales evaluated by third parties were done so off-site by blinded raters. Site staff, including the therapists, were also blinded. The observer- and personnel-blinding was maximized by investigators instructing patients not to discuss their mental state or subjective drug effects (or lack thereof) with the attending therapist. The Clinician-Administered PTSD Scale for DSM-V (CAPS-5), which was the primary measure, quantifies PTSD symptoms. It is considered to be the gold standard for evaluating PTSD severity, differentiates subtypes (i.e., dissociative subtypes), and is the scale by which PTSD is diagnosed in clinical practice in the USA (Maresanu et al. 2022). The instrument consists of 30 questions in which the clinician rates key PTSD symptom cluster severity and frequency in an interview format. The first 20 items pertain to the key PTSD symptom clusters (presence of intrusion symptoms, persistent avoidance of stimuli

associated with the trauma, negative alterations in cognition, and elevated arousal or reactivity) and their score of each these items is rated on a five-point scale, where the minimum score of zero refers to the symptom being absent, and the maximum score of four indicates an extreme or incapacitating facet of a symptom cluster. Only item scores greater than or equal to two (moderate or threshold) are considered clinically significant and contribute towards the total score and therefore diagnosis. Items scores two and three (severe or markedly elevated) evaluate symptom frequency and intensity. Criteria for a score of two is met if the symptom intensity is "clearly present" and the frequency minimum is met. The frequency minima vary based on the question. Similarly, scores of three are met based on the defined frequency minima and a minimum symptom intensity of "pronounced". The scores of the first 20 items are summed to indicate overall PTSD severity, but PTSD diagnosis is not determined by a specific score on the CAPS-5 scale. Rather, diagnostic criteria is met by experiencing trauma and scoring at least two on at least one item pertaining to of each of the four key symptom clusters (presence of intrusion symptoms, persistent avoidance of stimuli associated with the trauma, negative alterations in cognition, and elevated arousal or reactivity). Diagnostic criteria also require meeting the temporal requirements of the latter four symptom clusters (they must be present for at least a month after the initial trauma at the time that the instrument is administered); impairments in participating in and fulfilling normal, every-day obligations and activities regarding work or school, family and home, sociability, or recreational activities (APA 2013; Weathers et al. 2018). A minimal overall CAPS-5 score sum that indicates PTSD diagnosis (provided the other diagnostic criteria is met)

would therefore be 10 (indicating mild overall symptom severity and frequency), and the maximum score being 80, see Figure 4 for more details on these diagnostic parameters. The CAPS-5 scale has changed iteratively since its introduction in 2015, a more recent version of the clinician guide for administering it that includes the items is available from Weathers et al. (2018b).

The Sheehan Disability Scale (SDS) is a self-rated questionnaire that measures the magnitude of functional impairment of everyday activities (including that of work or school, leisure activities, and social and family life) by PTSD and was obtained as a secondary measure. These two scales were administered at baseline (prior to therapy) and during the integration session following each experimental session (for a total of four times each; Mitchell et al. 2021).

As mentioned, PTSD is highly comorbid with other psychiatric illnesses, the most prevalent being depression (Mithoefer et al. 2019). In this trial, as an exploratory measure, comorbid depression symptoms were also evaluated using the Beck Depression Inventory II (BDI-II), which is a self-administered instrument that evaluates the somatic and psychiatric symptoms of non-specific depression (Wang and Gorenstein 2013). This instrument was administered once at baseline and again upon study termination (Mitchell et al. 2021).

Fourth and finally, as important safety assessments, suicidality, cardiac symptoms, and other treatment-emergent adverse- or side-effects were also tracked throughout the study. These were tracked qualitatively as records of single-events, or quantitatively for suicidality using the Columbia Suicide Severity Rating Scale (Mitchell

et al. 2021).

To eliminate the variable introduced by ongoing therapies, in the first phase 3 trial, participants were instructed to discontinue psychiatric medication use, if prescribed for PTSD. The length of the taper was dose-dependent, with longer taper lengths required for patients on larger doses of medications. The taper length ranged from 0 days to 103 days (Mitchell et al. 2021). Inclusion criteria for participants included meeting the DSM-V criteria for current PTSD with symptoms that have persisted for at least six months prior to the start of the study. The study also required participants with baseline CAPS-5 severity scores of at least 35 at the start of the study, indicating "very severe" PTSD symptoms. Phase 2 studies only enrolled participants that inadequately responded to at least one pharmacotherapy or psychotherapy, though this was not discussed nor was it listed as necessary inclusion criteria in the first phase 3 trial. It may be inferred, but cannot be definitively stated, that this decision in the phase 2 studies looks at only treatment-resistant PTSD and not all PTSD as the patients may initially present in the clinic. Moreover, dissociative subtypes of PTSD are harder to treat and this decision may disproportionately select for studying this treatment in these subtypes (Mithoefer et al. 2019, Mitchell et al. 2021).

Exclusion criteria for the phase 3 study included certain psychiatric illnesses such as bipolar I disorder, dissociative identity disorder, eating disorders with active purging, primary psychotic disorder, personality disorders, and current alcohol and substance use disorders. Participants were also instructed to discontinue the use of alcohol, marijuana, and other drugs, and non-adherence to this is included in the exclusion criteria.

Pregnancy or lactation and cardiovascular medical conditions such as chronic uncontrolled hypertension and history of arrhythmia (due to the cardiovascular conditions that may arise in these patients as a result of the cardiotropic effects of MDMA) are also listed as exclusion criteria. Ethnicity, age, sex, duration of PTSD diagnosis, PTSD severity, and subtypes were controlled for such that these variables did not differ significantly across placebo and experimental groups (Mitchell et al. 2021).

Results of the First Phase 3 Clinical Trial of MDMA-Assisted Psychotherapy for the Treatment of PTSD

The first phase 3 trial indicated a high safety profile in the experimental group for MDMA-assisted psychotherapy. Eleven participants dropped out of the study prior to reaching the study end point, which was nine weeks after the third experimental session and included three additional integration sessions followed by a final assessment of BDI-II, SDS, and CAPS-5 scores, so 79 (37 in the placebo group and 42 in the experimental group) of the randomized 90 participants reached the study endpoint; these participants are referred to as the completers. Of the 46 participants randomized to the experimental group, 42 completed the third experimental session; two withdrew due to COVID. One withdrew due to becoming distressed from a CAPS-5 assessment, which was followed by reported depression following the first experimental session. One withdrew after the second session due to “feeling cured”. This dropout rate data in the treatment group from the phase 3 trial of 8.7% (four participants out of 46) is consistent with that from the phase 2 trials (7.6%, Mithoefer et al. 2019), indicating that the treatment is well tolerated

(Jerome et al. 2020).

Over eighty percent (37 out of 44) of participants randomized to the control group completed three experimental sessions and did not drop out prior to the planned study endpoint. In the seven participants that dropped out of the study, two withdrew due to COVID, three completed the third experimental session but resumed taking their psychiatric medication prior to reaching the study endpoint, and four were withdrawn due to suicide attempts. Three of these participants that withdrew from the study agreed to participate in the other treatment interventions (integration sessions and index assessments; Mitchell et al. 2021).

In studies with missing data, especially clinical trials with human participants, in which much time and money is invested in data collection, it is important to use as much of the available data as possible and have statistical analysis plans for reporting results derived from data sets in which data are missing or the treatment was altered. Estimands are frameworks used to describe results from these data sets or account for missing data (Pohl et al. 2021). Results from wo types of estimands were reported in the stage 3 clinical trial for this treatment, the de jure and de facto estimands. *De jure* estimands refer to results which are determined based only on the experimental data obtained from participants that adhere to the protocol and omits missing data and data from modified treatment protocols. For example, the data from a participant that hypothetically drops out after the first integration session would be included in calculations of the average change in primary measures across their cohort in the post-first session data set, but not in subsequent data sets (i.e., post-session 2 and 3) would not be included in the de jure

results. The de facto estimands include data from participants that receive modified treatments after withdrawing from the intended treatment. Specifically, in Mitchell et al. (2021), this estimand is used to assess the effects of missing data from the three placebo group participants that dropped out prior to the primary study endpoint but adhered to modified treatment protocols that included remote integration sessions and taking primary measures. The data from the modified treatment these participants received, were not included in the de jure estimands (Mitchell et al. 2021).

Results in the trial concerning physiological side-effects and suicidal ideation further supported the safety profile of MDMA. Ninety percent of patients of participants across both treatment groups reported suicidal ideation at least once in their lifetime. The baseline suicidal ideation at the start of the study was also high across both groups; 37 % and 32 % of participants in the MDMA and placebo groups respectively reported suicidal ideation prior to the treatment (Mitchell et al. 2021). For comparison, globally, the lifetime prevalence of suicidal ideation in the general population is 11.5 % (Farooq et al. 2021). It should be noted that this comparison is confounded by the countries in which the studies took place. Farooq et al. (2021) included data from the populations of over ten countries, while Mitchell et al. (2021) collected data on populations residing in only three countries. The prevalence of suicidal ideation did not increase throughout the study in the experimental group, indicating that suicidal ideation is not a prevalent risk from MDMA use under the experimental conditions. Minor and transient increases in blood pressure, heart rate, and body temperature were observed in the experimental group, but were not deemed to be seriously adverse or life-threatening (Mitchell et al. 2021).

With respect to changes in CAPS-5 scores and PTSD diagnosis, “loss of diagnosis” is defined no longer meeting the diagnostic criteria of PTSD described in the PTSD section and Figure 4. “Remission” is defined as a loss of diagnosis and a total CAPS-5 score ≥ 11. “Responders” to the treatment are defined as those that show a clinically significant improvement to the treatment in PTSD severity, defined as a decrease in the CAPS-5 scale of ≥10 points.

The results of this trial for these parameters in each group following experimental sessions are displayed graphically in Figure 5. Following the treatment and upon study termination, loss of diagnosis criteria was met by 67% of participants in the experimental group and 32% of the control group. Remission criteria was met by 33% of the experimental group compared to 5% of the control group. There were no significant correlations between the temporal parameters including onset of PTSD diagnosis and previous treatment intervention type with treatment efficacy; that is, neither the length of time in which the participant has experienced PTSD nor tried treating it was found to correlate with MDMA-assisted psychotherapy treatment efficacy (Mitchell et al. 2021).

A visual display of the phase 3 trial results concerning the average changes in CAPS-5, SDS, and BDI-II scores in the study groups are summarized in Figure 6. The bold lines in these images represent the mean changes in instrument scoring, while the shaded area around them represents the standardized error of the mean (SEM), which quantifies the variability of mean parameter changes across each cohort. In contrast, standard deviation measures the variability of individual data points compared to the mean value of the data set. Cohen’s d (d) was chosen in data analysis to indicate effect

size. The de jure estimand of the mean changes (Δ) between the baseline value (T1 in Figure 6A) and the post-third experimental CAPS-5 scores (T4 in Figure 6a) was -24.4 (pooled standard deviation (SD) = 11.6). In contrast this change was smaller in the placebo group (Δ = -13.9, SD = 11.5). The Cohen's d between these measurements was 0.91.

These results in CAPS-5 scores did not vary significantly with respect to the dissociative and non-dissociative subtypes of PTSD; for dissociative subtypes, the MDMA group (n = 6, Δ = -30.8, SD = 9) showed a greater average change than that in the placebo group (n = 13, Δ = -12.8, SD = 12.8), for non-dissociative subtypes: MDMA Δ = -23.6 (SD = 11.7) placebo Δ = -14.3 (SD = 11.2).

The de jure estimand of mean changes in SDS scores indicated that functional impairment was significantly improved in the MDMA group (Δ MDMA = -3.1, SD = 2.6) as compared with that in the placebo group (Δ = -2.0, SD = 2.4, d = 0.43).

The de jure estimand in the mean changes in depression severity as measured with the BDI-II scores similarly favored the treatment group (Δ = -19.7, SD = 14.0) compared with the placebo group (Δ = -10.8, SD = 11.3, d = 0.67), Mitchell et al. 2021).

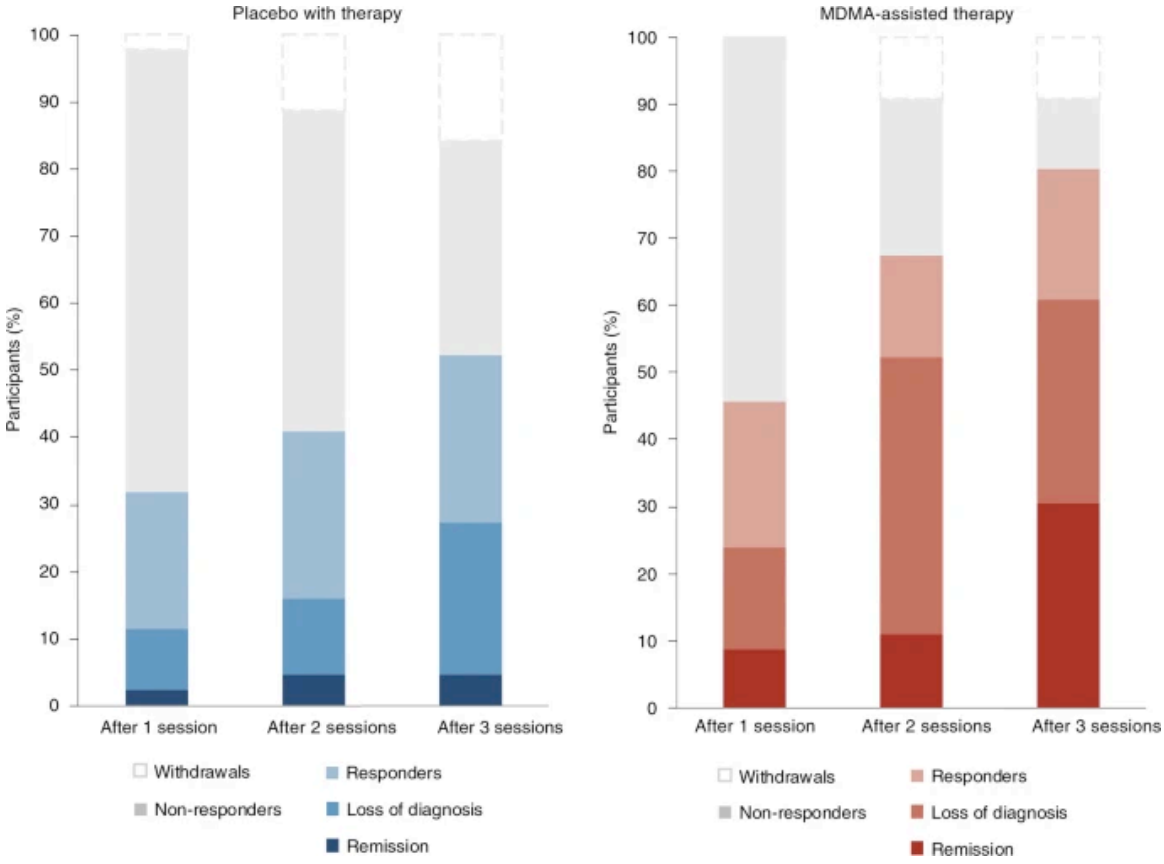

Figure 5. Results of the first phase 3 trial for MDMA-assisted psychotherapy for the treatment of PTSD with respect to the distribution of individual participants' changes in PTSD severity and diagnosis as measured by the CAPS-5 assessment. "Loss of diagnosis" is defined no longer meeting the diagnostic criteria of PTSD described in the PTSD section and Figure 4. "Remission" is defined as a loss of diagnosis and a total CAPS-5 score ≥ 11. "Responders" to the treatment are defined as those that show a clinically significant improvement to the treatment in PTSD severity, defined as a decrease in the CAPS-5 scale of ≥10 points. (Mitchell et al. 2021).

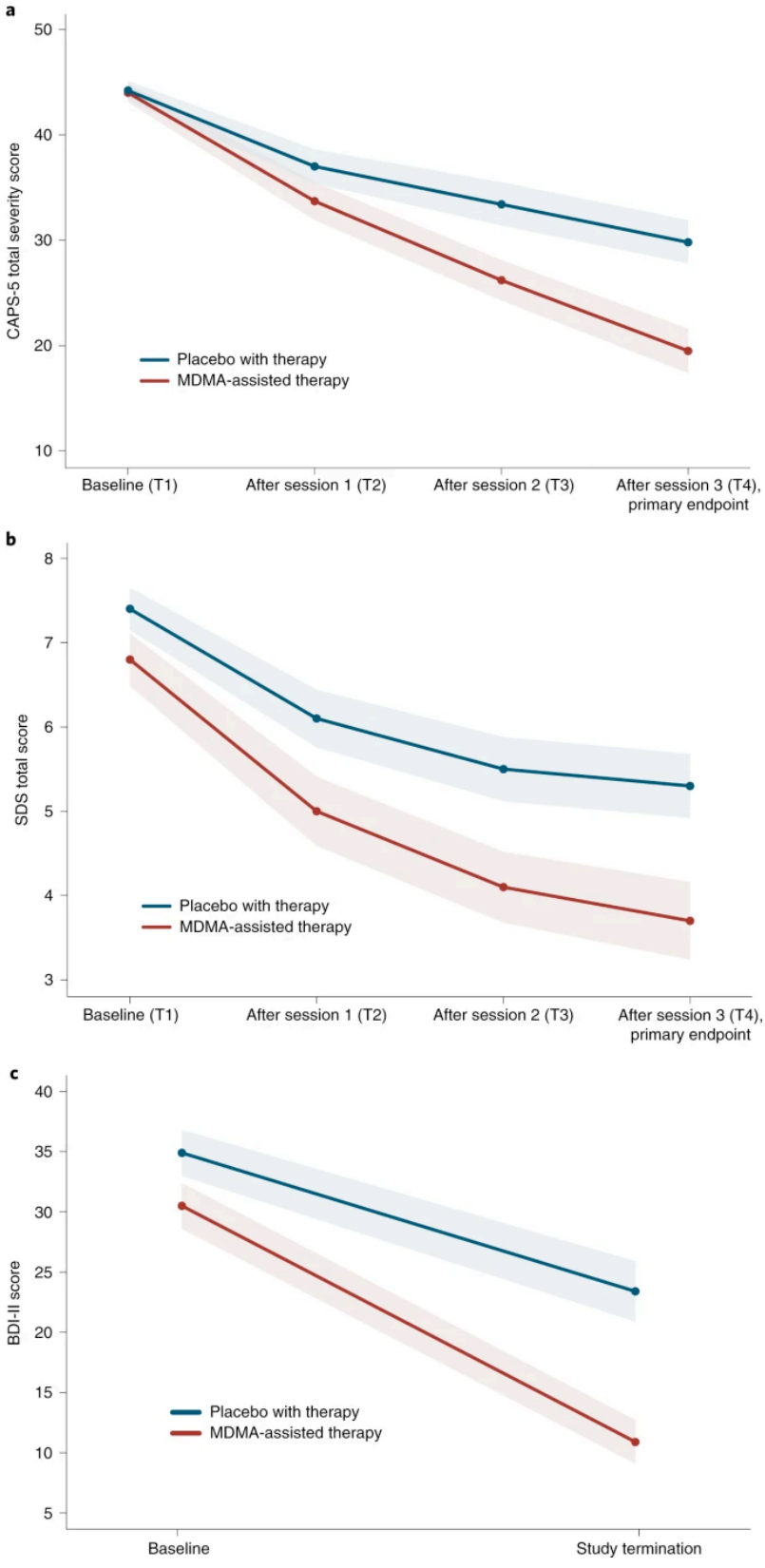
a
CAPS-5 total severity score
50
40
30
20
10
Placebo with therapy
MDMA-assisted therapy
Baseline (T1)
After session 1 (T2)
After session 2 (T3)
After session 3 (T4), primary endpoint
b
SDS total score
8
7
6
5
4
3
Placebo with therapy
MDMA-assisted therapy
Baseline (T1)
After session 1 (T2)
After session 2 (T3)
After session 3 (T4), primary endpoint
c
BDI-II score
40
35
30
25
20
15
10
5
Placebo with therapy
MDMA-assisted therapy
Baseline
Study termination

Figure 6. Results of the first phase 3 trial of MDMA-assisted psychotherapy for the treatment of PTSD with respect to the average changes in CAPS-5, SDS, and BDI-II scores before and after treatment. The bold lines show the average instrument scores at the time points specified on the X-axis. The shaded area around the lines represents the SEM. The blue lines represent data from the placebo group, and the red represents that from the MDMA group (Mitchell et al. 2021).

Limitations of the First Phase 3 Trial

While the first phase 3 trial discussed above yielded exciting results, a few limitations exist for the conclusions that can be derived from the data and are discussed in this section. The participant population lacked ethnic diversity, which is partly due to the low ethnic diversity in the countries in which the trials were conducted, namely Israel, the US, and Canada. As more studies are conducted, it will be interesting and crucial to see how these data are affected by genetic and environmental variability associated with different ethnicities and geographic areas. Similarly, long-term follow-up data are important for assessing the overall treatment efficacy and the time course in which these effects are sustained. This is not yet available.

Finally, the patient blinding is impaired in such studies in which the subjective mental effects of drugs affect the treatment outcomes and adherence. Only 16% (7 of 44) of participants in the placebo arm and 4% (2 of 46 participants) in the treatment group inaccurately guessed their group designations (determined after the study ended). Lack of blinding in the placebo arm of the study may cause these participants to drop out of the study earlier than they would have if they were sufficiently blinded, possibly due to the patient perceiving the treatment as ineffective and not worth their time or effort. Higher dropout in the placebo group can introduce bias and cause tolerability data to favor the

treatment (Mitchell et al. 2021). It is unlikely that participants in the MDMA group would be not feel any subjective effects of the MDMA because the dosages they received were sufficiently high for the subjective effects to be perceived as indicated by the post-study blinding patient blinding assessments and phase 2 trials (Mithoefer et al. 2019).

Comparison of the Efficacy of MDMA-Assisted Psychotherapy for Treating PTSD with that of FDA-Approved PTSD Treatments

A conclusive and valid comparison of the efficacies of PTSD treatments would require a randomized clinical trial in which two or more treatments are compared directly in the same trial with as many variables as possible held constant between the treatment groups. In this case, these variables may include treatment length, instruments for measuring PTSD diagnosis and severity, statistical analysis, and population inclusion and exclusion criteria. Such study design limits the possibility of bias that may skew the data to favor one treatment over another (Leichsenring et al. 2022). Such trials are yet to be conducted with MDMA-assisted psychotherapy for the treatment of PTSD because of the novelty of the treatment. Despite this lack of data, this section will attempt to compare the efficacies of the treatments for PTSD.

Meta-analyses on the psychotherapeutic treatments for PTSD (CPT and prolonged exposure) have indicated a wide range of findings across trials in which the therapy is compared with a placebo with respect to their efficacy in treating PTSD. Such research has indicated that CPT and prolonged exposure produce nearly the same treatment efficacy and dropout rates and will be discussed together. The clinical trials on the

psychotherapeutic treatments for PTSD are similarly not easily compared as they employ different methodological variables, the most significant being instrumentation and treatment duration. Moreover, as with the reclassification of PTSD in the DSM-V, the CAPS instrument was revised accordingly, so it should be noted that older clinical trials used a different instrument to evaluate treatment efficacy.

One meta-analysis conducted in 2005 found a significantly higher effect size of psychotherapeutics as compared with that of pharmacotherapeutics (standardized mean deviation (SMD) = 0.8 and 0.5 respectively; NICE 2005). This led to the designation of psychotherapeutic interventions as first-line treatments and pharmaceutical interventions as second-line treatments for PTSD by the World Health Organization (Hoskins et al. 2010). A newer meta-analysis found insignificant differences in the treatment efficacies of pharmaceutical and psychological therapies for PTSD (SMD = 0.50 and 0.54 respectively, Leichsenring et al. 2022). In addition to the different methodological variables employed in these analyses, the placebo effect is also believed to account for the observed differences in the efficacies of these treatments; one trial on the pharmaceutical interventions for treating PTSD in which an inactive placebo was employed as the control found a 40% reduction in PTSD symptoms in the placebo group, indicating its importance in designing such randomized clinical trials and interpreting the data from them (Hoskins et al. 2010).

Another meta-analysis on newer forms of these clinical trials (in which the CAPS-5 was used to evaluate PTSD diagnosis and symptom severity) reported that an average of 50% - 70% of patients that received these psychotherapies achieved a clinically

significant reduction in their PTSD symptoms and 30% - 40% no longer fit the diagnostic criteria. This study used data from five trials of CPT that included a total of 481 participants who received the psychotherapy treatment and four trials of prolonged exposure that included a total of 402 participants who received the prolonged exposure treatment. This analysis, however, failed to report the corresponding averaged data of the control groups in these studies, but did report some of the between-group effect sizes from pretreatment to post treatment CAPS scores for each trial, which ranged from d = 0.27 - 0.98 (Steenkamp et al. 2015). In contrast, a more recent meta-analysis of such trials reported a medium effect size for psychotherapy for PTSD treatment (SMD = 0.54, Leichsenring et al. 2022). Such studies evaluated in both these meta-analyses failed to report key treatment outcomes including symptom remission, treatment response, and loss of diagnosis, further calling the conclusiveness of the comparisons of these studies into question. According to the earlier meta-analysis of these trials for which the three- and six-month follow-up data were available, there were no significant decreases in loss of diagnosis or reduction in clinically significant symptoms but a significant decrease in remission criteria was reported (Steenkamp et al. 2015). The newer meta-analysis reported that the medium effect size of the treatment on CAPS-5 scores was sustained at 12-month follow-ups after psychotherapy treatment termination (Leichsenring et al. 2022).

Based on several parameters such as safety, tolerability, and treatment efficacy that are qualitatively discussed in the PTSD section and more quantitatively discussed in this section. MDMA-assisted psychotherapy appears to be a superior treatment across all

these parameters. Participant dropout in clinical trials is a good indicator of treatment tolerability and is therefore another important parameter to track and report in such studies. The dropout rate in the trials for PTSD psychotherapies evaluated by Steenkamp et al. (2015) ranged from 13% - 39%, with an average of 25%. Many of these trials failed to report reasons for patient dropout, and treatment dropout definitions and criteria are not consistent across the trials, which makes comparisons of this parameter across these studies less conclusive (Steenkamp et al. 2015). Based on the dropout rates of SSRIs for treating PTSD from a meta-analysis of five randomized clinical trials with a total of 3500 participants, their use is generally well-tolerated, but not without risk. Such studies found dropout rates due to adverse events in the SSRI groups of 9%. Moreover, this analysis reports that across eight randomized clinical trials including 1078 participants, clinically significant reductions in PTSD symptoms were observed in 58% of participants in the SSRI group compared to 35% of participants in the placebo group (Williams et al. 2022); the effect size for these data is not reported, but another meta-analysis reports a standardized mean deviation of 0.50 for SSRI groups in comparison to placebo for treating PTSD (Leichsenring et al. 2022). This figure for responders in the SSRI groups may be a high estimate, as other, more recent meta-analyses have indicated that 40% - 60% of PTSD patients do not respond to SSRI treatment for PTSD (Steenkamp et al. 2015). Moreover, head-to-head comparison of treatment efficacies of SSRIs and other PTSD treatments does not produce conclusive data because this research may be confounded by lifetime history of SSRI use. In the aforementioned phase 3 trial for MDMA-assisted psychotherapy, 65.6% of participants reported lifetime SSRI use,

making it difficult to distinguish the cause of results between the effects of the treatment and long-term SSRI use. In the experimental group of the phase 3 study, however, there were no observed effects of SSRI use history on the efficacy of MDMA-assisted psychotherapy for PTSD treatment (Mitchell et al. 2021).

Proposed Mechanisms of Action of MDMA-Assisted Psychotherapy for Treating PTSD

Several mechanisms of action have been proposed that may explain how MDMA-assisted psychotherapy is effective in treating PTSD. While some investigators may believe that one of these mechanisms better account for the treatment efficacy, these are not necessarily mutually exclusive and each may exist in conjunction with one another to explain the effects of MDMA-assisted psychotherapy on different levels such as the molecular, cellular, and behavioral scales. This section will provide and discuss these mechanisms.

The simplest and oldest proposed mechanism applies to the behavioral level of MDMA effects and PTSD symptoms and was formulated upon the development of the treatment before 1980 by Shulgin and his group of therapists and clinicians that first administered the drug to patients in clinical psychotherapeutic settings and reported the effects. Shulgin initially believed that MDMA and other empathogens could be used as therapeutic agents to treat psychopathologies resembling stressor- or trauma-related disorders (which were not characterized until 2013, APA 2013) because of the notable drug-induced subjective effects of acutely increased confidence, self-efficacy, trust, and

extroversion, which are characteristically impaired in such disease states and psychotherapeutic contexts (Nichols 1986). In such contexts, when clinicians attempt to talk about the trauma with the patient, they are often met with resistance, inattentiveness, distrust, and social withdrawal by the patient in response to recalling memories related to their trauma, especially in patients with the dissociative subtype of PTSD. This phenomenon is referred to as the patient being "triggered" and inhibits the intended psychotherapeutic processes, which may be prevented by the mental states induced by MDMA. Consistent with this observation in trauma-focused psychotherapy, the extent to which a patient trusts in and is comforted by the therapist is believed to be an important factor in patient adherence to and efficacy of the therapy. According to this mechanism, the subjective effects of MDMA may produce a "window of tolerance," a time period in which PTSD patients can revisit and constructively reconsolidate traumatic memories without being triggered (Mithoefer et al. 2019, Mitchell et al. 2021). The favorable effects of MDMA on the emotional valence of recalled memories (discussed in the PTSD neurobiology section) may play a role in explaining this mechanism and account for this MDMA-catalyzed window of tolerance (Carhartt-Harris et al. 2014, Mitchell et al. 2021).

Specific time periods exist during development in which neuronal organization and circuitry is highly sensitive to changes due to environmental stimuli and behavioral learning. These are called critical periods. They mediate learning specific behaviors and have underlying mechanisms that are conserved across species involving particular neurons, neurotransmitters, and brain regions. A critical period for social reward learning has been identified and shown to be mediated by the neuropeptide, oxytocin (Nardou et

al. 2019). In addition to the previously discussed functions of oxytocin, it has also been shown to enhance empathy, reduce amygdala-mediated responses to fear-inducing stimuli, and facilitate fear extinction (Vizeli et al. 2022). The early termination of this critical period (typically as a result of traumatic experience) limits constructive brain adaptability to conditioned fear-inducing stimuli despite termination of adverse stress-inducing conditions. MDMA has been shown to reopen this critical period in adult mice. MDMA-induced increased serotonin concentrations, which is released by the axons of nucleus accumbens cells that project to the hypothalamus, stimulate these hypothalamic cells to produce and release oxytocin throughout the brain. This induces plasticity in the post-hypothalamic synapses and is believed to in part account for the prosocial behavioral effects of MDMA. In mice, prosocial behaviors were elicited within six hours of MDMA administration and lasted two-to-four weeks, far longer after the drug was cleared from their bodies (Nardou et al. 2019). These long-lived neurologic effects of MDMA are consistent with the long-term effects of MDMA on serotonergic neurons and neurotransmission discussed in the MDMA pharmacology section. The mechanism by which these long-term effects are invoked are yet to be elucidated. It is possible that these long-term effects result from changes on the genomic level of the effected cells; that is, MDMA and oxytocin, their metabolites, or secondary intracellular signaling molecules may activate or inhibit the transcription of some genes. The MDMA metabolites (MDA, HMMA, and HHMA), their pharmacological and pharmacokinetic profiles including their formation over time may also play a role in the sustained effects of MDMA administration.

The mechanism of induced neuroplasticity in this critical period and the formation of new functional serotonergic synapses following the long-term phase after single-dose MDMA administration (described in the MDMA section, Baumann et al. 2007) are not well-characterized, but could act through a similar genomic mechanism described above. The current prevailing theory across biology is that such long-term changes (in this case, the restructuring and restoration of the acutely "damaged" neurons by single-dose MDMA administration, not induced by chronic administration) are typically results of disease states or transcriptional changes on the genomic level. Cancer is one example in which genomic alterations cause disease states. Moreover, the observed prosocial effects are consistent with the prosocial endogenous function of oxytocin. This critical period, the effects of reopening it, and its ability to be reopened by MDMA in adult mice has recently been elucidated (Nardou et al. 2019). This oxytocin-dependent mechanism may relate to or account for the observation that reduced amygdalar serotonin transporter activity and concentration (resulting in increased extracellular serotonin concentrations) is correlated with increased susceptibility to developing PTSD and increased fear- and anxiety-related behaviors and induces increased amygdalar activity in response to traumatic reminders. Further, the amygdala is highly innervated by serotonin-secreting axons, and both amygdalar activity and serotonin concentrations in the amygdala increase upon exposure to fear-inducing stimuli. These observations are consistent with the observed amygdalar hyper-activation in stress-related disease states (Mitchell et al. 2021).

The final mechanism that may account for the high efficacy of MDMA-assisted

psychotherapy for PTSD treatment involves the effects of MDMA on memory reconsolidation and fear extinction (which are discussed in a previous section on PTSD and memory). Specifically, this mechanism postulates that MDMA treats PTSD by enhancing fear-extinction training (Mitchell et al. 2021), consistent with the observation that MDMA decreases amygdalar activity in response to fear-inducing stimuli and the hypothesis that MDMA may enhance the processing and weakening of trauma-related memories (Bedi et al. 2009). Animal studies, in which a non-threatening stimulus was conditioned to induce fear and the recall of the emotional affect of this response, has been tested under MDMA or placebo conditions and have generated conflicting findings. In the MDMA-group in these studies, MDMA is administered prior to fear-extinction training. Using mice as model organisms, MDMA has been shown to facilitate the extinction of conditioned fear responses (Young et al. 2015). This was not shown in similar research using rats as model organisms. Instead, these studies demonstrated that MDMA treatment disrupts fear-memory reconsolidation in rats, indicating an acute memory-impairing effect of MDMA (Hake et al. 2018).

Similar studies were also conducted in humans (Vizeli et al. 2022). Such research indicated that MDMA increased the extinction of non-threatening conditioned stimuli in one of two models of fear extinction. The intensity of the subjective effects of MDMA was correlated with increased fear extinction in both models compared with control-groups. This finding largely supports the idea that the effects of MDMA-assisted psychotherapy are mediated by a fear-extinction mechanism, but more research is needed to determine why this effect was found in only one of the two models of fear extinction.

Moreover, this study also measured peripheral oxytocin concentrations and found increases in peripheral oxytocin concentrations in the MDMA group, but no significant changes in plasma oxytocin that were correlated with changes in fear extinction. This latter finding is consistent with the work of Nardou et al. (2019) on oxytocin-mediated critical period reopening in mice, in which it was found that peripheral injections of oxytocin failed to facilitate social reward learning, while intra-cerebrospinal fluid injections succeeded in this. This is a result of differential regulation between plasma and cerebrospinal fluid oxytocin concentrations because the peptide hormone does not cross the blood-brain barrier.

CONCLUSIONS AND FUTURE DIRECTIONS

MDMA-assisted psychotherapy has been shown to be effective as a treatment for PTSD in one phase 3 clinical trial and will need additional randomized clinical trials and safety data before it is introduced into the general population. Moreover, it not only treats PTSD symptom severity, but it also treats major PTSD symptoms and comorbidities, including depression and functional impairment related to the pathology (Mitchell et al. 2021). This section will discuss the future directions of research concerning this treatment.

The first obvious direction is addressing the limitations of the first phase 3 trial on MDMA-assisted psychotherapy in future randomized clinical trials. Specifically, the lack of ethnic diversity among the participants in this trial could be easily addressed by conducting another trial in which this variable is controlled. Similarly, obtaining long-term follow-up data from this trial on the sustained effects of the treatment on PTSD diagnosis and severity will be crucial for evaluating overall treatment effectiveness (Mitchell et al. 2021).

Conducting randomized clinical trials in which the efficacy of MDMA-assisted psychotherapy is directly compared to that of other treatments for PTSD will provide data that is necessary for conclusive comparisons of these PTSD treatments. As was performed in the development of other PTSD treatments, randomized clinical trials should be conducted in which the treatment efficacy of MDMA-assisted psychotherapy is assessed across different populations (Steenkamp et al. 2015, Leichsenring et al. 2022). In the context of PTSD patients, these populations may include, but are not limited to

combat veterans, female sexual assault victims, or civilians exposed to fatal natural disasters.

Future research should also include further investigation into the proposed mechanisms of action that confer the efficacy of MDMA-assisted psychotherapy for treating PTSD. For example, as MDMA neurotoxicity remains a subject of debate, elucidating the mechanisms of action by which it produces its psychological and neurological effects may provide insight into development of a new pharmaceutical that produces similar effects to MDMA, but with a better safety profile and that may show reduced adverse side-effects. This particular area of research may improve the accessibility of drug-assisted psychotherapy for PTSD treatment, as the phase 3 study treatment exclusion criteria (particularly those of cardiac and somatic nature) highlights potential conditions that are contraindicated for the treatment, thereby limiting such patients' ability to receive MDMA in any capacity in a clinical setting. In general, such research into the mechanisms of action the treatment may produce opportunities for fine-tuning and improving the methods by which the treatment is administered for the purpose of bolstering its efficacy and safety as a treatment for PTSD.

MDMA-assisted psychotherapy is a novel therapeutic agent for PTSD, a pathology that places a large burden on society and highly efficacious treatments for it are not yet known. It is also the first treatment regime approved for investigation by the FDA in which a psychedelic or psychedelic-like agent is employed therapeutically or in which a psychoactive agent is employed alongside psychotherapeutic treatments. Psilocybin and its therapeutic application have been a popular topic in

psychopharmacology over the last five years. Phase 2 trials for the application of psilocybin for the treatment of anxiety and depression surrounding terminal cancer diagnoses have been published within the last 4 years displaying a high efficacy for treating this pathology, further supporting the notion of that drug-assisted psychotherapy has a well- earned place in psychiatric research, and desperately warrants further research (Griffiths et al. 2016). It is a shame that legal barriers effectively terminated this research on drug-assisted psychotherapy in the late 1960s, and only had begun in the early 2000s. Given the information presented in this thesis, one may speculate on the current state of psychiatric research and drug-assisted psychotherapy in medical practice had these substances been readily available to researchers during this period of inactivity in the field.

Further investigations on MDMA-assisted psychotherapy to treat substance use disorder and depression are currently being conducted in phase 2 trials. This research has lagged behind that on MDMA-assisted psychotherapy for the treatment of PTSD, and many believe MDMA-assisted psychotherapy research and its apparent efficacy and clinical application has helped pave the way for similar clinical studies on other pathologies and psychedelic compounds (Rieser et al. 2021). Further research into these therapeutics may not only solve society's PTSD problem, but also provide insight into the development of similar treatments for other psychiatric diseases.

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