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DEGREE FINAL PROJECT

Use of MDMA in the treatment of Post-traumatic Stress Disorder

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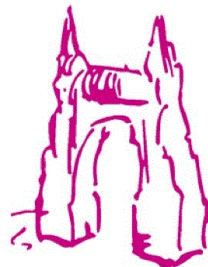
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1. SUMMARY

3,4-methylenedioxy-N-methylamphetamine (MDMA; also known as "ecstasy") is a psychoactive drug that was first synthesized in 1912 by the pharmaceutical company Merck. This amphetamine derivative has been investigated for clinical purposes as it has various interesting mood-altering properties, although in the 1980s was Schedule-I controlled in the United Kingdom, which implies a non-approved medical use, potential for high abuse and illegality in terms of possession. Since MDMA was banned, there has been a campaign to maintain interest in the potential therapeutic value of MDMA, including post-traumatic stress disorder (PTSD). PTSD is a prevalent and disabling disorder, frequently chronic and associated with significant morbidity, poor quality of life, and high personal, social and economic costs. For many patients, the traumatic memories are so powerful and distressing that they cannot bear the emotions subsequent to their recovery, and therefore find themselves unable to complete the therapy. MDMA has the ability to reduce the brain responses to threats, which may allow patients to engage fully in the treatment. This work analyzes the latest reports about this treatment and also revise evidence from randomized controlled trials (RCTs) for the efficacy of acute and long-term pharmacotherapy for PTSD, including the treatment of refractory PTSD with MDMA.

Keywords: MDMA, MDMA psychotherapy, PTSD, post-traumatic stress disorder

La 3,4-metilendioxi-N-metilamfetamina (MDMA; també coneguda com èxtasi) és una molècula psicoactiva que va ser sintetitzada per l'empresa farmacèutica Merck l'any 1912. Aquest derivat amfetamínic s'ha investigat amb objectius clínics degut a les seves propietats interessants d'alteració de l'estat d'ànim. Als anys 80 va ser categoritzat al Regne Unit com a substància de categoria 1, "Schedule I", i en conseqüència va definir-se com a substància sense ús mèdic aprovat, amb potencial d'abús alt i de possessió il·legal. Des que es va prohibir, hi ha hagut una campanya per mantenir interès en el seu potencial terapèutic, incloent el tractament del trastorn d'estrès post-traumàtic (TEPT). El TEPT és un trastorn prevalent i inhabilitant, freqüentment crònic i associat a una elevada morbiditat, qualitat baixa de vida i costos elevats personals, socials i econòmics. Per molts pacients, les memòries de la situació traumàtica que ha desencadenat en la malaltia són tan fortes i desagradables que no poden tolerar les emocions resultants de la recuperació, i per tant no poden completar la teràpia. L'MDMA té l'habilitat de reduir les respostes neuronals a aquestes amenaces, fent que els pacients puguin afrontar el tractament de forma completa. Aquest treball analitza les últimes informacions sobre aquest tractament i també revisa l'evidència d'assajos clínics randomitzats per l'eficàcia de la farmacoteràpia a llarg plaç per el TEPT, incloent el tractament de TEPT refractari amb MDMA.

Paraules clau: MDMA, psicoteràpia amb MDMA, TEPT, trastorn d'estrès post-traumàtic

2. AREAS INCLUDED IN THE PROJECT

The main area of this undergraduate dissertation is pharmacology, the area of biomedical science that studies how medicines and other drugs work and are processed by the body, the drug action. Pharmacology is crucial for discovering new medicines to help fight diseases and it is essential for improving the effectiveness and reducing the unwanted side effects of medicines, understanding why individuals differ in the way they respond to certain drugs, and why some others cause addiction. This project focuses on the use of MDMA as a therapeutical option for diseases, in particular post-traumatic stress disorder, and move it away from the recreational night scene that is related to.

On the one hand, toxicology is the second area included because it is the field of science that helps to understand the harmful effects that MDMA can have on people, animals, and the environment. It is important to keep in mind that not everyone will respond to substances in exactly the same way and that the dose of the chemical or substance a person is exposed to is another relevant factor, and this is why toxicology is important in this project.

On the other hand, the third area includes Physiology and Pathophysiology, because of the study of the functional changes associated with or resulting from disease or injury, the post-traumatic stress disorder in this case.

3. INTRODUCTION

In this report, the substituted phenethylamine 3,4-methylenedioxy-N-methylamphetamine (MDMA) and post-traumatic stress disorder (PTSD) will be properly studied. MDMA is a commonly used illicit drug and is the sole or one of the ingredients in "ecstasy". It was synthesized and patented by Merck in 1912 but not originally intended for human consumption, because it was made as a precursor in a new synthesis process for hemostatic substances. It was tested in animals and interrogation enhancement studies were carried out by the United States (US) military starting in the 1950s (1). In 1985, the Drug Enforcement Agency (DEA) labeled it a Schedule I drug, meaning no approved medical use, high abuse potential and illegal to possess. Before its placement into the most restrictive category of drug regulation internationally, uncontrolled published reports suggested that MDMA, when administered in conjunction with psychotherapy, could yield substantial benefits for those afflicted with a variety of disorders (2). MDMA is hypothesized to support and enhance psychotherapy by increasing the subject's access to emotionally-upsetting material, modulating the associated level of arousal and strengthening the therapeutic alliance (3). It produces unique changes in emotions in humans through a complex combination of pharmacological effects. MDMA is not the only monoamine releaser with particularly prominent effects on serotonin, but it also elevates serum oxytocin, which is a neuropeptide believed to play a role in affiliation and bonding in mammals (4). Brain imaging studies show there is reduced amygdalar activity after MDMA administration, plus changes in the response to angry and happy facial expressions (5). These findings suggest that MDMA may enhance the therapeutic alliance by increasing the likelihood of detecting positive expressions and finding them rewarding, while at the same time reducing the chance of excessive reactivity to fleeting or unintended expressions of anger or disapproval. Recent investigations support that there are positive effects on post-traumatic stress disorder (PTSD) symptoms severity by increasing self-acceptance, promoting interpersonal trust with therapists and catalyzing the effective processing of emotionally-distressing material, but due to its drug scheduling, this is difficult to conduct (6). PTSD is a prevalent disorder that can be a chronic, severely disabling condition causing sustained loss of functionality, accompanied by high rates of medical and psychiatric co-morbidity and risk of suicide. Recognition of neurobiological abnormalities associated with this condition suggests the potential efficacy of medication in its treatment. To date psychotherapy has been the mainstay of treatment for PTSD and has a larger effect size than pharmacological treatment. Cognitive behavioral therapies, particularly prolonged exposure and cognitive processing therapy, are considered among the most effective psychotherapies. Other methods such as psychodynamic therapy and eye movement desensitization and reprocessing (EMDR) have also proved to be effective in treating some aspects of PTSD symptoms (7). Due to the rate of treatment resistance, the need for research into a wider array of more effective treatments is widely recognized.

4. OBJECTIVES

The main objective for this research is showing the current status of the therapy of PTSD with MDMA, which could be a promising treatment for patients with PTSD.

To achieve this goal there are three specific steps which will be crucial to define the success of this research:

1. Study of the molecule of MDMA, and its general characteristics evaluating the safety and efficacy, in consideration of the studies that has been done;
2. Discuss the pharmacological treatments approved for PTSD and the efficacy of different medications in treating PTSD;
3. Describe how MDMA-assisted psychotherapy can be useful to PTSD patients.

5. MATERIALS AND METHODS

In this undergraduate dissertation I synthesize and critically analyze the information I have found in the literature about the use of MDMA in the treatment of PTSD, mainly based on the works by Michael Mithoefer and MAPS organization. I have made a literature review using mainly the free resource Pubmed®. PubMed® has provided me free access to MEDLINE®, the National Library of Medicine® (NLM®) journal citation database. There is another health-related database I have used, the Cochrane Library, a collection of databases that bring together research on the effectiveness of healthcare treatments and interventions.

This bibliographic review has been performed through the research of significant keywords: MDMA, posttraumatic stress disorder, PTSD, combat disorders, psychedelics, psychotherapy, drug abuse, treatment efficacy and ecstasy. More than 200 results were obtained from all types of articles, and the review was not limited by year of publication or text availability, although the language of the studies was filtered to English or Spanish. After the initial search, about 100 studies were excluded because they were to not be of relevance for the purpose of the review. The bibliographic references of the selected articles were also analyzed in order to include other potentially interesting articles for the review.

6. GENERAL INTRODUCTION TO MDMA

6.1. HISTORY OF "ECSTASY"

Ecstasy is the popular or "street" name for the substance identified chemically as N-methyl-3,4-methylenedioxy-amphetamine or 3,4-methylenedioxy-N-methylamphetamine. The initial letters of the major portions of the latter name (Methylenedioxy-Methylamphetamine) give rise to the acronym MDMA, by which this substance is commonly designated in the clinical and research literature. It is a synthetic drug that alters mood and perception, chemically similar to both stimulants and hallucinogens, producing feelings of increased energy, pleasure, emotional warmth, and distorted sensory and time perception. It is a ring-substituted amphetamine derivative structurally related to the hallucinogenic compound mescaline, found in the peyote cactus, to amphetamine (Amph) and phenylethylamine derivatives such as methamphetamine (Meth), and to the monoamine neurotransmitter serotonin (5-HT) (Figure 1), acting MDMA and other Amph derivatives as substrate-type releasers binding to the plasma monoamine transporters.

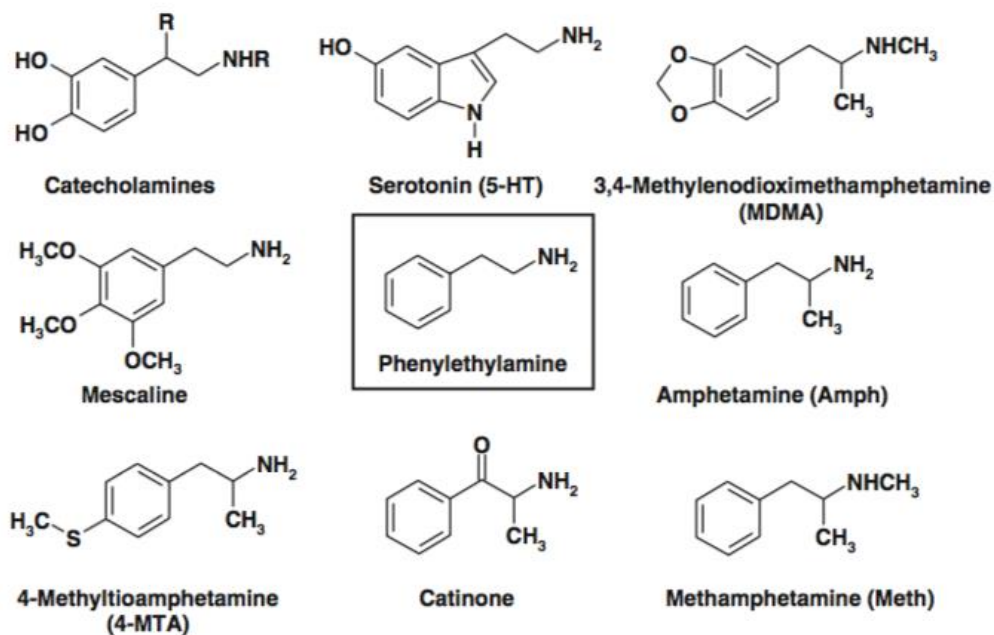


Figure 1. Chemical structures of MDMA and related amphetamines (8)

There is a closely related compound, N-ethyl-3,4-methylene-dioxyamphetamine (MDEA), that differs from MDMA only in having a 2-carbon ethyl group rather than a 1-carbon methyl group, attached to the nitrogen atom of the amphetamine structure.

MDMA was first synthesized and patented in 1912 by the German pharmaceutical company Merck under the name of "methysafrylamin". Many times it has been written erroneously that Merck had the intention of using therapeutic MDMA as an appetite suppressor. Instead, the company was trying to evade an existing patent for the synthesis of a clotting agent called "Hydrastinin" held by the German competitor Bayer/Elberfeld, being methysafrylamin a precursor for therapeutically active compounds.

For the next 15 years MDMA was not mentioned and in 1927, Merck's laboratory pharmacologically tested it for the first time, transforming MDMA from a free base to a hydrochloride salt for the testing. MDMA was as effective as ephedrine, a substance Dr Max Oberlin was interested in finding similar structures, at vascular smooth muscle tissue and stronger at the uterus. Oberlin concluded that the substance did not have "pure sympathetic effects" (9).

The toxicology of MDMA was examined in 1953 with other similar compounds at the University of Michigan in a classified research program sponsored by the USA military (1). In 1959, Merck's chemist Dr Wolfgang Fruhstorfer worked with MDMA and similar substances because he was interested in the production of new stimulants. There was no indication of MDMA testing in humans until 1960 (10). Then in 1978, Alexander Shulgin, a Californian chemist, synthesized and tested the drug and was the first one to describe that MDMA was a psychoactive drug in humans. In fact, he had synthesized MDMA for the first time in 1965 and sometimes he is called erroneously the "father" of MDMA (11). He presented the drug to professional therapists as a valuable adjunct to psychotherapy in therapeutic settings. By the early 1980s, over a thousand private psychotherapists in the USA were using MDMA in their clinical practice, because it was believed to increase patient self-esteem and facilitate therapeutic communication (10). Meanwhile, in 1977, the UK classified MDMA as a class A drug, meaning it is illegal to possess, sell, or give away. In the USA, MDMA became a Schedule I controlled substance in 1985 due to its high abuse potential, lack of clinical application, lack of accepted safety for use under medical supervision, and evidence that could be neurotoxic. This classification was severely criticized by some psychotherapists who realized that their research and medical use of MDMA could not continue.

6.2. DRUG ABUSE OF "ECSTASY"

The abuse of MDMA started in the USA the early 1980s and became popular in the streets as a "fun drug" that was "good to dance". In San Francisco, drug dealers sold MDMA under the name of "ecstasy", which they invented for commercial purposes (1). Moreover, its fame spread across the Atlantic to Europe and consequently to the rest of the world. Nowadays, The Netherlands and Belgium are the main illegal manufacturers by clandestine labs with the 80% of the total production. It is commonly consumed on weekends in warm crowded environments and combined with dancing.

After cannabis, ecstasy is the second most widely abused illegal drug in Europe, mostly sold and consumed orally in the form of tablets, which frequently contain symbols and are colored, though some swallow it in liquid form or snort the powder. Supposedly the tablets are pure, but much of them contain additives such as cocaine, ketamine, methamphetamine, ephedrine or synthetic cathinones. These substances may be dangerous when combined with MDMA and people may be putting themselves at even high risk for harmful health effects. However, the latest reports suggest that purity levels of "ecstasy" tablets, in terms of MDMA content, lie between 90% and 100% (12).

In assessments of single MDMA, most products contained 73-89 mg of MDMA but the range went from 20 mg up to 152 mg MDMA.

The risk of adverse events for a single tablet or powder packet of MDMA is not a precise science due to the inability to assure purity, potency, unadulteration, and stability of products (12). The risk of death from each single use of MDMA has been estimated between 1 in 20,000 and 1 in 50,000 (13). In the EU, the European Monitoring Centre on Drugs and Drug Addiction estimates that more than one million adults take "ecstasy" every month. Based on general population surveys, it has been estimated that almost 8.5 million Europeans have tried "ecstasy", and almost three million have used it in 2005 (14), and there is a clear pattern of gradually rising over the past years.

6.3. PHARMACOLOGY OF MDMA

MDMA and other ring-substituted amphetamine derivatives affect peripheral and central nervous system (CNS) functions by acting mainly on the monoaminergic system, inhibiting the following monoamine transporters: serotonin transporter (5-HTT), noradrenalin transporter (NAT), and dopamine transporter (DAT). It has been studied the mechanism in cultured intestinal cells, expressing the human transporters, and the potency order of potencies for MDMA to inhibit the monoamine transporters was NAT>5-HTT>DAT (15). In intestinal cells expressing the mouse transporter, the order of potencies for MDMA to inhibit the monoamine transporters was 5-HTT>NAT>DAT, which is in accordance with the data obtained in rats (15). In rat synaptosomes, it was found that the rank potency order of MDMA to inhibit monoamine transporters was 5-HTT>NAT>DAT. The rank order of potencies for MDMA inhibition of the uptake of the three monoamine transporters of humans, rats, and mice in comparison with (+)-amphetamine is shown in Table 1.

Table 1. (\pm)-MDMA and (+)-Amph potencies to inhibit the human, rat, and mouse 5-HTT, DAT and NAT transporters based on the K_i values (equilibrium dissociation constants)

Drug (substance)	Experimental model	5-HTT K_i (nM)	DAT K_i (nM)	NAT K_i (nM)
(+)-Amph	Cloned human transporters ¹	38,46 \pm 3,84	0,64 \pm 0,14	0,07 \pm 0,01
	Cloned mouse transporters ¹	23,82 \pm 1,71	0,56 \pm 0,11	0,12 \pm 0,02
	Rat synaptosomes ²	3,830 \pm 170	34 \pm 6	38,9 \pm 1,8
(\pm)-MDMA	Cloned human transporters ¹	2,41 \pm 0,73	8,29 \pm 1,67	1,19 \pm 0,13
	Cloned mouse transporters ¹	0,64 \pm 0,05	4,87 \pm 0,65	1,75 \pm 0,51
	Rat synaptosomes ²	238 \pm 13	1,572 \pm 59	462 \pm 18

¹Data from Han et al. (2006) (15)

²Data from Rothman et al. (2001) (16)

Data show that the major consequence of the methylenedioxy ring introduction in the molecule is the substantial increase of MDMA's potency to inhibit 5-HTT while reducing its potencies to inhibit DAT and NAT when compared to methamphetamine (Meth) or amphetamine (Amph). This brings the K_i values for all three monoamine transporters to a close range. Consistent with in vitro results, in vivo microdialysis experiments in the rat demonstrate that MDMA increases extracellular 5-HT and DA levels in the brain, with effects on 5-HT being greater in magnitude.

MDMA acts as a substrate-type releaser, like other amphetamine derivatives. They bind to the plasma membrane monoamine transporters, being transported and translocated into the cytoplasm, although at high concentration it may also enter by diffusion, stimulating neurotransmitter release via the transporter. Specifically concerning MDMA-induced 5-HT neurotransmitter release, MDMA produces an acute and rapid enhancement in the release of 5-HT from the storage vesicles, possibly by entering the vesicles via the vesicular monoamine transporter (VMAT) and depletes vesicular neurotransmitter stores via a carrier-mediated exchange mechanism. MDMA also inhibits tryptophan hydroxylase (TPH), the rate-limiting enzyme for 5-HT synthesis. In addition, MDMA might also increase extracellular levels of monoamines by partially inhibiting brain monoamine oxidase (MAO) activity, mainly MAO-B located in the outer membrane of the mitochondria of serotonergic neurons. MAO is the enzyme responsible for 5-HT degradation (17). Due to the increase in the free cytoplasmic pool of 5-HT, MDMA promotes a rapid release of intracellular 5-HT to the neuronal synapse via reversal of the 5-HTT activity. The hallucinogenic properties of MDMA are due to the agonism at the 5-HT_{2A} receptor. Like other hallucinogenic compounds, MDMA was found to possess an affinity for the 5-HT₂ receptor located in rat and human cortical neurons with an estimated affinity $K_i = 5\mu\text{M}$, likely through the 3,4-methylenedioxy ring (18).

In the rat, MDMA stereoisomers are substrates for 5-HTT, NAT, and DAT, with (+) isomers exhibiting greater potency as releasers. In particular, (+) isomers of MDMA and MDA (another drug of abuse and major MDMA metabolite) are much more effective DA releasers than their corresponding (-) isomers. When compared to amphetamine and methamphetamine, (+)-MDMA induce the release of 5-HT about ten times more potently than (+)-Meth, whereas (+)-MDMA release DA about six times less potently than (+)-Meth (16). This causes an elevation of mood and increased energy while also causing the secretion of numerous hormones including cortisol, oxytocin, and antidiuretic hormone. Cortisol concentrations significantly increase by 100-150% from baseline levels with MDMA ingestions of 0.5 and 2.5 mg/kg of body weight in the absence of physical exertion (19). When combined with hot temperatures and physical exertion while dancing, two usual characteristics when the drug is taken, cortisol concentrations significantly increase by 800% and maximal increases usually occur around 2-4 hours after ingestion (20).

6.4. EFFECTS OF OXYTOCIN ON EMOTIONAL PROCESSING

Oxytocin is becoming increasingly established as a prosocial neuropeptide in humans with therapeutic potential in treatment of social, cognitive, and mood disorders. One line of evidence suggests that MDMA produces the effects of increasing feelings of empathy by releasing this peptide in humans, involved in social bonding, in addition to its effects on dopamine, serotonin, and noradrenalin in the brain. However, the potential of oxytocin as a general facilitator of human learning and empathy is unclear. Down below there are explained different studies that had been done to describe the prosocial effects of MDMA and his relationship with oxytocine.

In animals, it has been demonstrated that MDMA increased social interaction in Wistar rats meeting for the first time (21). This was predominantly due to an increase in adjacent lying behaviour, where rats lie together for prolonged periods of time. This effect of MDMA was reversed by coadministration of the 5-HT_{1A} receptor antagonist N-N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-2-pyridinylcyclo-hexanecarboxamide maleate salt (WAY 100,635) (22). In this study there were included the emergence and elevated plus-maze tests, social interaction, cat odor avoidance and footshock-ultrasonic vocalizations. The results showed that MDMA increased anxiety-related behaviours in the emergence and elevated plus-maze tests at all dose levels (0, 1.25, 2.5 and 5 mg/kg of MDMA). The 5 mg/kg dose of MDMA reduced significantly the time spent in close proximity to an anxiogenic cat odor stimulus. The 5 mg/kg dose also significantly reduced footshock-induced ultrasonic vocalizations. In the social interaction test, MDMA decreased aggressive behaviours at all doses tested, while the highest dose (5 mg/kg) also significantly increased the duration of social interaction. These results indicated that MDMA has both anxiogenic and anxiolytic effects depending upon the test situation employed, so it has a dual effect (22). On the other hand, in rats, MDMA activates the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus, where the cell bodies of brain oxytocinergic neurons are located. The magnitude of this SON activation is greater when MDMA is administered at high ambient temperatures (23).

In humans, MDMA increases plasma levels of oxytocin, and these increases are correlated with feelings of sociability. Single doses of intranasal oxytocin can also produce prosocial, anxiolytic, and affiliative effects in healthy adults. For example, oxytocin has been shown to increase trust and generosity (24), reduce responses to social stressors, increase positive communication, and, like MDMA, enhance recognition of positive emotional states. The conditions under which oxytocin enhances, or impairs, social interaction remain to be determined. Inspection of the literature, reveals that the effects of oxytocin in the social domain are often weak and/or inconsistent. Other studies failed to detect prosocial effects of oxytocin, and indeed, found that it can produce antisocial effects such as feelings of envy and mistrust (5). The reasons for the differences are not known, but may include characteristics of the subjects samples (e.g. age, gender, and hormonal state) or testing environment (e.g. outcome measures used, social and physical context of testing).

Nevertheless, similar patterns of prosocial effects produced by MDMA and intranasal oxytocin contribute to the prosocial effects of MDMA. There is a study that investigated the acute effects of MDMA and oxytocin on social and emotional processing in the same healthy human volunteers to examine these patterns of behaviour (4). In this study, it was tested the subjective, cardiovascular, and behavioural effects of oral MDMA (0.75 and 1.5 mg/kg) and intranasal oxytocin (20 and 40 IU) in healthy young adults (N=65; 25 female, 40 male), with light-to-moderate past MDMA experience. The study used a within-and-between-subjects, double-blinded design in which subjects received two doses of MDMA, one dose of oxytocin, and placebo.

The results confirmed and extended previous reports on the prosocial effects of MDMA and intranasal oxytocin as it is showed in Figure 2. MDMA dose-dependently increased subjective feelings of friendliness and sociability and the larger dose (1.5 mg/kg) increased desire to socialize with others. Additionally, the larger MDMA dose decreased recognition of negative emotional faces, supporting previous evidence that the drug's prosocial behavioural effects might be partially explained by a decreased capacity to perceive negative emotional states in others. Intranasal oxytocin produced small increases in self-reported sociability but, in contrast to MDMA, oxytocin (40 IU) enhanced recognition of negative emotional faces suggesting that MDMA- and oxytocin-related effects are not synonymous. Overall, these data are consistent with previous reports of the prosocial effects of MDMA (25) and extend these earlier findings by demonstrating modest correlations between the effects of MDMA and oxytocin in the same individuals.

In conclusion, MDMA dose-dependently increased subjective ratings of sociability and "positive mood". The drug increased ratings of drug liking as well as feelings of friendliness, insightful, and sociable. The drug also increased several "negative" subjective ratings such as drug disliking, and feelings of anxiety and loneliness. This mixed profile of both positive and negative subject effects is consistent with the purportedly low abuse potential of MDMA relative to other amphetamines (25).

Intranasal oxytocin also increased subjective feelings of sociability and some measures of positive mood. Interestingly, the finding that the lower oxytocin dose produced greater effects on subjective feelings of sociability is consistent with previous studies indicating that the effects of oxytocin are non-linear. The full profile of subjective and behavioural effects of oxytocin remains to be determined. There were also qualitative differences in the drug effects: MDMA increase heart rate, blood pressure, and objective feelings of anxiety, whereas oxytocin did not affect cardiovascular measures and the lower dose (20 IU) reduced anxiety. These differences may be attributable to their differing mechanisms of action.

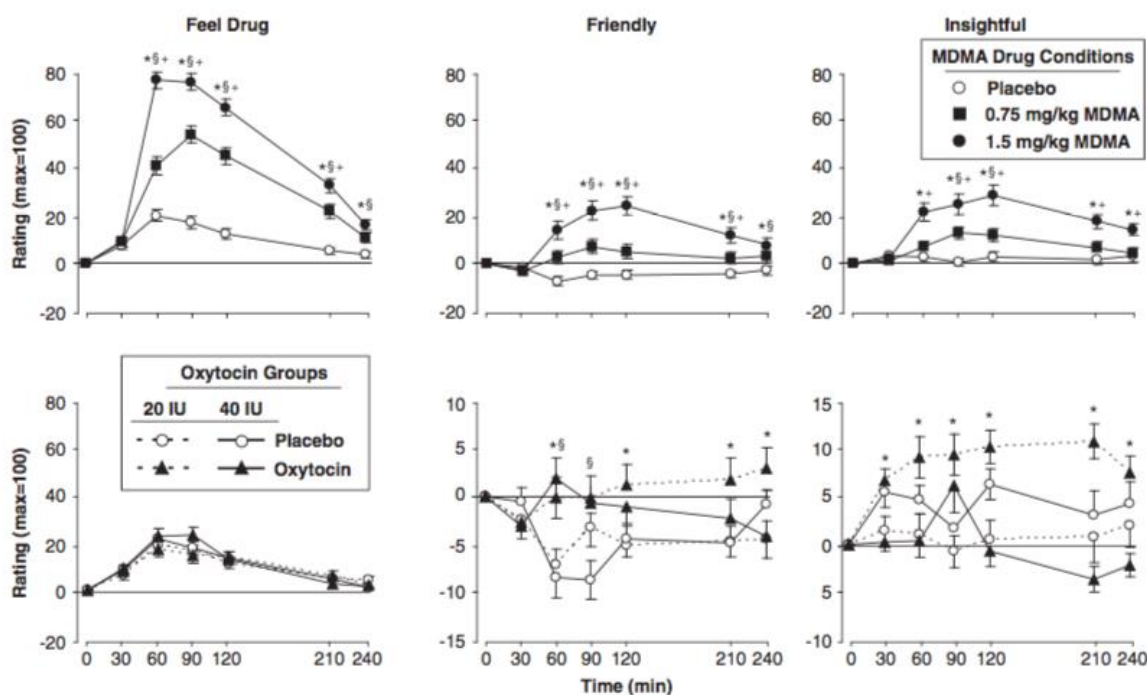


Figure 2. Results from the study by Kirkpatrick et al. (2014) showing:

Top panels: selected mean scores on subjective ratings following administration of MDMA or placebo as a function of dose and time. An * indicates 1.5 mg/kg MDMA significantly different from placebo ($p < 0.05$).

A ‡ indicates 0.75 mg/kg MDMA significantly different from placebo ($p < 0.05$). A + indicates 1.5 mg/kg significantly different from 0.75 mg/kg MDMA ($p < 0.05$). Bottom panels: Selected scores on subjective ratings following administration of oxytocin or placebo as a function of dose and time. An * indicates 20 IU oxytocin significantly different from placebo ($p < 0.05$).

A ‡ indicates 40 IU oxytocin significantly different from placebo ($p < 0.05$). Error bars represent one SEM. (4)

6.5. PHARMACOKINETICS

MDMA has a unique pharmacokinetic and drug interaction profile. First of all, MDMA and related amphetamine compounds are weak bases with pK_a values around 9.9, low molecular weight, low protein binding (around 20%), and high volume of distribution (26). These properties confer easy diffusion across cell membranes, lipid layers, and to tissues or biological matrices with a more acidic pH compared to blood. MDMA in humans is well absorbed when taken orally in the form of tablets, and maximum concentration (C_{max}) appears at 1.5-3 h (27). After the administration of five different doses of MDMA (50, 75, 100, 125 mg), it has been seen that the C_{max} and area under the curve (AUC) for 24h increased according to the administered dose. Meanwhile, for the 150 mg dose, the increase in MDMA kinetic parameters was not proportional to the dose, which clearly implies nonlinear pharmacokinetics (27).

Similarly to humans, the nonlinear pharmacokinetics of MDMA can also be found in rats. For instance, MDMA concentrations in the rat brain increase nonlinearly with the dose (28). In Figure 3, parallel MDMA concentration-time curves in plasma and brain according to the dose given to Sprague-Dawley rats are shown.

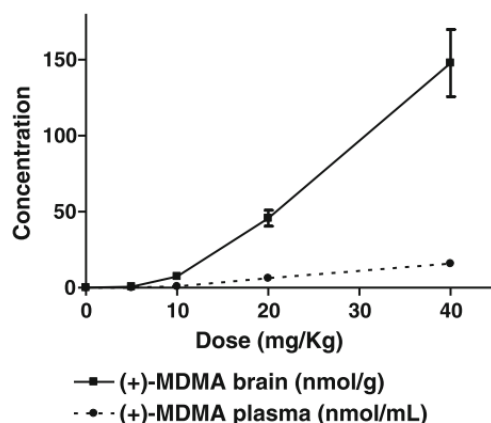


Figure 3. (+)-MDMA concentration time-curves in the plasma and brain as a function of the (+)-MDMA dose given to Sprague-Dawley rats. MDMA concentrations rise in a nonlinear manner with the increase of MDMA dose. The expected brain concentrations of MDMA, assuming a linear trend of concentrations with increasing doses, would be much lower than the ones actually found (28)

Several studies have been performed to evaluate humans pharmacokinetics of MDMA in controlled settings. In a randomized, double blind, crossover study (n=10), subjects were given MDMA 100 mg or MDMA 50 mg followed by 100 mg 2 hours later with pharmacokinetics assessed over 50 hours and dynamics assessed over 6 hours (3). There were elevations in maximal plasma concentrations (C_{max}) and area under the curve (AUC) with the higher vs. lower dose but no changes in other pharmacokinetic parameters. Physiological measures were recorded, and the average peak systolic and diastolic blood pressure differences from baseline were 48.8 and 148.9% greater over 6 hours with higher vs. lower dose MDMA ($p < 0.01$ for both). While not statistically significant, the average temperature difference from baseline comparison was 222% greater with higher vs. lower dose MDMA and the temperature difference between groups was significantly greater at the 2.3, 2.6, and 3.0 hour individual time point comparisons, so the increase in temperature was higher after repeated MDMA administration in comparison with single dose. Importantly, no significant changes were seen between groups in the 6 hour Addiction Research Center Inventory (ARCI) scales assessing euphoria or stimulant effects (19.4 ± 12.4 vs. 16.8 ± 1.03 , $p = NS$) but there was a 71.9% increase in the difference from baseline comparison for the average measures of dysphoria with higher vs. lower dose MDMA use (9.0 ± 4.3 vs. 5.2 ± 4.8 , $p = 0.007$). Furthermore, visual changes in color were decreased over 6 hours by 59.3% with the higher vs. lower dose MDMA (7.7 ± 12.1 vs. 18.9 ± 22.7 , $P = 0.04$).

This phenomenon of higher plasma concentrations without commensurate increase in positive psychological effects is attributed to a tolerance phenomenon. Given the dose dependent increases in blood pressure and temperature with tolerance to the desirable effects of MDMA, overdosing to try and overcome tolerance is concerning.

6.6. METABOLIC PATHWAYS AND DRUG INTERACTIONS

MDMA is metabolized mainly in the liver through cytochrome (CYP), mostly CYP2D6, although 3-8% of MDMA is eliminated unchanged in the urine over 36 hours post-ingestion (29).

MDMA metabolites, showed in Figure 4, are primarily cleared by CYP isoenzymes, catechol-O-methyltransferase (COMT), glucuronidation, or sulfation.

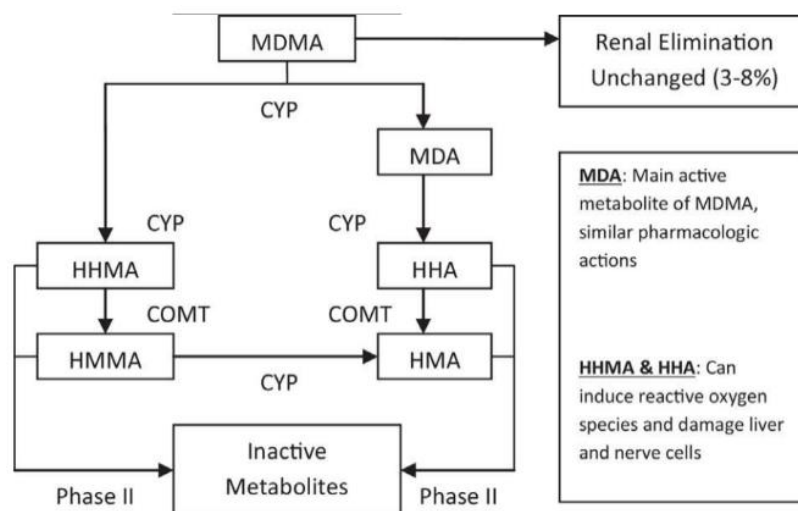


Figure 4. Metabolic degradation of MDMA and its metabolites (30)

CYP2D6 enzymes show genetic polymorphism and depending on the polymorphism and the number of alleles it impacts, can alter their ability to metabolize medications. Drugs that reduce CYP2D6 activity such as paroxetine, reboxetine, duloxetine, and fluoxetine increase MDMA C_{max} approximately 20-30%. However, these agents reduce the desirable effects and the risk of adverse events with MDMA. In a randomized, double-blind, placebo controlled crossover trial, the interaction between duloxetine and MDMA was explored (31). When people were pretreated with duloxetine and then ingested MDMA, it significantly attenuated the pharmacologic effects of increased well-being, emotional excitation, and extroversion versus MDMA alone. Mechanistically, duloxetine therapy attenuated binding of MDMA to NAT and 5-HTT. This is similar to more limited data showing that paroxetine and citalopram can also attenuate the blood pressure and heart rate effects of MDMA (32). MDMA is a potent CYP2D6 inhibitor and autoinhibitor. A single dose can inactivate ~75% of CYP2D6 activity within an hour and it takes approximately 2 days to regain 50% of the function and up to 10 days to fully regain function from its isoenzyme. MDMA inhibits its own metabolism, increasing subsequent plasma concentrations, especially when used more than weekly.

On the one hand, ritonavir, a potent CYP3A isozyme and modest CYP2D6 inhibitor, has been found to increase MDMA concentrations from standard dosing (~50-180 mg) to well above 1,000 ng/mL (usual C_{max} 200-300 ng/mL) (33). On the other hand, COMT is an enzyme available in a soluble and membrane bound form that degrades biological amines, and COMT inhibitors will not impact the metabolism of MDMA, and prevents the breakdown of the HHMA and HHA metabolites. In humans, the urinary recovery of HHMA conjugates are two-fold higher in subjects with low COMT activity polymorphisms.

7. POST-TRAUMATIC STRESS DISORDER

7.1. INTRODUCTION TO POST-TRAUMATIC STRESS DISORDER

It is estimated that as many as 80-100% of all people are exposed to traumatic events during their lifetimes (34). Depending on the nature of the trauma, approximately 5-9% of the general population go on to develop post-traumatic stress disorder (PTSD).

PTSD is a psychiatric disorder that can occur in people who have experienced or witnessed a traumatic event such as a natural disaster, a serious accident, a terrorist act, war/combat, rape or other violent personal assault. People with PTSD continue to have intense, disturbing thoughts and feelings related to their experience that last long after the traumatic event has ended. They may relive the event through flashbacks or nightmares; they may feel sadness, fear or anger; and they may feel detached or estranged from other people. Thereby, frequently becomes chronic and associated with significant morbidity, poor quality of life, and high personal, social and economic costs. It has been estimated that the US economy alone loses of 3 billion dollars annually due to PTSD-related loss in productivity (35).

A diagnosis of PTSD requires exposure to an upsetting traumatizing event. However, exposure could be indirect rather than first hand. For example, PTSD could occur in an individual who learns that a close family member or friend has died accidentally or violently. In the absence of scientific understanding of the pathophysiologic processes involved in PTSD development, the "gold standard" for defining it has been expert consensus as reflected in Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association (APA). These criteria have changed as clinical perspectives and scientific understanding have evolved. Despite periodic changes, there has been consistent agreement on three sets of symptom clusters considered characteristic of PTSD: the intrusive, avoidant and hyperarousal clusters.

1. The intrusive cluster encompass unwanted and repeatedly re-experienced memories, sensations or dreams associated with the trauma. Flashbacks may be so vivid that people feel they are re-living the traumatic experience or seeing before their eyes.
2. The avoidant is about behavioral avoidance of trauma reminders, that may include avoiding people, places, activities, objects and situations that bring on distressing memories. People may try to avoid remembering or thinking about the traumatic event. They may resist talking about what happened or how they feel about it.
3. The excessive physiological arousal and reactive symptoms may include being irritable and having outbursts of anger; behaving recklessly or in a self-destructive way, both in response to trauma cues or independently, for example because of sleep problems.

These core clusters have been embraced in DSM III, IV, and 5, but other symptoms or criteria have been added (negative affect or reckless behavior in DSM-5), deleted (trauma outside of usual human experience), or included descriptively (shame/guilt, dissociation).

Many people who are exposed to a traumatic event experience symptoms like those described above in the days following the event. For a person with PTSD, however, symptoms last for more than a month and often persist for years. Many individuals develop symptoms within three months of the trauma, but can appear later. PTSD often occurs with other related conditions, such as depression, substance abuse, memory problems and other physical and mental health problems. Shifting criteria create scientific challenges to sample homogeneity across time and undermine clinical efficacy when targets for intervention are imprecise and continuously moving.

Not everyone who experiences trauma develops PTSD, and not everyone who develops PTSD either requires psychiatric treatment. For some people, symptoms of PTSD subside or disappear over time. Others get better with the help of family, friends or clergy. But many people with PTSD need professional treatment to recover from psychological distress that can be intense and disabling. That distress is not the individual's fault, and PTSD is treatable.

7.2. PATHOPHYSIOLOGY

An inflexibility of the autonomic nervous system (ANS) may be the underlying mechanism for the increased morbidity that occurs with PTSD. There are psychophysiological indices of ANS function that show abnormal peripheral function, in reaction to trauma exposure, for example heart rate variability (HRV). HRV was measured in 459 middle-aged veteran male twins showing that combat exposure and current PTSD were associated with measures of autonomic inflexibility previously shown to have prognostic significance (36).

PTSD is also associated with exaggerated catecholamine response to trauma cues and elevated levels of NA and decreased levels of cortisol. It was shown that patients with current PTSD had significantly higher NA secretion compared to those without PTSD (37). Furthermore, patients in the lifetime PTSD group exhibited lower cortisol values compared to those without PTSD. Participants who never had PTSD showed the lowest NA and the highest cortisol values (37). Additional peripheral biological abnormalities linked include alterations in serotonin systems, dehydroepiandrosterone (DHEA) (38), neuropeptide Y (39), endocannabinoids (40) and endogenous opioids (41). It has been suggested that alterations in NA and 5-HT may have relevance to symptoms commonly seen in survivors with PTSD, including hypervigilance, exaggerated startle, irritability, impulsivity, aggression, intrusive memories, depressed mood, and suicidality (42).

Genetic work is rapidly expanding, and has identified PTSD-linked polymorphisms in the next genes:

- *FKBP5*: four SNPs of the *FKBP5* gene interacted with severity of child abuse as a predictor of adult PTSD symptoms (43).
- *CRHR1*: there is a role of *CRHR1* gene in the stress response following potentially a traumatic event exposure in youth (44).

- *ADRB2*: *ADRB2* SNPs are strongly associated with the development of PTSD symptoms in persons with a history of childhood adversity (45).
- *COMT*: the *COMT* gene is associated with anxiety disorders, psychosis, depression, and other conditions involving catecholamine pathway regulation (46).

7.3. TREATMENT

Psychiatrists and other mental health professionals use various effective methods to help people recover from PTSD. Both talk therapy (psychotherapy) and medication provide effective evidence-based treatments for PTSD. One category of psychotherapy, cognitive behavior therapies (CBT), is very effective. Cognitive processing therapy, prolonged exposure therapy and stress inoculation therapy are among the types of CBT used to treat PTSD. There is a good amount of evidence that prolonged exposure therapy is an effective treatment for PTSD (47) and it is a first-line treatment recommended in guidelines world-wide. Nevertheless, not all patients benefit from exposure therapy as clinical trials have shown. Approximately 50% of patients lose their PTSD diagnosis after exposure therapy and that proportion of patients achieving complete remission is even smaller (2). In an attempt to improve treatment efficacy, some researchers added other psychological interventions to exposure therapy, such as cognitive restructuring or imaginal rescripting. Although some studies found support for beneficial effects, overall the effect sizes did not exceed those of stand-alone exposure therapy in a clinically significant way.

Another way to improve treatment efficacy that is commonly seen in clinical care is the combination of exposure therapy and pharmacological treatment such as antidepressant medication. However, controlled studies investigating the efficacy of this combined treatment strategy are scarce. Rothbaum et al. (2006) examined the effect of adding prolonged exposure for selective serotonin reuptake inhibitors (SSRIs) non-responders (48). PTSD were provided with 10 weeks of open-label sertraline and those who did not remit were then randomized to either receive five additional weeks of sertraline alone or with 10 sessions of twice weekly prolonged exposure. Results show that the addition of 10 sessions led to increased treatment gains but only for patients who showed a partial response to phase I sertraline treatment. Prolonged exposure augmentation was associated with lower PTSD severity score, more remitters at 6 month follow-up, and maintenance of treatment gains. In a similar design, no beneficial effects were found for paroxetine enhancement when given in addition to prolonged exposure to exposure refractory patients (49). In contrast, it was found that when the combination of exposure therapy and paroxetine (an SSRI) was provided from the beginning of treatment, it was more effective than exposure therapy plus placebo, implying additive benefits. However, the additive benefits disappeared by follow-up. Even though initial treatment with exposure therapy and paroxetine may lead to good clinical outcome, there are also some important disadvantages of this combination strategy, such as adverse events of medication, higher treatment costs, lower treatment acceptability and the risk of relapse after medication discontinuation (50).

The SSRIs paroxetine and sertraline are currently the only medications approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the USA. However, not all patients with PTSD respond to the SSRIs, leading to the need for augmentation or combination treatment strategies, and to interest in agents such as tiagabine or MDMA that employ novel mechanisms of action. The main outcome measure on randomized clinical trials (RCTs) is the impact on the Clinician Administered PTSD Scale (CAPS), the gold standard assessment scale.

7.3.1. PHARMACOTHERAPY FOR PTSD

Below there is a review of the findings of RCTs of pharmacotherapy for PTSD:

- Monoamine oxidase inhibitors (MAOIs)

The MAOIs were one of the first class agents to be tested in RCTs for treating PTSD. The monoamine oxidase A enzyme is a deaminator of both noradrenalin and serotonin, neurotransmitters that have been implicated in PTSD.

- Reversible inhibitors of monoamine oxidase A (RIMAs)

The development of RIMAs overcame many of the factors limiting the clinical utility of MAOIs, such as their potential for serious drug-related adverse events and stringent dietary restrictions that reduced the likelihood of compliance. Nevertheless, results were disappointing (51).

- Selective serotonin reuptake inhibitors (SSRIs)

The SSRIs represent the most frequently investigated class of agents in placebo-controlled trials of PTSD.

- Paroxetine: paroxetine is registered by the EMA and the FDA for the short-term treatment of PTSD. All published randomized placebo-controlled trials of this medication have reported favourable results (52).
- Fluoxetine: a placebo-controlled trial comparing treatment with 20 or 40 mg/d fluoxetine in a sample composed primarily of women did not detect superiority of medication after 12 weeks between any of the comparison groups (n=411) (53).
- Sertraline: sertraline is registered by the EMA and the FDA for the short-term treatment of PTSD. It was suggested that sertraline was a safe, well-tolerated, and effective treatment for PTSD after only 2 weeks of sertraline treatment in 187 patients (54). In contrast, there is a RCT of sertraline for PTSD that did not detect significant differences between sertraline and placebo on any of the primary or secondary efficacy measures at endpoint, and in consequence sertraline was not demonstrated to be efficacious in the treatment of PTSD in the Veteran Affairs (VA) clinic settings studied (55).

The limited evidence reviewed above suggests that treatment with SSRIs may be beneficial over the long term. However, a large portion of patients with PTSD fail to respond to treatment with pharmacotherapy, and few trials of pharmacotherapy in non-responders to first-line treatments for PTSD have been conducted, the majority of them add a course of antipsychotics to ongoing treatment with SSRIs. In general, findings from trials of PTSD appear to support the efficacy of this strategy, at least with respect to combat-related traumas. There is less evidence regarding the management of PTSD in civilian populations.

There is evidence that prazosin, an α 1-adrenergic antagonist, appears to be a promising and well-tolerated agent for the management of PTSD-related nightmares and sleep-related symptoms (56). For refractory cases, olanzapine was found to significantly reduce CAPS scores in the only RCT evaluating it, and risperidone was only effective in 1 of 3 studies (57). There is little empirical support for the efficacy of benzodiazepines in the treatment of PTSD, and contrary to expectations, the early administration of benzodiazepines to trauma survivors with high levels of initial distress did not have a salient beneficial effect on the course of their illness (58).

Medication appears to alleviate PTSD symptoms associated with sympathetic hyperarousal and intrusive recollections of the trauma but seems ineffective against avoidant symptoms. Pharmacotherapy alone is rarely sufficient to provide complete remission of PTSD. Symptom relief provided by medication facilitates the patient's participation in individual, behavioral, or group psychotherapy (59).

8. CLINICAL TRIALS ASSESSING MDMA IN PTSD

New research has shown that MDMA, used as a catalyst in psychotherapy, is effective in treating post-traumatic stress disorder. In the mid-1990s, the majority of research done on MDMA was focused on the potential dangers of the drug because it was categorized as a Schedule I drug. This legislation caused all clinical research to be terminated or severely restricted while the illicit use continued. Also, the therapists that were using MDMA in their practices were either forced to discontinue using the drug with their clients or ignore the law and risk legal punishment. Many studies found that MDMA had neurotoxic effects in animal models and in human retrospective studies. However, some of the erroneous beliefs about MDMA revolve around flawed studies or involved heavy drug abusers. Although there are risks involved with the use of any drug, the FDA has already concluded that MDMA has an acceptable risk to benefit ratio in a clinical setting.

It was not until 2008 when the first RCT data on MDMA in PTSD was published. The world's first clinical trial to evaluate the safety and effectiveness of MDMA-assisted psychotherapy was a Spanish study that started in 2000, carried out by José Carlos Bouso in Madrid. This first study was designed as a randomized, double-blind, placebo-controlled trial assessing five dosages of MDMA in combination with psychotherapy: 50 mg, 75 mg, 100 mg, 125 mg, 150 mg (60), in patients with PTSD caused by sexual assault. Six of the 29 subjects were treated before pressure from the Madrid Anti-Drug Authority led to the revocation of permission to use the study site. As of May 13, 2002, when the study was shut down for political reasons, they had completed treating four patients in the 50 mg dose group (three patients received 50 mg and one received placebo), and two people in the 75 mg dose group (one patient received 75 mg and one received a placebo). All underwent 7 psychotherapy sessions of 90 minutes' duration, with only 1 session accompanied by MDMA or placebo. This psychotherapy session (session 4 of 8) began with MDMA ingestion and lasted for 6 hours, with patients resting for 2 additional hours after this psychotherapy session before being driven home. The overall Severity of Symptoms Scale for PTSD (SSSPTSD) scales score, the main outcome, reduced by an average of 26.8% with MDMA plus psychotherapy (60).

This previous study was sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS). Founded in 1986, MAPS is a non-profit research and educational organization that develops medical, legal, and cultural contexts for people to benefit from the uses of psychedelics and marijuana. Their highest priority project is funding clinical trials of MDMA-assisted psychotherapy for the treatment of PTSD, and also for anxiety associated with life-threatening illness and social anxiety in autistic adults. MAPS is currently the only organization in the world funding clinical trials of MDMA-assisted psychotherapy. Below are shown the completed, ongoing and planned studies sponsored by MAPS.

8.1. COMPLETED STUDIES AND RESULTS

The first study carried out in 2010 by the investigator Michael Mithoefer, when the Drug Enforcement Administration (DEA) informed that it had approved his Schedule 1 license. It was a randomized, double-blind, placebo-controlled trial assessing the impact of 125-mg MDMA-assisted psychotherapy in refractory patients with PTSD (61). The subjects that met all enrollment criteria were 20, aged 21-70 years, with replacement of two dropouts. They were required to meet DSM-IV-R criteria for the diagnosis of crime or war-related chronic PTSD, and to have treatment-resistant symptoms, defined as a CAPS ≥ 50 (signifying moderate to severe symptoms), following at least 3 months of prior SSRI or serotonin-noradrenalin reuptake inhibitor (SNRI) treatment in addition to at least 6 months of psychotherapy. Patients underwent 11 regular nondrug psychotherapy sessions of 90 minutes' duration along with 2 MDMA 125-mg or inactive placebo sessions, in a ratio of 60% MDMA (n=12) to 40% placebo (n=8). The blind was broken for each subject after the follow-up visit 2 months after the second experimental session, and all subjects who initially received placebo were offered participation in an open-label crossover segment. Subjects were required to abstain from all psychotropic medication during study participation except sedative hypnotics or anxiolytics used as-needed between MDMA or placebo sessions. After preliminary evidence of safety and efficacy had been established, a protocol amendment was approved allowing the last nine subjects to receive a supplemental dose of MDMA or placebo in all experimental sessions. The purpose of that was to prolong the therapeutic window of MDMA effects and gather pilot data about dose for design of future clinical trials.

The primary outcome was the CAPS score, a widely used structured interview for quantifying PTSD symptoms (62), and secondary outcomes measures were the Impact of Events Scale-Revised (IES-R), a 22-item self-report measure that assesses subjective distress caused by traumatic events (63), and the Symptom Checklist 90-Revised (SCL-90-R), a brief self-report psychometric instrument design to evaluate a broad range of psychological symptoms of psychopathology. Blood pressure, pulse and temperature were monitored during all experimental sessions, and also neurocognitive measures such as tests of attention and processing speed, expressive language, visual-spatial and constructional abilities, and memory.

The experimental sessions lasted 8-10 h, followed by an overnight stay, with a male and a female co-therapist team present for all sessions, one a psychiatrist, the other a psychiatric nurse. The first dose of MDMA or placebo was given in a capsule by mouth at 10a.m. Subjects then rested in a comfortable position listening to a program of music that was initially relaxing and later emotionally evocative. Throughout the experimental sessions, periods of conversation alternated with periods during which subjects were encouraged to focus on introspection. The optional supplemental dose of 62.5 mg MDMA or placebo was administered 2-2.5h after the initial dose. The therapists stayed with the subject until at least 5p.m. or until the physical and psychological effects of the session had substantially subsided and the subject was judged to be in stable condition. The effects of MDMA occurred 45-75 minutes after the initial dose, and reached

a peak at 2-2.5h and lasted 4-5h in the 11 subjects who received a single dose, and 5-6h in the nine who received a supplemental dose. Effects diminished gradually over several hours, and elevations of blood pressure, pulse, and body temperature were greater in the MDMA group.

There were no resulting medical complications, and the side effects that occurred more frequently in the MDMA group on the day of experimental sessions were: jaw tightness, nausea, feeling cold, dizziness, loss of appetite, and impaired balance. However, more common effects in the placebo group on the day of experimental sessions were: anxiety, insomnia, headache and fatigue. In the week following experimental sessions, some of the most common side effects were reported at similar incidence by both groups: fatigue, anxiety, low mood, headache and nausea, with anxiety being slightly more frequent in the MDMA group and low mood slightly more frequent in the placebo group. During this week, irritability and loss of appetite were more frequently reported in the MDMA group, and insomnia was reported more often in the placebo groups. Side effects typically resolved over a period of hours or days, usually spontaneously, sometimes with short-term symptomatic treatment, but no medical treatment was required during any experimental sessions nor serious drug-related adverse effects occurred.

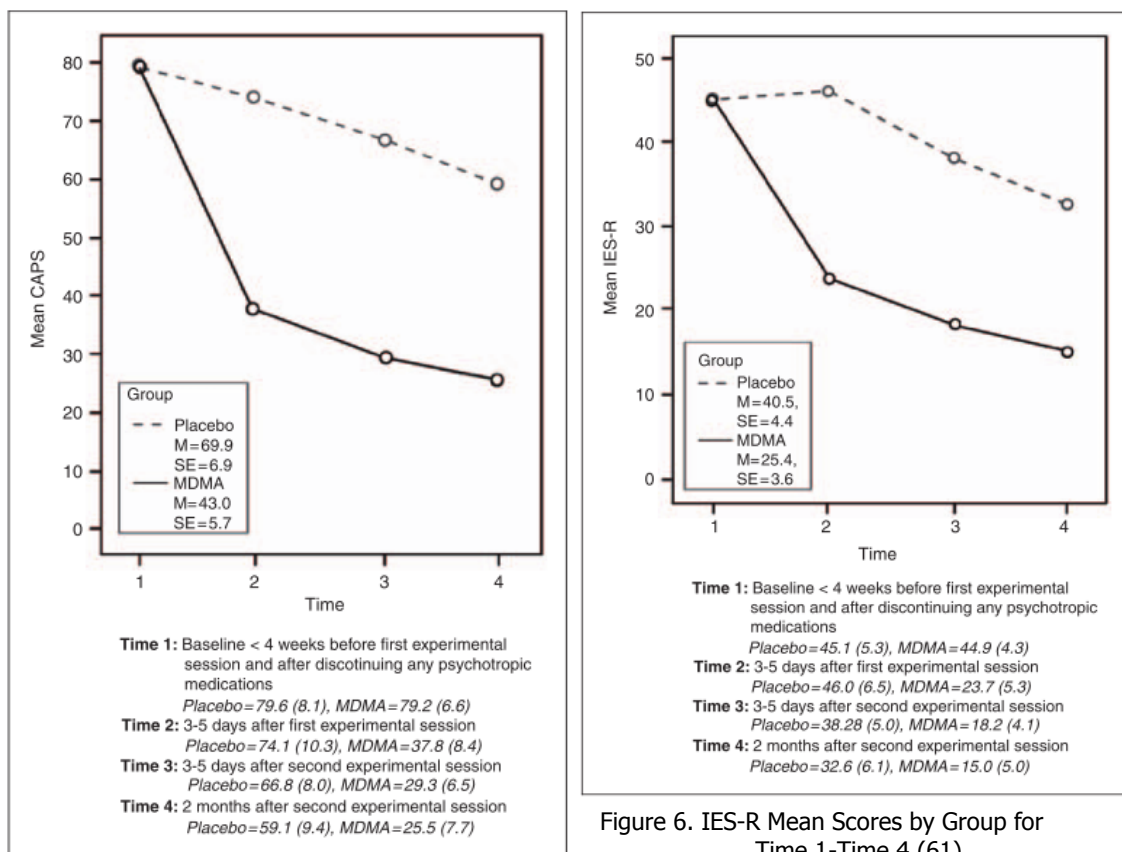


Figure 5. CAPS Mean Scores by Group for Time 1-Time 4 (61)

PTSD symptoms measures by CAPS improved over time in both groups, as it shows Figure 5, but the MDMA group showed significantly greater improvement. Similar results were found for the IES-R, shown in figure 6, that improved over time in both groups but the MDMA group also showed significantly greater improvement. The clinical response was defined as >30% reduction

from baseline in CAPS total severity score, and by the report that all three subjects who had been unable to work because of PTSD were able to return to work. In the first stage, the clinical response was 83.3% (10/12) in the MDMA group, versus 25% (2/8) in the placebo group, and 10 subjects of the MDMA group no longer met DSM-IV criteria for PTSD, compared with 2 of the placebo group. Seven of the eight placebo subjects chose to enroll in the crossover arm, and showed significant decreases in CAPS (Table 2) and IES-R scores from end of the control trial to 4-6 weeks after two MDMA sessions were completed.

Table 2. Crossover Post-hoc Group Comparisons of CAPS at Time 1c- Time 4c (61)

Crossover Arm	CAPS	Time 1c (Baseline)*	Time 4c**	Change Time 1c-Time 4c
MDMA	Mean	65.5	33.9	-31.7***
	<i>n</i>	7	7	7
	Std. Dev.	24.3	12.8	15.0

*Crossover Time 1c is pre-MDMA and at least 2 months post-placebo

**4-6 weeks after second MDMA session

*** $p < 0.05$ Post-hoc paired *t*-test determined statistical significance of mean difference between times

This study demonstrated that MDMA-assisted psychotherapy with close follow-up monitoring and support can be used with acceptable and short-lived side effects in carefully screened group of subjects with chronic, treatment-resistant PTSD. In this group, MDMA-assisted psychotherapy with inactive placebo produced clinically and statistically significant improvements in PTSD symptoms measured by standard symptom scales. This difference was immediate and was maintained throughout the time period.

However, the study had several limitations and should be considered only a preliminary step toward exploring MDMA as a possible therapeutic adjunct. For example, the sample size was small as is appropriate in a Phase II pilot study, where there should be less than 400 people but more than 100. The majority of participants were female and all were caucasian, and gender/or ethnic differences in response to MDMA-assisted psychotherapy could exist. In fact, there is limited data about whether or not patients with war related PTSD are more difficult to treat than those with PTSD from other causes, such as sexual assault. Furthermore, at baseline, the placebo group had history of more prior psychotherapy than the MDMA-treated group, which could mean that the placebo group was more treatment-resistant.

The second study by Michael Mithoefer reported follow-up data evaluating the long-term outcomes for the first completed trial of MDMA for chronic, treatment-resistant PTSD (6). All of the 19 subjects who received MDMA-assisted treatment in the original trial participated in the long-term follow-up (LTFU), with 16 out of 19 completing all the long-term outcome measures, which were administered from 17 to 74 months after the original study's final MDMA session. The CAPS, as in the original trial, remained the primary outcome measure, and the IES-R was used as a secondary outcome measure. It was created a LTFU questionnaire for use in LTFU

evaluations of MDMA-assisted psychotherapy, designed specifically to capture the perceived benefit or harm of MDMA-assisted psychotherapy and changes in any areas not addressed by standard outcome measures, such as changes in relationships or creativity. Additionally, the questionnaire included items addressing participant beliefs concerning the potential benefit of receiving an additional MDMA-assisted psychotherapy session, any psychiatric treatment after the study, and their use of "ecstasy" and/or any other illicit psychoactive substances plus any perceived changes in cognition after study participation. It was found that the mean CAPS and IES-R scores at LTFU for the 16 study completers were not statistically different from their 2-month (short-term) mean scores, as it can be seen in Tables 3 and 4. At LTFU, two subjects had CAPS scores above 50, which indicates relapse with moderate-to-severe PTSD symptoms.

Table 3. Early final study CAPS, 2 months after two MDMA-assisted sessions, versus the LTFU scores obtained in this study, for the same subjects.

CAPS	n	Mean	SD	t	df	p
2-month	16	24.6	18.6	0.1	15	.91
LTFU	16	23.7	23.7			

Table 4. Early final study IES-R, 2 months after two MDMA-assisted sessions, versus de LTFU scores obtained in this study, for the same subjects.

IES-R	n	Mean	SD	t	df	p
2-month	16	19.8	19.5	0.4	15	.72
LTFU	16	22.1	21.8			

In the LTFU questionnaire, all subjects reported a benefit from participation in the study, with at least some benefit persisting, and described the experimental treatment as being helpful, but also being difficult at times. At the time of enrollment, 16 of 19 study participants were in active psychotherapy. At LTFU, only 8 of 19 were in psychotherapy, being cognitive behavioral psychotherapy and EMDR the most common types. These results indicated that there was a favorable long-term risk/benefit ratio for PTSD treatment with just a few doses of pure MDMA administered in a supportive setting, in conjunction with psychotherapy.

The third study, by Oehen et al. (2013) (64) was a randomized, double-blind comparison of psychotherapy assisted by low-dose MDMA (25mg + 12.5-mg supplementary dose) versus high-dose MDMA therapy (125mg + 62.5-mg supplementary dose) during three experimental doses interspersed with weekly non-drug-based psychotherapy sessions, enrolling 12 patients for treatment. All subjects who were enrolled met the DSM-IV-text revision criteria for PTSD with treatment-resistant symptoms, as was indicated by CAPS score of ≥ 50 and having previously undergone at least 6 months of psychotherapy and 3 months of treatment with an SSRI. Subjects were required to stop all psychotropic medication before entering the study. One female subject could not complete de 12-month follow-up because she died 6 months after finishing the MDMA-assisted treatment from a brain metastasis arising from a relapse of breast cancer, although she

had been in breast cancer remission for over 10 years. In the first stage, eight subjects were randomized in a double-blind manner to the full dose and four to the "active placebo" condition (2:1) to better assess the safety of the full dose and to enhance recruitment efforts. The outcome measures included two measures of PTSD symptoms: the CAPS scale and the Posttraumatic Diagnostic Scale (PDS), a validated self-reporting measure to assess the presence of PTSD symptoms. The psychotherapy used in the sessions was the same as Michael Mithoefer (61).

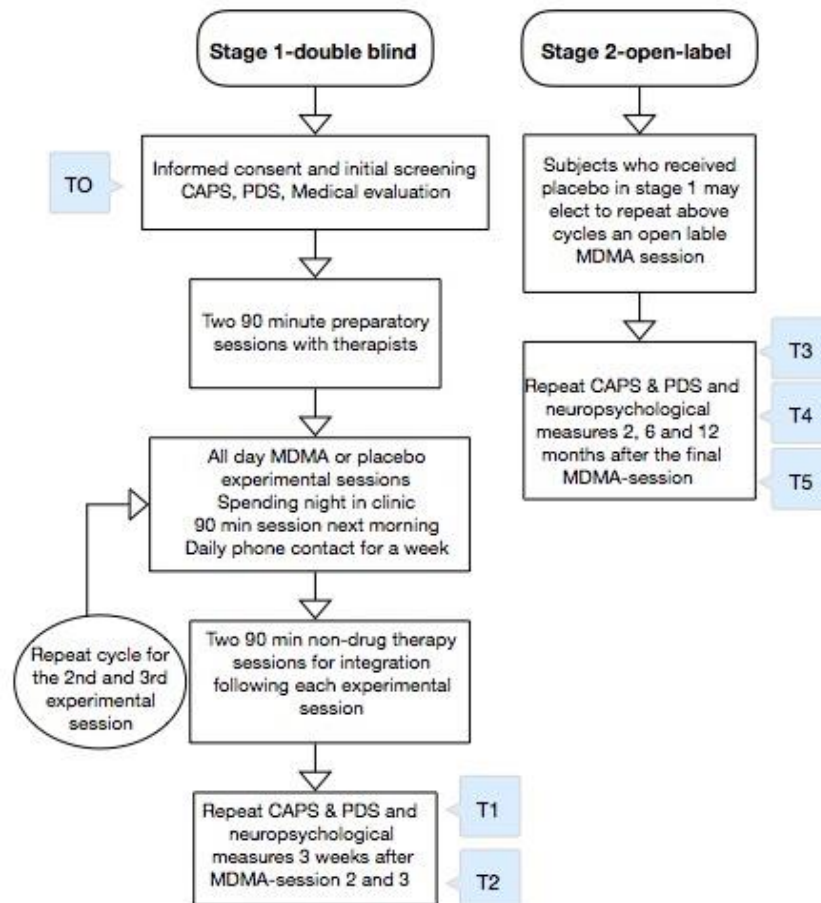


Figure 7. Study visits

The results showed the average CAPS scores in the "active placebo" increased slightly from T1 to T2 as shown in Figure 8. The high-dose group showed a distinct decrease in CAPS scores with time as compared to the active placebo group, but missed statistical significance. On average, CAPS scores decreased 15.6 points in the full-dose subjects. PDS scores decreased in the full-dose group (Figure 8), as compared to an increase in the "active placebo" group. Clinical response was observed in four out of eight subjects in the full-dose group, with all of them fulfilling PTSD criteria, but with a reduction in severity. Three full-dosage subjects met criteria for being non-responders and they were enrolled in "Stage 3", receiving either a full or higher dose of MDMA, but additional sessions did not lead to any further improvements in CAPS scores.

In the "Stage 2" crossover group, all four subjects responded to the treatment, two of four subjects no longer fulfilled PTSD criteria and two had improved, but still had moderate PTSD. At the one-year follow-up, CAPS scores had decreased by a mean of 24 points compared to baseline

in the full-dose group, while there was a 35-point decrease in the crossover group, with nine subjects showing a significant clinical improvement.

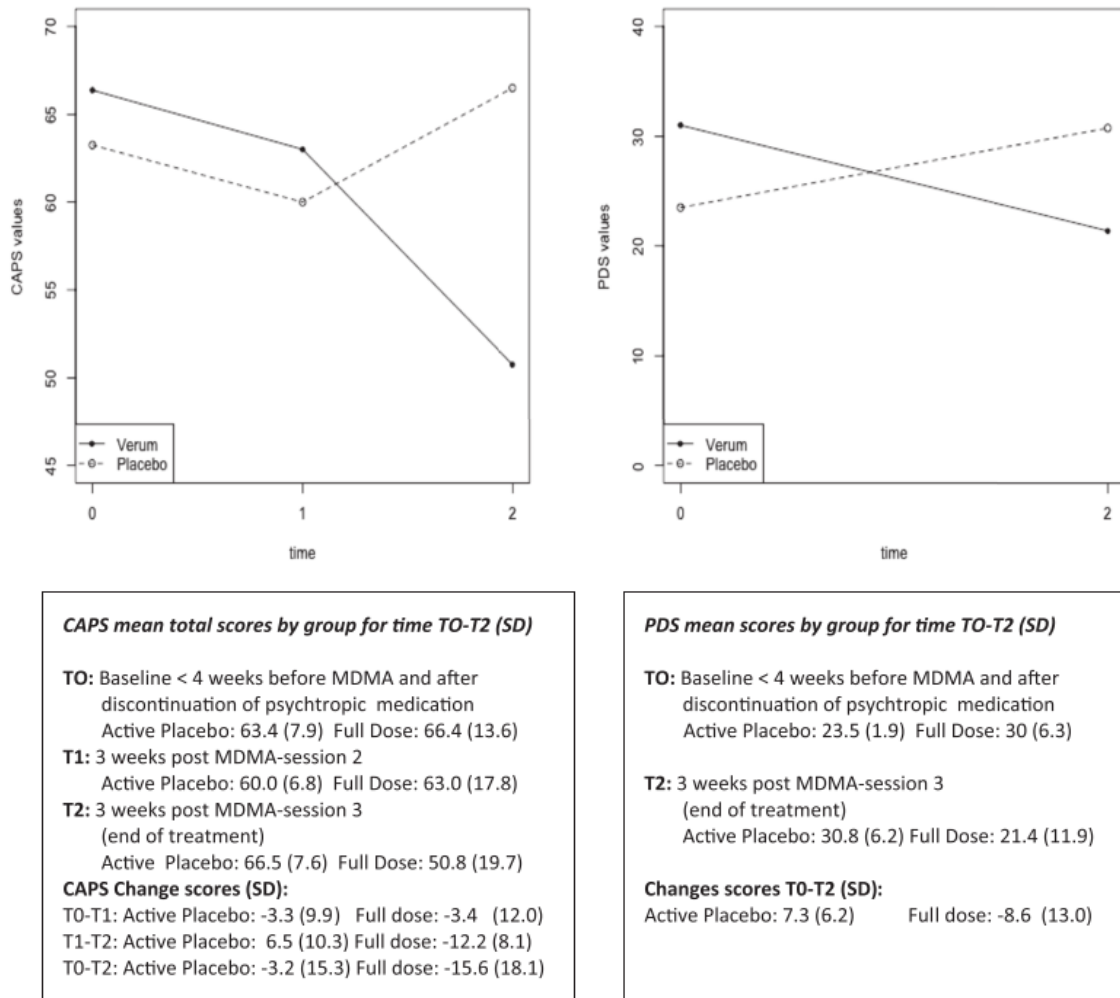


Figure 8. CAPS and PDS scores by groups for time T0-T2 (64)

Also at LTFU, five of 12 subjects no longer met the diagnostic criteria for PTSD, two had switched to having mild PTSD, and four had moderate PTSD, while one had died of a cause not related to the study. One of four subjects on disability and three who were fit for limited employment at baseline had been able to return to work full-time by the 1-year follow-up. A comparison of the safety profiles between 25mg and 125mg doses did support that the 125mg dose was associated with more drug-related reactions in general.

The fourth study got the final approved study protocol in April 25, 2015 by the Israeli Ministry of Health. It has been taking place in Beer Ya'akov Mental Hospital, Israel by the principal investigator Moshe Kotler (65). The study is a randomized, double-blind, active placebo-controlled Phase 2 Pilot Study that investigates the safety and efficacy of MDMA-assisted psychotherapy in 10 people with chronic, treatment-resistant PTSD. It includes an open-label lead-in in two subjects followed by a randomized, double-blind arm comparing 125 vs. 25mg MDMA in eight participants, and an open-label arm for participants who received active placebo during two experimental psychotherapy sessions, each lasting six to eight hours and scheduled three to five

weeks apart. The extent of PTSD symptoms were assessed at baseline, and two months after the second experimental session using a self-report measure. Subjects enrolled in Stage 1 who received the active placebo, had the opportunity to enroll in Stage 2 of the protocol and complete open-label experimental sessions with the fully active dose of MDMA on the same schedule as Stage 1 and were assessed 12 months after the second Stage 2 experimental session. This study allows comparison between the impact of active placebo and full dose MDMA on PTSD symptoms, and on symptoms of depression and sleep quality. Latest news are that on November 10 and November 28, 2016, the fifth and sixth of 10 participants completed their 12-month follow-up interviews.

The fifth completed study investigated the effectiveness of MDMA-assisted psychotherapy for PTSD when one member of the standard male/female co-therapist team is a healthcare intern (being trained in therapy, social work, or nursing) (66). The other member of each team is a professional therapist trained in the MAPS treatment method. The principal investigator is Marcelona Ot'alora, and is being developed in Boulder, Colorado. This Phase 2 pilot study examines the safety and efficacy of manualized MDMA-assisted psychotherapy in 23 subjects with chronic, treatment-resistant PTSD of at least six months duration who were unable to achieve remission despite having received prior treatment with either pharmacotherapy or psychotherapy of adequate dose/duration or who discontinued treatment due to lack of tolerability. Two types of co-therapist teams conducted the study. Each team had an experienced therapist with a background consistent with that required in the treatment manual paired with either another experienced therapist or an "intern" co-therapist that is either pre-licensure, is licensed but with less experience, has a different therapy background than indicated in the manual, or practices a different healing profession (physician, nurse, social worker). On February 24, 2017, investigators gathered for the formal closeout of the study, and all treatment sessions and long-term follow-up interviews have now been completed. The final results are being prepared for publication.

The sixth completed Phase 2 pilot study is a randomized, double-blind, placebo controlled study in 12 subjects that estimates the effect sizes of full dose and comparator dose MDMA as an adjunct to manualized psychotherapy by the principal investigator Ingrid Pacey in Vancouver, Canada (67). The study is officially completed and investigators gathered for the formal closeout on November 27, 2016. The final results are being prepared for publication.

The final results of the last two studies are being prepared for publication as a part of a global meta-analysis of MDMA-assisted psychotherapy results by MAPS.

8.2. ONGOING STUDIES

Encouraging data has been obtained and submitted to the FDA from MAPS's completed studies, and MAPS is currently sponsoring other Phase 2 studies all over the world (68).

The first study will investigate the effects of MDMA on startle testing learning in health volunteers in comparison a placebo control. This study will be conducted by the principal investigator Barbara Rothbaum at Emory University in Atlanta, Georgia.

The second study is a "Training protocol for MDMA-assisted psychotherapy" by the principal investigators Michael Mithoefer, Ann Mithoefer and Marcela Ot'alora. This Therapist Training/Phase 1 psychological effects protocol is a placebo-controlled, double-blind, randomized, cross-over study that allows MAPS to administer a single MDMA-assisted psychotherapy session to therapists as part of their training to conduct MAPS' MDMA/PTSD studies, while also conducting a series of evaluations of the psychological effects of MDMA administered to healthy volunteers in a therapeutic context.

The third MDMA-assisted psychotherapy study is a Phase 1/2 open-label treatment development study of MDMA-assisted CBT integrated with MDMA-assisted psychotherapy for the treatment of PTSD. This study will enroll 10 pairs consisting of one participant diagnosed with PTSD, and one concerned significant other who does not have a current PTSD diagnosis but who is experiencing problems associated with the psychosocial circumstances related to the PTSD participant's diagnosis. The primary outcome measure is the CAPS scale according to DSM-5 administered to the participant with PTSD but additional measures evaluate the qualities of the relationship between the participants, and psychological distress in the significant other.

Nowadays, there is one planned study by MAPS that will evaluate the safety and effectiveness of MDMA-assisted psychotherapy in 12 subjects with chronic, treatment-resistant PTSD in Australia. Seven subjects will be allocated to the full dose condition (125mg with a supplemental 62.5mg), with the remaining five to the low dose condition (30mg with a supplemental 15mg). The study is in the protocol approval stage.

All studies presented take part in the main goal of MAPS, that is undertaking a \$25 million plan to make MDMA into a FDA-approved prescription medicine by 2021. Ongoing and planned Phase 2 studies are laying the groundwork for an eventual End-of-Phase 2 meeting with FDA and possible Phase 3 multi-side MDMA/PTSD research studies.

8.3. DISCUSSION

The psychopharmacology of MDMA has been extensively studied over the past 20 years as it is presented in this paper work. However, attempts by scientists and the government to show the neurotoxic effects in humans have only produced equivocal results. For many years, MDMA research had been biased towards showing the neurotoxic effects of the drug while ignoring the clinical applications because just as the drug was becoming well known in the clinical sphere, it was also being used recreationally before the neuroscientific mechanisms of this property could be investigated, unfortunately. Moreover, neurotoxicity of MDMA has only been reported in heavy abusers or in animal models using high and repeated doses (69).

Furthermore, a large number of different classes of psychoactive drugs like MDMA are controlled under national laws. This is supposedly aimed to reduce the use of the drug because of the harms it cause, even though in many cases these harms may be less than those of some prescription drugs or even legal drugs such as alcohol. Despite more than two decades of studies

on MDMA neurotoxic effects, the underlying mechanisms of neurotoxicity still remain to be fully elucidated.

The use of Schedule I substances, such as MDMA, is to be severely restricted, and this means that research using these substances can be undertaken only after approval of a government agency. As a consequence, many researchers who would like to work on this substance can not afford to do so. For example, it took more than 4 years to obtain approvals to import MDMA from Switzerland for the Oehen et al. (2013) trial, even after Health Canada had approved the protocol design. So, the approach of putting penalization of illegal drug possession has severely limited neuroscience research and the discovery of new treatments for brain disorders in general. If MDMA achieves its status as potential therapeutic agent, it would have to be moved to a lower Schedule in the drugs legislation, that is less restrictive and would make it much more accessible for research.

It is important to note that MDMA is thought to be a therapeutic catalyst rather than a "cure" for PTSD. Non-drug psychotherapy sessions are conducted before and after the MDMA-assisted psychotherapy. The initial non-drug sessions are to prepare the patient for the MDMA experience, while the follow-up sessions are used to solidify any insight gained or alleviate any difficulties experienced during the drug therapy sessions. A wide range of psychopathological scales are being used in order to measure not only PTSD symptoms, but also its associated comorbidities such as anxiety, depressions, phobias, maladjustment and damaged self-esteem. Blood pressure, heart rate and other somatic side effects are also being assessed and til now they have showed no significant elevation, suggesting that the doses administered were psyshologically safe. Low doses of MDMA administered as an adjunct to psychotherapy are found to be safe and there are promising signs of efficacy and reduced PTSD symptomatology.

Most of the clinical trials carried out added LTFU of the study subjects who received MDMA-assisted psychotherapy, as an amendment to an initial study design. Because it is not practical nor ethical to mantain a placebo group for over a year, nor to control for other treatments for that period of time, this limitation is commonly found in LTFU studies. In light of this limitation, it is possible that the favourable results of the LTFUs study were caused by resolution of symptoms due to natural history or to other variables that were not controlled for after the follow-up. Evaluation of longer-term outcomes may contribute significantly to the understanding and treatment of chronic mental illnesses like PTSD and their associated morbidity and disability. For example, LTFU studies could help to formulate treatment guidelines, permit evaluation of the rates of sustained symptom reduction or remission, predict the need for maintenance treatment, permit the assessment of long-term tolerability and help rule out a placebo response.

Practice guidelines for the treatment of PTSD accept the need for replication of previous studies, as well as the need for novel treatments, more specifically pharmacological agents that could augment psychotherapy, such as MDMA. Moreover, further studies with a larger sample

size and with the administration of higher doses of MDMA are clearly needed in order to clarify both the safety and the efficacy of MDMA-assisted psychotherapy in patient populations.

In my opinion, the use of MDMA plus psychotherapy can be helpful in PTSD-treatment, because increased interpersonal closeness may permit patients to explore upsetting thoughts, memories or feelings. Facilitated recall and unusual and potentially innovative shifts in thinking and perception could contribute to generating new perspectives about past or current thoughts, feelings and experiences. It is important to remember that trauma may lead to severe distress and considering the high rate of comorbid depression in PTSD patients, the negative mood post-MDMA intake calls for caution. Implementation in routine clinical care is further complicated by the need for physical monitoring during MDMA enhancement, especially with its known cardiac effects. And notably, the use of MDMA as an adjunctive to treatment is not without controversy, as its use as a recreational drug is criminalized in most countries, and because of its Schedule-I category, that makes it more difficult to study.

Even though there are questions regarding safety and tolerability of MDMA, clinical results showed that MDMA-assisted psychotherapy was safely administered with no drug-related serious adverse events, in small samples of treatment-resistant patients who were suffering from chronic PTSD.

9. CONCLUSIONS

MDMA acts mainly on the monoaminergic system, and it also produces oxytocin release, which improves bonding and raises levels of empathy.

MDMA-assisted psychotherapy is a promising therapy for refractory PTSD. It possesses unique pharmacological and psychological properties that may make it specially well suited for use as an adjunct to psychotherapy. It facilitates the communication and connection with the psychotherapists, increases the positive mood, increases access to emotionally intense material and compassion for the self and others.

Now that safety parameters for limited use of MDMA in clinical settings have been established, a case can be made to further develop MDMA-assisted therapeutic interventions that could support social anxiety or similar types of distress.

Preliminary results from clinical trials show that MDMA-assisted psychotherapy with close follow-up monitoring and support can be used with acceptable and short-lived side effects in a carefully screened group of subjects with chronic, treatment-resistant PTSD.

Even though clinical trials show promising results and benefits are appreciable over the long term, there are methodological weaknesses, and are not definitive.

More research is needed to solidify these findings and to further develop the treatment.

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