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Efficacy of MDMA-assisted psychotherapy in the treatment of chronic PTSD

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ABSTRACT

Objective: To assess the effectiveness of MDMA-assisted psychotherapy in treating patients with chronic refractory PTSD using a systematic review.

Methods: Literature search was performed on PubMed and PsychINFO using search terms "PTSD" and "MDMA" to identify randomized control trials within the past 10 years.

Results: Two out of the three studies found statistically significant data in the treatment of refractory PTSD. Mithoefer, M. et al and Ot'alora, M. et. al found a statistically significant decrease in CAPS-IV total scores, decrease in depression symptoms, decreased in dissociative symptoms, and increase in sleep quality.

Conclusion: The use of MDMA-assisted psychotherapy may be beneficial in treating chronic PTSD patients who have failed previous treatment methods. Additional studies with a larger sample size are necessary to determine the efficacy of MDMA-assisted psychotherapy in treating chronic PTSD.

INTRODUCTION

Although humans evolved by overcoming stressful situations and surviving life-threatening events, some experiences overwhelm our coping mechanisms and alter our physiologic functioning. In post-traumatic stress disorder (PTSD), a traumatic event elicits a series of complex adaptations including a persistent avoidance of triggers, intrusive thoughts/memories, negative changes in cognition, and alterations in arousal.[1,2] All of these adaptations can significantly impact a person's ability to function on a daily basis, placing a large burden on one's personal, professional, and social life. A large majority of our population is at risk due to the multitude of common traumatic events that have been highly associated with the development of PTSD. Currently, the lifetime prevalence of PTSD in the United States and Canada ranges from 6.1 to 9.2 percent with a higher incidence among sexual violence victims, combat veterans, childhood abuse victims, family members with deceased or dying loved ones, and survivors of life-threatening accidents or injuries.[3,4]

The physiologic mechanisms underlying the development of PTSD are not well understood, so treatment options focus on symptomatic relief rather than physiologic abnormality correction. Treatment options for patients diagnosed with PTSD include psychotherapy or serotonergic reuptake inhibitors (SRI) depending on patient preference, treatment availability, and past treatment's effectiveness.[5,6,7] Research has shown psychotherapy to have clinically significant symptom improvement; however, patients continue to meet diagnostic criteria for PTSD after completion. Psychotherapy is also associated with a high dropout rate due to symptom worsening and hospital admission.[6] SRIs are shown to modestly improve avoidance and alterations in arousal,

but do not improve intrusive symptoms.[8] Considering intrusive symptoms are a detriment to most patients with PTSD and the long-term impact of psychotherapy is minimal, current treatment options are not appropriately managing PTSD symptoms. Therefore, researchers are currently performing clinical trials on other treatment options that may be more effective. One of the current treatment options undergoing clinical trials is 3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy.[6,7]

MDMA is a sympathomimetic amphetamine that stimulates serotonin, dopamine, and norepinephrine release, as well as inhibits serotonin reuptake.[7] By increasing serotonin levels, MDMA is providing the same basic pharmacologic effects as SRIs. However, MDMA is thought to exceed SRIs by also increasing dopamine, which induces a positive emotional/mental state and reduces fear. Utilizing MDMA during psychotherapy sessions may improve the psychotherapeutic process by allowing the patient to process traumatic events openly and associate with them positively.[7] Therefore, the purpose of this review is to assess the effectiveness of MDMA-assisted psychotherapy on reducing PTSD severity in patients diagnosed with chronic PTSD compared to an "active" placebo control.

CLINICAL QUESTION

In men and women ≥ 18 years old diagnosed with chronic PTSD with an inadequate response to at least 1 pharmacotherapy or psychotherapy, does MDMA compared to an "active" placebo decrease severity of PTSD?

METHODS

In September 2019, a literature search was performed on PubMed and PsychINFO to identify randomized control trials utilizing MDMA to treat PTSD with comparable control groups. Using the search terms "PTSD" and "MDMA," a total of 333 articles were identified. Approximately 62 articles were screened of which 53 were excluded due to lack of relationship to topic and format as an academic review rather than a research article. Of the 9 remaining articles fully assessed for eligibility, 6 articles were excluded due to inappropriate study format (case control, cohort, or follow-up study rather than randomized control trial) and incomparable control groups. Therefore, only 3 articles fulfilled the criteria to analyze the efficacy of MDMA in treating chronic PTSD.

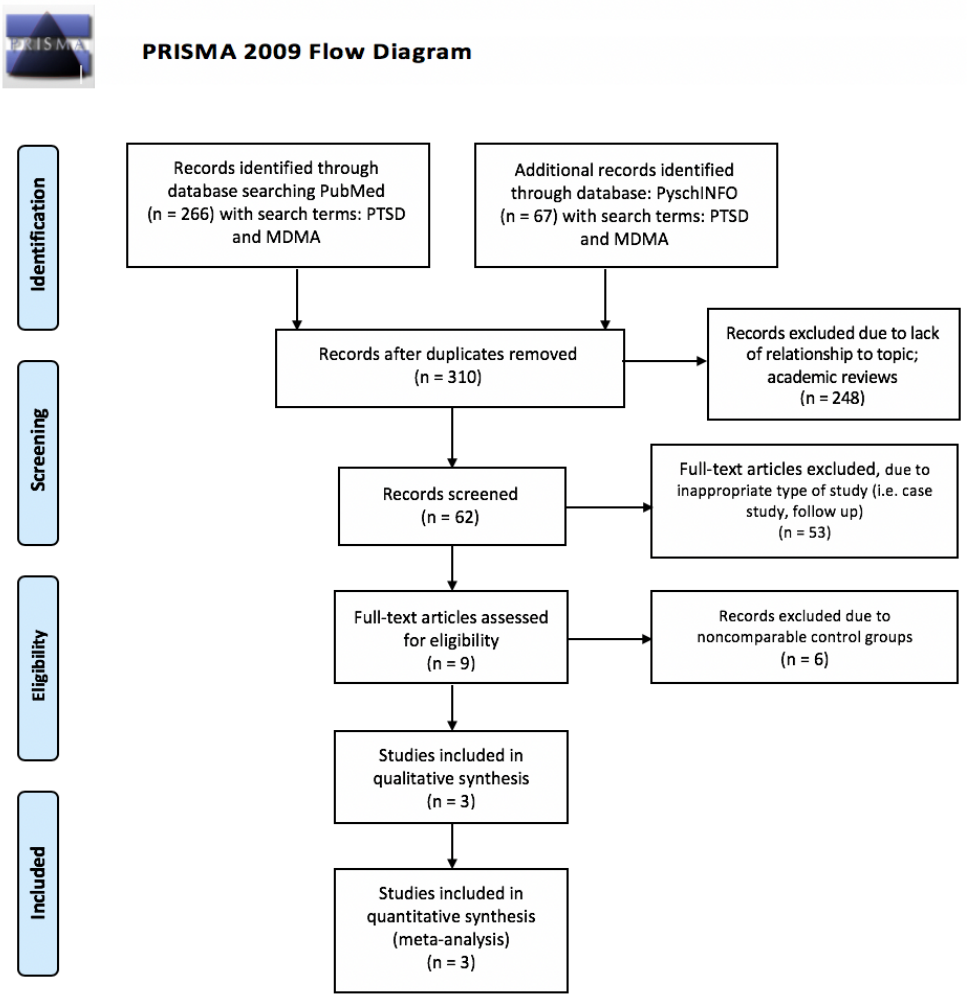

Figure 1. PRISMA Flow Diagram.

RESULTS

Study #1:

A randomized controlled, pilot study of MDMA-assisted psychotherapy for treatment of resistant, chronic PTSD. Oehen P, et al.

Objective: To evaluate the use of MDMA assisted psychotherapy as a treatment for chronic PTSD patients and the use of 25mg of MDMA as an "active placebo" in order to maintain blinding during the treatment.

Study Design: This was a randomized controlled pilot study of 14 recruited subjects from psychiatric hospitals, trauma counseling centers, psychiatrist and psychotherapist in Switzerland

for MDMA-assisted psychotherapy treatment of resistant, chronic PTSD. Table 1 outlines inclusion and exclusion criteria.

Inclusion Criteria	DSM-IV Criteria for PTSD with treatment resistant symptoms: Clinician Administered PTSD Scale (CAPS)* score of ≥50
	Previously undergone at least 6 months of psychotherapy and 3 months of treatment with a SSRI
	Structured Clinical Interview for the DSM-IV Axis I and II Disorders (SCID I and II) diagnosis of PTSD
Exclusion Criteria	Significant medical conditions, except for hypothyroidism under hormonal replacement
	Psychiatric conditions: history of psychotic illness, bipolar disorder type I, borderline personality disorder, dissociative identity disorder, and substance abuse or dependence within 60 days of enrollment
	Subjects who had taken MDMA on more than five occasions or less than 6 months prior to enrollment.

Table 1: Inclusion and exclusion criteria for Study #1 (*Oehen P, et al). *Please refer to appendix A.*

A full dose of 125mg MDMA, followed 2.5 hours later by 62.5mg MDMA was compared to the active placebo of 25mg MDMA, followed 2.5 hours later by 12.5mg MDMA. The 14 subjects underwent double blind randomization. 9 subjects were in the full dose group; 5 were placed in the active placebo group. 2 subjects (1 from each group) withdrew after adverse effects of the first MDMA session. The study was designed in three stages.

Stage 1 included subject given 3 full dose MDMA and 3 active placebo dose MDMA with 3 all day long MDMA assisted psychotherapy sessions and 12 non-drug therapy sessions. Clinician Administered PTSD Scale (CAPS) and Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I) substance abuse module were administered at baseline, 3 weeks after MDMA session number 2, 3 weeks after MDMA session number 3, and at 2, 6, 12-month intervals after the MDMA session number 3. Posttraumatic Diagnostic scale (PDS) was administered at one day after each

MDMA session, 3 weeks after the third MDMA session, and at 2, 6, 12-month intervals after the third MDMA session. All of the outcome measurements were done by independent raters.

Stage 2 of the experiment allowed the active placebo subjects the option to switch over to the full dose MDMA. This open label broke the blind. All 4 subjects chose to enter the open label. These subjects underwent 3 full dose MDMA sessions and 12 non-drug psychotherapy sessions. The CAPS scores from the 3-week post active placebo MDMA session number 3 was used as baseline for Stage 2. CAPS and PDS were completed at 2,6,and 12 months after the final MDMA session.

Stage 3 was created as an amendment to protocol for subjects who showed insufficient clinical response to experimental full doses following preliminary data analysis. Insufficient clinical response included: CAPS score changes ≤15 from baseline to 2 months post MDMA experimental session number 3, CAPS item #25 ≥3, and overall CAPS score still ≥ 50 2 months after the third MDMA session, and investigator and patients' subjective interpretation of lack of improvement. This allowed 2 additional MDMA assisted psychotherapy sessions and 7 non-drug psychotherapy sessions. 3 subjects participated in this stage. The subjects were given 150mg MDMA and a supplemental dose of 75mg MDMA.

The CAPS and PDS scores were analyzed via ANOVA comparing stage 1 and stage 2 (primary outcome). Wilcoxon signed-rank test was used for CAPS data collected from stage 2 and stage 3. P value was set to a significance of 0.05.

Study Results: The full dose group showed a substantial decrease in CAPS scores compared to the active placebo group but missed statistical significance ($p = 0.066$). The full-dose subjects had on average a 15.6-point (23.5%) reduction on their CAPS score. The simple effect of time in the full dose group was significant ($p = 0.002$), while the active placebo group did not show a significant simple effect of time ($p = 0.475$). The PDS scores decreased in the full-dose group, while the PDS score increased in the active placebo group. The PDS scores revealed a significant interaction effect of group and time ($p = 0.014$). There was a significant decrease in CAPS score between the 3 weeks post MDMA session #2- and 3-weeks post MDMA session #3 ($p = 0.016$), thus showing three MDMA sessions were more effective than two. No medical intervention was used during the MDMA sessions and no serious drug-related side effects occurred.

Study Critique: This study was groundbreaking for the first time use of an active placebo in order to increase the blinded effects of the study compared to prior MDMA assisted psychotherapy studies. The use of the active placebo did help the previous issues of the double-blind experiment

but this study allowed patients to cross over into the full dose groups. This limited the statistical data that could be used for comparing the effects of full-dose and active placebo. The 12 months follow up showed a continuous reduction of CAPS scores in all individuals, but statistical significance was unable to be determined due to the fact that all subjects crossed over to the full-dose losing the ability to compare between active placebo and full-dose.

An unexpected outcome from the study was the increase in PDS scores following the active placebo dose. The patients clinically had the negative issues of PTSD but no positive benefits from the MDMA. This suggests that partial activation of the MDMA occurred causing vivid memories and emotions of the traumatic events but did not help the subjects view this state differently as the full-dose subjects did. This caused the subjects to have an increased need for the therapist help and cause one patient to drop out due to fear of occurrence.

Overall, this study did not find statistical significance of their primary outcome in the use of MDMA-assisted therapy. The study was done safely and subjects reported a decrease in symptoms. There is promising information Further studies are necessary to evaluate the use of MDMA in the treatment of refractory PTSD patients.

Study #2:

"3,4-methylenedioxymethamphetamine(MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomized, double-blind, dose-response, phase 2 clinical trial." Mithoefer, M. et al

Objective: The purpose of this study was to assess the efficacy and safety of MDMA-assisted psychotherapy in military veterans, firefighters, and police officers with PTSD that developed due to their time of service. This study also wanted to verify the results of two previous clinical trials of MDMA-assisted psychotherapy that showed large effect sizes, low dropout rates, and long-lasting improvements.

Study Design: This study is a double-blind, randomized, dose response phase 2 clinical trial at an outpatient psychiatric clinic in Charleston, SC. The subjects were recruited via referrals from mental health providers, advertisements, and word of mouth. 22 subjects were selected following the inclusion and exclusion criteria listed in table 2. The selected subjects consisted of 22 veterans, 3 firefighters, and 1 police officer.

Inclusion Criteria	18 years and older
	Female or male veterans, firefighters, or police offices suffering with chronic PTSD resulting from traumatic experiences during their service
	PTSD duration of 6 months or more
	CAPS score of ≥ 50
	Failure to respond to or inability to tolerate previous pharmacotherapy or psychotherapy
Exclusion Criteria	Major medical conditions except controlled hypertension or adequately treated hypothyroidism
	Pregnant or lactating women or women not using effective contraception
	Bipolar disorder type 1

Table 2: Inclusion and exclusion criteria for Study #2 (*Mithoefer, M. et al*).

The study separated the participants into a total of three groups. A 75mg MDMA full-dose, 125mg MDMA full-dose, and 30mg MDMA active control. The subjects were randomly assigned to their respective group 24 hours before the first experimental MDMA session. Three 90-minute psychotherapy sessions were done prior to the first MDMA session to establish trust with the providers and educate the subjects about the MDMA experience. There were two blinded sessions that occurred 3-5 weeks apart. During these, the initial dose was given to the participants and 1.5-2 hours later were given the options of a supplemental dose of half the initial dose. The subjects stayed overnight immediately following the session for precautions, then contacted 7 days later via telephone, and a total of three 90-minute psychotherapy sessions. MDMA was administered during the 8-hour experimental sessions at monthly intervals. Outcome measurements were administered at baseline and 1 month after the second experimental session right before the blind was broken (primary endpoint). Primary outcome included the mean change in CAPS total score. In summary, the subjects underwent 18 hours of psychotherapy and 16-24 hours of MDMA assisted psychotherapy. After the end of the primary endpoint, the subjects assigned to the 125mg MDMA

had one additional open-label session and integrative visits within 3-5 weeks of the previous blinded MDMA session. Outcome measurements were taken at the 2 months follow up visit. This concluded the stage 1 of the experiment.

The subjects that were assigned 30mg and 75mg MDMA crossed over to have 3 open-label sessions of flexible dosing of MDMA (100-125mg) within 5 months of the primary endpoint. The open label sessions were spaced a month apart and included integrative visits. Outcome measurements were taken 2 months after the 3 sessions (secondary endpoint), ending stage 2. Data was also collected at the 12-month follow up of all the participants. The secondary outcomes included BDI-II, PSQI, PTGI, NEO-PI-R, DES-II, and GAF (*Table 3*).

CAPS-IV	Clinician Administered PTSD Score for DSM-IV. (See *Appendix A*)
BDI-II	Beck Depression Inventory-II
PSQI	Pittsburgh Sleep Quality Index
PTGI	Post-Traumatic Growth Inventory
NEO-PI-R	Neuroticism- Extroversion-Openness-Personality Inventory-Revised
DES-II	Dissociative Experiences Scale II
GAF	Global Assessment of Functioning

Table 3: Secondary outcome definitions.

The efficacy of the dose response and secondary outcomes were analyzed on the intention to treat population using ANOVA and pre-planned t tests. The cross over open label data used scores of the primary endpoint, stage 2 secondary endpoint, and 12-month follow-up to baseline.

Study Results: The primary outcomes are included in table 4. The 75mg and 125mg group showed a significant difference in PTSD symptom severity compared to the 30mg MDMA active control group. There was no significant difference between the 75mg and 125mg groups ($p = 0.185$). At the primary endpoint, many subjects no longer met the PTSD criteria with the CAPS score. 86% in the

75mg group and 58% of the 125mg did not meet PTSD criteria, compared to 29% in the 30mg group.

MDMA mg dose group	Mean change in CAPS IV total score (SD)	P-value
30mg	-11.4 (12.7)	NA
75mg	-58.3 (9.8)	0.0005
125mg	-44.3 (33.8)	0.004

Table 4: Primary Outcome – Mean change in CAPS total score from baseline to 1 month after the 2nd blinded experimental session of MDMA assisted psychotherapy.

After two active doses of MDMA, a 30% CAPS score decrease or more was reached by 100% of the 75mg group, 67% of the 125mg, and 29% of the 30mg group. The results from the secondary outcomes are in table 5. The BDI-II (depression) was significantly reduced in the 125mg group compared to the 30mg group but was not significant between the 75mg and 30mg. Sleep quality as well as dissociative symptoms significantly improved during the course of treatment in the full dose group compared to the active control dose group. PTGI scores increased in the active MDMA doses. PTGI measures the ability of the subject to view themselves, others, and life events in a more positive way, thus showing the potentially benefits beyond solely PTSD symptom reduction. The GAF scores in the active dose group, revealed a significant improvement in psychological, occupation, and social function compared to the placebo group. There was statistical significance in personality trait changes such as a reduced neuroticism and increased openness, in the 125mg and 75mg groups respectively. These positive significant changes in the subjects continued to improve over the 12 months.

In the 30 mg MDMA active control subjects that crossed over to the 2 open label sessions of 100-125mg, CAPS total score revealed an additional 27-point average decline. However, after the 3rd open label session, 50% of these individuals no longer qualified as having PTSD, which was more than the other groups. The 30mg MDMA active control group was actually found to have counter-therapeutic effects, thus making them harder to treat.

Study Critique: This study was a well-designed randomized, double blind, dose response pilot control study. The results showed that the 75mg and 125mg MDMA active doses significantly improved PTSD symptoms in veterans and first responders that have previously been refractory to

treatment. This study further proves the significant findings in other studies of MDMA-assisted psychotherapy.

Secondary Outcome	30mg	75mg	125mg
Mean BDI-II score			
Change†	−4·6 (8·8)	−15·4 (9·5)	−24·6 (10·6)
p value‡	NA	0·052	0·0003
Mean PSQI			
Change†	1·8 (2·8)	−6·4 (7·1)	−4·8 (4·1)
p value‡	NA	0·01	0·02
Mean PTGI score			
Change†	−11·6 (12·2)	36·1 (12·0)	33·7 (24·0)
p value‡	NA	<0·0001	<0·0001
Mean GAF score			
Change†	1·1 (4·6)	19·4 (6·1)	18·4 (14·4)
p value‡	NA	0·004	0·002
Mean DES-II score			
Change†	1·8 (0·9)	−8·6 (1·9)	−8·8 (6·2)
p value‡	NA	0·02	0·01
Mean NEO-PI-R score			
Neuroticism			
Change†	−4·6 (5·5)	−12·0 (3·6)	−16·5 (11·8)
p value‡	NA	0·23	0·03
Extroversion			
Change†	2·2 (4·3)	10·0 (9·4)	8·0 (9·4)
p value‡	NA	0·17	0·22
Openness			
Change†	−0·6 (9·9)	15·6 (5·3)	2·0 (10·5)
p value‡	NA	0·02	0·62
Agreeableness			
Change†	−1·2 (8·4)	5·4 (8·0)	5·9 (4·9)
p value‡	NA	0·13	0·05
Conscientiousness			
Change†	−3·2 (7·9)	2·4 (15·0)	6·5 (13·4)
p value‡	NA	0·50	0·17

Table 5: Secondary outcome results. *All outcomes are based on the intention-to-treat population. †Change from baseline. ‡Compared with 30 mg MDMA.

The study sample size is small and could possibly skew data. The active control dose did improve the study blind as compared to previous studies, but still came with issues. The study collected data on the therapists' and participants' guess of the dose they were receiving. The therapists incorrectly guessed 42.6% of the sessions and the participants incorrectly guessed 42.6% of the time. Thus, showing partial blinding was intact, but there is still evidence that it did not work leading to possible bias and limitations of the study. The researchers attempted to preserve the study blind by the use of an observer blind that rated independent outcomes not present during the sessions.

The participants crossed over to the open label, thus every single subject received at least one full dose of MDMA. The 12-month follow up data was then unable to be compared to the control group, as no control group existed at this point of time. This leaves speculation as to a long-term benefit from the 30mg dose.

Study 3

3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: a randomized phase 2 controlled trial. Ot'alora et al.

Study Objective: The purpose of the study was to evaluate the safety and efficacy of MDMA use during psychotherapy in patients with chronic PTSD.

Study Design: This study is a double blind, phase 2 dose response trial performed in Boulder, CO between October 2012 and February 2017. 77 candidates were recruited through internet ads and referrals from mental health professionals. Further screening occurred over the telephone using a scripted interview and in-person using a psychological assessment, physical exam, and electrocardiogram. 28 participants were then selected based off of inclusion and exclusion criteria (*Table 6*).

Before the trial, participants were interviewed by an independent rater to assess baseline primary and secondary outcomes. The primary outcome assessed during this study was the CAPS IV score, which is the gold-standard PTSD measurement. The secondary outcomes included depression symptoms via Beck Depression Inventory-II (BDI-II), dissociation via Dissociative Experiences Scale-II (DES-II), and sleep quality via Pittsburgh Sleep Quality Index (PSQI).

Participants also underwent three 90-minute sessions with a therapy team member to establish a comfortable therapeutic alliance before the MDMA sessions. Any psychiatric meds were tapered off and discontinued before MDMA administration.

Inclusion Criteria	18 years and older
	Physically healthy
	PTSD duration of 6 months or more
	CAPS score of ≥ 50
	Failure to respond to or inability to tolerate at least 1 previous pharmacotherapy or psychotherapy
Exclusion Criteria	Psychiatric or medical contraindications to treatment with MDMA
	Pregnant or lactating women or women not using effective contraception

Table 6: Inclusion and exclusion criteria for Study 3 (*Ot'alora, M. et. Al*).

After preparation, participants were randomized through a web-based system into three treatment groups: 40 mg of MDMA ("active" placebo), 100 mg of MDMA (active dose), and 125 mg of MDMA (active dose). Each treatment group underwent two double-blind 8-hour psychotherapy sessions a month apart. 90 minutes after the first dose, each participant was offered a supplemental dose that was half the quantity of the initial dose. In order to assess the safety of MDMA, participants ate dinner after the effects of MDMA resolved and remained in the clinic overnight.

Upon completing each experimental session, three integrative sessions were scheduled to assess the participant's psychological state and stability, as well as facilitate experiences during the experimental sessions. The first integrative sessions occurred the morning after the experimental session, while the following two integrative sessions were scheduled some time within a month. For a week after each experimental session, participants were contacted daily over the telephone for a 15-60-minute call.

A month after the second experimental session, each participant was re-assessed by the same independent rater to measure primary and secondary outcomes. Participants also completed self-report measures. After collecting the primary endpoint data, the procedure was unblinded.

Participants in the "active" placebo group were crossed over to the active dose group, then participated in one preparatory session and three open-label sessions with associated integrative sessions. Meanwhile, participants in the active dose groups had a third open-label session. Participants were re-assessed to measure primary and secondary outcomes a month after the second open-label session, two months after the third open-label session, and twelve months after the final experimental session. Safety outcomes, including adverse events, adverse reactions, vital signs, and suicidal ideations, were monitored throughout the treatment period. The primary and secondary efficacy outcomes were deemed as the change from baseline to one month after the second double-blind session. Both outcomes were analyzed via ANOVA with $\alpha=0.05$.

Study Results: Considering 2 participants discontinued treatment after the first experimental session and 3 participants were removed due to discovery of secondary psychiatric diagnoses during treatment, the researchers utilized both intention to treat (ITT) and per protocol (PP) to analyze the primary outcome after the second double-blind experimental session (phase 1). Utilizing the intention to treat analysis on the primary outcome, no statistically significant differences were discovered. However, the active dose group assigned 125 mg of MDMA showed the greatest reduction in PTSD symptom severity (*Table 7*). Utilizing the PP analysis on the primary outcome, a statistical significant reduction in the CAPS-IV total scores was discovered when comparing the 125 mg MDMA group with the "active" placebo group (*Table 7*). Furthermore, the 100 mg MDMA group displayed a trend towards significance compared to the "active" placebo group.

For secondary outcomes, the researchers utilized ITT to analyze the following data points after the second double-blind experimental session: the number of participants meeting diagnostic criteria for PTSD, the percentage of participants with at least a 30% decrease in CAPS-IV total scores, the change in depressive symptoms via BDI-II, the change in sleep quality via PSQI, and the change in dissociative symptoms via DES-II. Overall, a large number of participants, especially in the active dose groups, no longer met the diagnostic criteria for PTSD and experienced at least a 30% decrease in PTSD symptom severity (*Table 8*). Although not statistically significant, all groups displayed a slight improvement in quality of sleep and the active dose groups reported fewer dissociative experiences (*Table 8*). Participants did not display a change in depressive symptoms.

	ITT Analysis		PP Analysis	
MDMA group	**Mean change (SD) in CAPS IV total score**	**P-value**	**Mean change (SD) in CAPS IV total score**	**P-value**
40mg ("active" placebo)	-11.5 (21.2)	N/A	-4 (11.9)	N/A
100mg (active dose)	-24.4 (24.2)	0.36	-24.4 (24.2)	0.10
125mg (active dose)	-26.3 (29.5)	0.27	-37 (20.9)	0.01

Table 7: Primary Outcome – Mean change in CAPS IV total score from baseline to 1 month after the 2nd double-blind experimental session (phase 1) of MDMA assisted psychotherapy

Two months after the open-label sessions (phase 2), the researchers measured and analyzed the primary and secondary outcomes once again. The "active" placebo group crossed over to the active dose during open label sessions displayed a statistically significant decrease (p value = 0.01) in CAPS-IV total score after two open-label sessions with an active dose of MDMA. Also, four out of the five participants (80%) experienced at least a 30% decrease in CAPS-IV total score and no longer met diagnostic criteria for PTSD. Furthermore, the crossover group experienced a statistically significant change in depression symptoms via BDI-II (p = 0.01) and dissociative symptoms via DES-II (p = 0.04). Scores did not reveal a significant change two months after the third open-label session for the crossover group.

Primary and secondary outcomes were recollected twelve months after each participant's last active dose of MDMA. The 12 month follow up data was compared to the baseline data and revealed a statistically significant decrease in CAPS-IV total scores, decrease in depression symptoms, decreased in dissociative symptoms, and increase in sleep quality ($p < 0.0001$). Furthermore, 76% of participants no longer met PTSD diagnostic criteria.

Study Critique: Overall, the first phase of the study was a well-designed double-blind randomized control trial. The patients were randomized through a computer system to minimize bias. Inter-rater bias was also eliminated by utilizing the same person to score each patient throughout the

entire study. Furthermore, the independent rater was not involved in the experimental sessions, so the possibility of guessing the participant's assigned dosage and creating bias was minimal.

MDMA group	**40mg ("active" placebo)**	**100mg (active dose)**	**125mg (active dose)**
Participants NOT meeting PTSD diagnosis, number (percent)	2 (33.3%)	4 (44.4%)	5 (41.7%)
Participants with ≥ 30% decrease in CAPS-IV total score, number (percent)	1 (16.7%)	5 (55.6%)	6 (50%)
BDI-II change, mean (SD)	-11.5 (7.8)	-9.9 (13.3)	-11 (13.7)
PSQI change, mean (SD)	-0.8 (2.5)	-3.6 (6.2)	-2.0 (4.7)
DES-II change, mean (SD)	-0.2 (6.9)	-13.3 (15.3)	-5.9 (12)

Table 8: Primary Outcome – Mean change in CAPS IV total score from baseline to 1 month after the 2nd double-blind experimental session (phase 1) of MDMA assisted psychotherapy

One issue with this study was the loss of four participants after initiating treatment. Although most of the patients were removed from the study due to discovery of secondary psychiatric diagnoses during treatment, loss of participants during a study can definitely skew data. However, the researchers appropriately accounted for the loss of participants by utilizing both ITT and PP to analyze the data. Another issue with the study is the low sample size and, therefore, the low statistical power. Considering the amount of statistically significant findings and extremely low p-values with such a small sample size, the credibility of this data is questionable. The final issue with this study is the utilization of an open-label trial. The open-label trial with the crossover group revealed the more statistically significant data than the both of the double-blind active dose groups, which may be a concern for skewed data due to "placebo effect." If the data from the open-label trial was in fact skewed, then the final 12-month follow-up data collected would also be skewed. However, in reality patients receiving MDMA-assisted psychotherapy would be aware of their prescribed MDMA dosage, so the study's results may still be applicable.

Regardless of issues present, the study revealed data that MDMA-assisted psychotherapy may be an extremely useful treatment for people with chronic PTSD. A large percentage of the participants no longer met diagnostic criteria for PTSD and experienced a significant decrease in PTSD symptom severity after treatment. Although research is still limited on this topic, MDMA-assisted psychotherapy may become a useful resource for treating chronic PTSD, especially patients also experiencing symptoms of depression, dissociation, and low sleep quality.

DISCUSSION

The focus of this statistical review is to determine the effectiveness of MDMA-assisted psychotherapy in treating patients with chronic, refractory PTSD. Each of the three studies utilized similar inclusion and exclusion criteria ensuring comparable sample populations. All three studies also implemented at least two phases: a double-blind phase and an open-label phase. One of the more significant differences in study design was the MDMA dose provided; however, the second and third studies produced very similar data despite the slight difference in dosage.

Although the experiment designs were not exactly the same, the second and third studies implemented very similar, yet improved designs from the first study that allowed for better data collection. Considering study 1 was one of the earliest studies to utilize an "active" placebo dose rather than an actual placebo, the data collection was more complicated and less inclusive to other forms of measurement. Study 2 used a more thorough, yet simple form of data collection. However, study 2 still had room for improvement because it did not include 12-month follow-up data due to lack of placebo for comparison. Study 3 was the most recent and refined study analyzed for this review. Study 3 had a very similar study layout and form of data collection as study 2; however, study 3 included 12-month follow-up data and compared it to each individual patient's baseline. Further differences between the studies are noted in Table 9. Overall, the studies seemed to have effectively minimized bias by decreasing inter-rater bias with independent interviewers and decreasing intra-rater bias by utilizing each patient's individual baseline for comparison.

Considering two of the three studies revealed statistically significant data while the other study was trending towards significance, MDMA-assisted psychotherapy appears to be an effective form of treatment for patients with chronic PTSD unresponsive to other forms of therapy. Both studies 2 and 3 revealed statistically significant decreases in depression and dissociative symptoms, as well as an increase in sleep quality. Considering that these are all characteristics of PTSD, significant improvement in these realms is another outcome supporting the use of MDMA with psychotherapy. Study 2 also discovered an increase in patient's openness and willingness to discuss

traumatic events after completing the experiment. With this mild change in personality, patients were experiencing more significant improvements in psychological symptoms during therapy sessions outside of this experiment. Therefore, MDMA-assisted psychotherapy may still contribute to symptom improvement even long term.

Beyond the effectiveness of MDMA, the safety of MDMA needs to be assessed before its application in PTSD treatment. Although one study did not reveal any serious drug-related adverse side effects nor did it require medical intervention during or after the experimental sessions, the other two studies revealed some serious adverse side effects and required medical intervention. Some serious adverse side effects were reported including suicidal ideation and an increase in an individual's number of premature ventricular contractions. Although the most commonly reported adverse side effects included anxiety, headache, fatigue, jaw clenching, muscle tension, and sleep-related reactions. Most of the adverse side effects requiring medical intervention were psychiatric in nature, mainly anxiety and depression with suicidal ideation. Some of the adverse side effects, such as appendicitis, stage 1 breast cancer, ruptured ovarian cyst, and fractured lower limb required, required medical intervention, but were deemed unrelated to the MDMA.

Overall, the main qualms with these studies are the slight differences in MDMA dose, small sample sizes, use of open label trials, and lack of 12-month follow-up data. Open-label trials may skew the data; however, they may be a more accurate representation of the results patients will experience upon real-life application. Future studies with larger sample sizes and a study design with data collection similar to study 3 need to be performed for further confirmation of this statistically significant data. Considering the possible adverse side effects that may occur during treatment with MDMA, researchers should consider excluding patients with a history of suicidal ideation and contemplate the possible forms of treatment patients are able to receive for the anxiety and sleep issues that may increase during treatment.

	Study 1- Oehen , P. et al	**Study 2- Mithoefer, M. et al**	**Study 3- Ot'alora, M. et al**
Sample size	N=12	N = 26 (22 veterans, 3 firefighters, 1 police officer)	N = 28
Study Outline	Double-blind trial - Full dose (n=9) - "Active" placebo (n=5) Open label trial - Full dose (n=7)	Double-blind trial - Full dose (n=19) - "Active" placebo (n=7) Open label trial - Full dose (n=24)	Double-blind trial - Full dose (n=22) - "Active" placebo (n=6) Open label trial - Full dose (n=26)
Intervention	125mg	75mg (n=7) 125mg (n=12)	100mg (n=9) 125mg (n=13)
Control	25mg	30mg	40mg
Follow-up	- Baseline - 3 wks after 2nd double-blind experimental session - 3 wks after 3rd double-blind experimental session - 2, 6, and 12 months after 3rd double-blind experimental session -2, 6, and 12 months after 3rd open label trial	- Baseline - 1 month after 2nd double-blind experimental session - 1 month after 2nd open label trial - 12 months after last active dose of MDMA	- Baseline - 1 month after 2nd double-blind experimental session - 2 months after open-label experimental sessions - 12 months after last active dose of MDMA
Conclusion	Although the data was not statistically significant, the full dose group showed a trend towards significance in CAPS-IV total scores ($p = 0.066$).	Statistically significant difference in CAPS-IV total score in both active dose groups (75 mg $p = 0.0005$, 125 mg $p = 0.004$) when comparing baseline to 1 month after 2nd experimental session. Compared to the placebo group, the active dose groups showed a statistically significant decrease in CAPS-IV score ($p = 0.001$).	Using PP analysis, the 125 mg active dose group compared to the placebo group showed a statistically significant decrease in CAPS-IV total scores ($p = 0.01$). After the open label trial, the crossed over group showed a statistically significant decrease in CAPS-IV (p value = 0.01). Furthermore, the 12 month follow up when compared to baseline revealed a statistically significant decrease in CAPS-IV ($p < 0.0001$).
NNT*	N/A	2	2.8

Table 9: Comparison chart of all three studies utilized in this systematic review. *NNT to decrease CAPS-IV total scores by ≥ 30% utilizing data from the active dose groups in the double-blind trial.

CONCLUSION

These studies appear to demonstrate the effectiveness of MDMA-assisted psychotherapy in PTSD patients who have previously failed other mainstay treatments. Two of the three articles reached a statistical significance in the improvement of PTSD symptoms. The first article found clinical improvement in their patients, but narrowly missed significance ($p=0.066$). Secondary outcomes such as depression, sleep quality, and post-traumatic growth were significantly improved in the MDMA active dose participants. Administration of the drug was done safely with minimal adverse effects. Vitals were closely watched in all of the articles. All three of these articles are double blind randomized control trials that suffered from small sample sizes. An unforeseen observation and statistical data of the active placebo group revealed the counter-therapeutic effects of partial activation of MDMA suggesting that the correct dose of MDMA is crucial to its potential benefits. This is a growing field and many new studies have been done since the 2013 pilot study.

There has been a total of 6 phase 2 trial studies showing similar significant results, including 2 of the articles listed above. This has been the foundation for the continuation onto phase 3 trials. FDA granted “Breakthrough Therapy” for MDMA-assisted psychotherapy for PTSD patients that accelerate the drug development process. The upcoming phase 3 trials will enroll about 200-300 participants, addressing the small sample size limitation in previous studies. If the phase 3 trials can replicate the results of phase 2, PTSD patients will be able to use MDMA-assisted psychotherapy for treatment. The implication of these findings are important for chronic PTSD patients refractory to other medications. MDMA-assisted psychotherapy is a breakthrough treatment for PTSD but the time, money, and resources are potential concerns for the clinical application in the future.

REFERENCES

1. *Diagnostic and statistical manual of mental disorders. [electronic resource] : DSM-5.* 5th ed. ed. American Psychiatric Association; 2013. https://search.ebscohost.com/login.aspx?direct=true&AuthType=cookie,ip,cpid,athens,shib&custid=s8863137&db=cat00024a&AN=vmc.b2710297x&site=eds-live&scope=site http://dsm.psychiatryonline.org/book.aspx?bookid=556.
2. Van der Kolk, B A, Pelcovitz D, Roth S, Mandel FS, McFarlane A. Dissociation, somatization, and affect dysregulation: The complexity of adaptation of trauma. *Am J Psychiatry*. 1996;153(7):83-93. https://doi.org/10.1176/ajp.153.7.83. doi: 10.1176/ajp.153.7.83.
3. Goldstein, Risë B R. B. The epidemiology of DSM-5 posttraumatic stress disorder in the united states: Results from the national epidemiologic survey on alcohol and related conditions-III. *Soc Psychiatry Psychiatr Epidemiol*. 2016;51(8):1137; 113-1148; 1148.
4. Kessler, Ronald C R. C. How well can post-traumatic stress disorder be predicted from pre-trauma risk factors? an exploratory study in the WHO world mental health surveys. *World psychiatry*. 2014;13(3):265; 26-274; 274.
5. Mithoefer, Michael C M. C. MDMA-assisted psychotherapy for treatment of PTSD: Study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology (Berlin, Germany)*. 2019;236(9):2735; 273-2745; 2745.
6. Mithoefer, Michael C M. C. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: A randomised, double-blind, dose-response, phase 2 clinical trial. *The lancet.Psychiatry*. 2018;5(6):486; 48-497; 497.
7. Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (±3,4-methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic post-traumatic stress disorder (PTSD). *J Psychopharmacol*. 2013;27(1):40-52. https://doi.org/10.1177/0269881112464827. doi: 10.1177/0269881112464827.
8. Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress DisorderA randomized controlled trial. *JAMA*. 2000;283(14):1837-1844. https://doi.org/10.1001/jama.283.14.1837. Accessed 10/2/2019. doi: 10.1001/jama.283.14.1837.

Appendix

Appendix A: CAPS DSM-V

CAPS-5 SUMMARY SHEET

Name: _____ ID#: _____ Interviewer: _____ Study: _____ Date: _____

A. Exposure to actual or threatened death, serious injury, or sexual violence	
Criterion A met?	(0) = NO (1) = YES

B. Intrusion symptoms (need 1 for diagnosis)		Past Week
Symptom	*Sev*	*Sx (Sev ≥ 2)?*
(1) B1 – Intrusive memories		(0) = NO (1) = YES
(2) B2 – Distressing dreams		(0) = NO (1) = YES
(3) B3 – Dissociative reactions		(0) = NO (1) = YES
(4) B4 – Cued psychological distress		(0) = NO (1) = YES
(5) B5 – Cued physiological reactions		(0) = NO (1) = YES
B subtotals	*B Sev =*	*#B Sx =*

C. Avoidance symptoms (need 1 for diagnosis)		Past Week
Symptom	*Sev*	*Sx (Sev ≥ 2)?*
(6) C1 – Avoidance of memories, thoughts, feelings		(0) = NO (1) = YES
(7) C2 – Avoidance of external reminders		(0) = NO (1) = YES
C subtotals	*C Sev =*	*#C Sx =*

D. Cognitions and mood symptoms (need 2 for diagnosis)		Past Week
Symptom	*Sev*	*Sx (Sev ≥ 2)?*
(8) D1 – Inability to recall important aspect of event		(0) = NO (1) = YES
(9) D2 – Exaggerated negative beliefs or expectations		(0) = NO (1) = YES
(10) D3 – Distorted cognitions leading to blame		(0) = NO (1) = YES
(11) D4 – Persistent negative emotional state		(0) = NO (1) = YES
(12) D5 – Diminished interest or participation in activities		(0) = NO (1) = YES
(13) D6 – Detachment or estrangement from others		(0) = NO (1) = YES
(14) D7 – Persistent inability to experience positive emotions		(0) = NO (1) = YES
D subtotals	*D Sev =*	*#D Sx =*

E. Arousal and reactivity symptoms (need 2 for diagnosis)		Past Week
Symptom	*Sev*	*Sx (Sev ≥ 2)?*
(15) E1 – Irritable behavior and angry outbursts		(0) = NO (1) = YES
(16) E2 – Reckless or self-destructive behavior		(0) = NO (1) = YES
(17) E3 – Hypervigilance		(0) = NO (1) = YES
(18) E4 – Exaggerated startle response		(0) = NO (1) = YES
(19) E5 – Problems with concentration		(0) = NO (1) = YES
(20) E6 – Sleep disturbance		(0) = NO (1) = YES
E subtotals	*E Sev =*	*#E Sx =*

PTSD totals	Past Week	
Totals	*Total Sev*	*Total # Sx*
Sum of subtotals (B+C+D+E)		

F. Duration of disturbance	Current
(22)	NOT APPLICABLE

G. Distress or impairment (need 1 for diagnosis)	Past Week	
Criterion	*Sev*	*Cx (Sev ≥ 2)?*
(23) Subjective distress		(0) = NO (1) = YES
(24) Impairment in social functioning		(0) = NO (1) = YES
(25) Impairment in occupational functioning		(0) = NO (1) = YES
G subtotals	*G Sev =*	*#G Cx =*

Global ratings	Past Week
(26) Global validity	
(27) Global severity	
(28) Global improvement	

Dissociative symptoms (need 1 for subtype)	Past Week	
Symptom	*Sev*	*Sx (Sev ≥ 2)?*
(29) 1 – Depersonalization		(0) = NO (1) = YES
(30) 2 – Derealization		(0) = NO (1) = YES
Dissociative subtotals	*Diss Sev =*	*#Diss Sx =*