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Does MDMA-Assisted Psychotherapy Result in Symptom Improvement in Adults with Posttraumatic Stress Disorder (PTSD)?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not MDMA-assisted psychotherapy (MAP) results in symptom improvement in adults with Posttraumatic Stress Disorder (PTSD).

Study Design: Systematic review of three randomized control trials (RCTs) published between 2017 and 2018.

Data Sources: All three RCTs were written in English and published in peer-reviewed journals found via PubMed. Each analyzed the effect of MAP on PTSD symptom severity.

Outcomes Measured: The primary outcome in all three studies was PTSD symptom changes. The Clinician-Administered PTSD Scale (CAPS-IV) and NEO PI-R Personality Inventory (NEO) were used to assess symptoms before and after intervention.

Results: All three studies showed improvement in PTSD symptoms after MAP, but only one of these studies had results reaching statistical significance without eliminating outlier data. Specifically, Mithoefer et al. found a CAPS-IV mean difference of -11.4 for the 30 mg group and -44.3 for the 125 mg group, with a statistically significant p-value of 0.004 (*Lancet Psychiatry*. 2018;5(6):486-497. doi: S2215-0366(18)30135-4 [pii]).

Conclusions: There is not enough statistically significant data to conclude that MAP improves PTSD symptoms. Future studies with larger, more diverse populations must be conducted to strengthen the statistical significance and generalizability of Mithoefer et al.'s findings. Moreover, drug accessibility and treatment monitoring must be considered as limiting factors to implementing MAP.

Key Words: MDMA, PTSD

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a psychiatric condition characterized by having flashbacks, overwhelmingly negative emotions, and avoidant behavior that begins or persists for more than one month following a traumatic event. Symptoms can be debilitating and linger for years and current treatment options demonstrate only minimal effectiveness. It is also a relatively common disorder when considering that 33% of the population endures a traumatic experience that places them at risk for PTSD and 25% of those individuals will go on to develop PTSD.[1] In 2005, the Veterans Benefits Administration reported that PTSD was the most expensive diagnosis for the Veterans Administration.[2] Among veterans alone, the annual treatment cost for PTSD is estimated to be $600 million.[3] The commonality and cost associated with PTSD make it necessary to identify effective treatment options.

PTSD affects a large, heterogeneous portion of the population and can be a chronic, disruptive, and debilitating condition. Research is still needed to determine which combination of treatment modalities results in the most effective management of symptoms. Cognitive behavior therapy is the psychotherapeutic treatment of choice for PTSD, while selective serotonin reuptake inhibitors are considered the first line pharmacologic treatment. Paroxetine and sertraline are the only two drugs approved by the FDA for PTSD. Propranolol, clonidine, and trazadone are often prescribed for off-label use, but getting insurance approval for this is often difficult. A recent study found that among individuals recently diagnosed with primary PTSD, over half received no therapy sessions, 10% received $\geq$ 12 therapy sessions in the first 6 months following diagnosis, and 47% received psychiatric prescriptions.[4] Additionally, 28% of patients received no treatment, 19% only received pharmacotherapy, 27.6% only receive

therapy, and 25.3% received therapy and pharmacotherapy.[4] These findings suggest a mixed picture of treatment approaches and healthcare utilization.

PTSD is a common diagnosis with treatment options that are limited in number and effectiveness. Only two drugs with similar mechanisms of action are FDA-approved for PTSD treatment. For patients with refractory symptoms, additional medications are often prescribed for off-label use, but their efficacy has not been extensively studied in the context of PTSD. Psychotherapy is considered to be more effective than medications in treating PTSD, but dropout rates are high, in part because of the disease itself and patients' avoidant behavior.

3,4-Methylenedioxymethamphetamine (MDMA) is a synthetic Schedule I drug that is structurally similar to amphetamines. It acts by influencing the amount of monoamine neurotransmitters available in synapses, predominantly serotonin.[5] Psychological effects that have been associated with MDMA include increased empathy, improved mood, and a heightened desire for connection to others.[5] Psychotherapy coupled with MDMA administration may allow patients to better process their trauma, connect with their therapist, and more effectively manage their PTSD.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not MDMA-assisted psychotherapy (MAP) results in symptom improvement in adults with PTSD.

METHODS

The key words "MDMA" and "PTSD" were searched in PubMed. Only articles that were primary resources, written in English and published in peer-reviewed journals after August 2017 were considered. Systematic reviews and patient populations that included individuals < 18 years old were excluded.

Three double-blind randomized control trials that met the above criteria were selected for review. Each trial contained a population of males and females who were ≥ 18 years old and had been diagnosed with PTSD based on DSM-IV or DSM-IV-TR criteria. The intervention being studied in each trial was MAP. All three trials measured PTSD symptom severity before and after intervention using statistical values such as numbers needed to treat (NNT), absolute benefit increase (ABI), relative benefit increase (RBI), p-values, and/or mean changes.

Two trials compared the outcomes of psychotherapy with a low inactive dose of MDMA to the same psychotherapy assisted by one of two different higher active doses of MDMA.[6,7] Wagner et al. compared the outcomes of psychotherapy with 125 mg of MDMA to the outcomes of the same psychotherapy assisted only by a placebo.[8] Table 1 summarizes the demographics and characteristics of the studies included in this review.

Table 1 Demographics & Characteristics of included studies

Study	Type	# pts	Age (years)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Ot'alora (2018)[6]	Double blind RCT	28	22-66	≥ 18 years; PTSD for ≥ 6 month; CAPS ≥ 50; failed at least one course of pharmacotherapy and/or psychotherapy	Pregnant or lactating females, medical contraindications to receiving MDMA	1	2 MDMA psychotherapy sessions 1 mo apart (40 mg, 100 mg, or 125 mg then 20 mg, 50 mg, or 62.5 mg dose 90 min later)
Mithoefer (2018)[7]	Double blind RCT	26	Mean age 37.2	Veterans, firefighters, or police officers; ≥ 18 years; PTSD for ≥ 6 month; CAPS ≥ 50; failed at least one course of pharmacotherapy and/or psychotherapy; taper and abstain psychotropic drugs except	Major medical conditions (except controlled hypertension or adequately controlled hypothyroidism); pregnant or lactating women; women not using effective contraception; additional criterion not being	2	MDMA 30 mg, 75 mg, or 125 mg during two psychotherapy sessions followed by a supplemental dose at half the strength of the first 1.5-2hr later. Sessions were spaced 3-5 weeks apart.

				sedative hypnotics or anxiolytics used PRN between MDMA sessions	disclosed until completion of future phase 3 trial		
Wagner (2017)[8]	Double blind RCT	23	Mean age 40.4 +/- 7.2	Meet DSM-IV-TR criteria for chronic PTSD; tx-resistant symptoms defined as CAPS score ≥ 50 following ≥3 months of SSRI or SNRI in addition to ≥6 months of psychotherapy	Patients with major medical conditions or psychiatric conditions besides PTSD or major depression; current substance abuse	2	Two experimental sessions + Placebo or 125 mg MDMA

OUTCOMES MEASURED

The primary outcome in each study was PTSD symptom improvement. Two studies used the Clinician-Administered PTSD Scale (CAPS-IV) to assess symptom improvement, which is a gold standard, semi-structured interview that quantifies PTSD symptoms through diagnostic and symptom severity scores. Blinded independent raters conducted CAPS-IV interviews. Higher scores are associated with more severe PTSD. Wagner et al. measured symptom improvement by evaluating changes in key personality traits associated with PTSD. They did this by comparing openness and neuroticism variables from the NEO PI-R Personality Inventory (NEO) before and after psychotherapy sessions assisted by placebo or MDMA. The NEO PI-R is a well-validated, 240-item self-report tool that has been used for decades to define personality. The higher the score for a trait, the more the individual embodies that trait.

RESULTS

The study completed by Ot'alora et al.[6] in 2018 was a double blind control study that enrolled and consented 28 patients who met the criteria outlined in Table 1. Baseline CAPS-IV scores were collected. Three 90-minute sessions of psychotherapy were conducted prior to MDMA administration to build rapport and foster a safe environment. Psychiatric medications were tapered and discontinued before patients were randomized to one of three dose groups (40

mg, 100 mg, or 125 mg). Two 8-hour MDMA blinded sessions were completed a month apart. Integrative sessions were completed the day after MDMA sessions to assess subjects' wellness and discuss the experiences and insights gained during the experimental session. Patients also received phone calls daily for one week following each experimental session. CAPS-IV scores were reassessed one month after the second blinded experimental session, which served as the study's primary endpoint. At this time, the blind was broken and a crossover portion of the study was completed. This review focuses on the primary endpoint findings for the 40 mg and 125 mg groups.

No serious adverse events (SAEs) occurred in this study during the blinded portion.[6] Three SAEs were reported during later portions of the study, but none of them were considered related to MDMA.[6] There were dose related changes in heart rate and systolic blood pressure, which rose as the dose rose, but no medical interventions were required.[6]

There were originally six participants in the 40 mg low dose group, nine participants in the 100 mg high dose group, and 13 participants in the 125 mg high dose group. One participant from the 40 mg group discontinued treatment after just one blinded MDMA session because efficacy was attained.[6] This individual completed primary outcome assessments and was included in the intention-to-treat (ITT) analysis but not the per protocol (PP) analysis. One participant from the 125 mg group withdrew from the study for undisclosed reasons before completing primary outcome assessments.[6] This individual's data could not be assessed in ITT or PP analyses. Three additional participants in the 125 mg group were included in ITT analysis but excluded from PP analysis because they withheld psychiatric diagnoses during the screening period that would have excluded them from participating.[6]

CAPS-IV total scores at baseline were compared to CAPS-IV scores one month after the second experimental session by using an analysis of variance (ANOVA) with $\alpha = 0.05$. Descriptive statistics were used to convey the percentage of subjects that no longer met CAPS-IV PTSD diagnostic criteria at the primary endpoint. Pre- and post-treatment values are summarized in Tables 2a, 2b, and 3.

In the ITT set, the 40 mg group had a baseline CAPS-IV total score of 84.8 and a post-experimental session total score of 73.3, which represents an 11.5 decrease.[6] The 125 mg group had a baseline CAPS-IV total score of 93.5 and a post-experimental session total score of 64.3, which represents a 26.3 decrease and a $p = 0.27$ compared to the 40mg group.[6] In the PP set, the 40 mg group had a baseline CAPS-IV total score of 84.6 and a post-experimental session total score of 80.6, which represents a 4.0 decrease.[6] The 125 mg group had a baseline CAPS-IV total score of 91.6 and a post-experimental session total score of 54.6, which represents a 37.0 decrease and a $p = 0.01$ compared to the 40 mg group.[6] At baseline, all participants in the 40 mg and 125 mg groups met CAPS-IV criteria for the diagnosis of PTSD. After two blinded MDMA sessions, 2 of the 6 subjects (33.3%) in the 40 mg group and 5 of the 12 subjects (41.7%) in the 125 mg group no longer met CAPS-IV criteria for PTSD.[6]

The control event rate (CER) was 0.667, the experimental event rate (EER) was 0.583, the absolute benefit increase (ABI) was 0.084, the relative benefit increase (RBI) was 0.13, and the numbers needed to treat (NNT) was 12. These values are summarized in Table 4.

Table 2a CAPS-IV total scores, mean (SD), ITT

Intention to Treat Set				
	Baseline	Post 2 blinded sessions	Change	P Value[a]
40 mg MDMA	84.8 (8.0)	73.3 (24.5)	-11.5 (21.2)	--
125 mg MDMA	93.5 (20.0)	64.3 (33.6)	-26.3 (29.5)	0.27

Table 2b CAPS-IV total scores, mean (SD), PP

Per Protocol Set				
	Baseline	Post 2 blinded sessions	Change	P Value [a]
40 mg MDMA	84.6 (9.0)	80.6 (18.8)	-4.0 (11.9)	--
125 mg MDMA	91.6 (19.7)	54.6 (31.9)	-37.0 (20.9)	0.01

[a] as compared to 40 mg group

Table 3 CAPS-IV PTSD diagnostic criteria met post 2 blinded sessions, # (%)

	Baseline	Post 2 blinded Sessions
40 mg MDMA (n = 6)	Yes 6 (100%) No 0 (0%)	Yes 4 (66.7%) No 2 (33.3%)
125 mg MDMA (n = 12)	Yes 13[a] (100%) No 0 (0%)	Yes 7 (58.3%) No 5 (41.7%)

[a] n=13 at baseline but one patient withdrew

Table 4 Analysis of Treatment Efficacy

CER	EER	ABI	RBI	NNT
0.667	0.583	0.084	0.13	12

Mithoefer et al.[7] published a double blind randomized control study in 2018 that assessed the efficacy and safety of MAP specifically in veterans and first responders who were being treated at an outpatient psychiatric clinic in the United States. The study design was the same as that used in the Ot'lora et al. study, with the addition of two more 90-minute integrative sessions after the one week of follow up phone calls.

Four SAEs were reported. Three of these were determined to be unrelated to the study drug. One participant had premature ventricular contractions at baseline, which increased in the crossover portion of the study and required an overnight hospital stay for observation.[7] The patient fully recovered without evidence of lasting damage, but the SAE was considered possibly related to the study drug.[7]

In total, 26 participants met criteria and were randomized to one of three different MDMA dose groups. There were seven participants in the 30 mg group, seven participants in the 75 mg group, and 12 participants in the 125 mg group. This review focuses on the primary

endpoint findings for the 30 mg and 125 mg groups. All of the participants who were randomized completed the primary outcome assessments and were included in the analysis. The primary outcome for this study was the mean change in CAPS-IV total scores between baseline and one month after the completion of the second blinded session. These scores were analyzed using an ANOVA with $\alpha = 0.05$. Descriptive statistics were used to convey the percentage of subjects that no longer met CAPS-IV PTSD diagnostic criteria at the primary endpoint. Pre- and post-treatment values are summarized in Tables 5 and 6.

The 30 mg group had a mean CAPS-IV score of 87.4 at baseline and a post-experimental session score of 76.0, which represents an 11.4 decrease.[7] The 125 mg group had a mean CAPS-IV score of 89.7 at baseline and a post-experimental session score of 45.3, which is a 44.3 decrease from baseline with a $p = 0.004$ compared to the 30 mg group.[7]

At baseline, all participants in the 30 mg and 125 mg groups met CAPS-IV criteria for the diagnosis of PTSD. After two blinded MDMA sessions, 2 of the 7 subjects (29%) in the 30 mg group and 7 of the 12 subjects (58%) in the 125 mg group no longer met CAPS-IV criteria for PTSD.[7]

The CER was 0.710, the EER was 0.420, the ABI was 0.290, the RBI was 0.400, and the NNT was 4. These values are summarized in Table 7.

Table 5 CAPS-IV total scores, mean (SD)

	Baseline	Post 2 blinded sessions	Change	P Value[a]
30 mg MDMA	87.4 (14.1)	76.0 (23.4)	-11.4 (12.7)	--
125 mg MDMA	89.7 (17.3)	45.3 (33.8)	-44.3 (28.7)	0.004

[a] as compared to 40 mg group

Table 6 CAPS-IV PTSD diagnostic criteria met post 2 blinded sessions, yes or no (%)

	Baseline	Post 2 blinded Sessions
30 mg MDMA (n = 7)	Yes 7 (100%) No 0 (0%)	Yes 5 (71%) No 2 (29%)
125 mg MDMA (n = 12)	Yes 12 (100%) No 0 (0%)	Yes 5 (42%) No 7 (58%)

Table 7 Analysis of Treatment Efficacy

CER	EER	ABI	RBI	NNT
0.710	0.420	0.290	0.400	4

Wagner et al.[8] published a randomized, double blind, placebo controlled trial in 2017 that investigated the role of MAP and symptom improvement by evaluating changes in openness and neuroticism personality traits as measured by the NEO PI-R. The study design was very similar to the studies already discussed, with a few key differences: participants were randomized to a placebo group or 125mg MDMA group, only two introductory psychotherapy sessions were completed prior to beginning experimental sessions, and study measures were collected at baseline then four days after each experimental session rather than one month later. As with the other studies being reviewed, only the blinded portion of this study will be discussed. There were no drug related SAEs reported in this study.[8]

In total, 23 participants were enrolled but only 20 completed the experimental sessions, baseline testing, and follow-up testing at the primary endpoint. Two participants withdrew before the second experimental session.[8] One resumed a medication that made him ineligible to participate, and the other felt the travel demands were too difficult.[8] A third subject was removed after it was discovered that he did not meet the criteria for treatment resistant PTSD.[8]

Twelve subjects were randomized to the MDMA group and had baseline NEO PI-R scores of 67.67 and 54.58 for neuroticism and openness respectively.[8] After the experimental sessions, the neuroticism score was 55.833 and the openness score was 57.75.[8] The placebo group had a baseline score of 65.88 and 63.12 for neuroticism and openness respectively.[8] The neuroticism score dropped to 60.62 and the openness score to 60.00 after follow up testing.[8] There were no significant differences between groups for openness or neuroticism at baseline

compared to follow up because p was ≥ 0.05 for all measures. These findings are summarized in Table 8.

The mean change between baseline and follow up neuroticism values for the MDMA group was 11.837, indicating that participants had lower neuroticism scores at follow up compared to baseline. The mean change between openness values for the MDMA group was negative 3.17, indicating that participants had higher openness scores at follow up compared to baseline. The mean change between neuroticism values at baseline to follow up for the placebo group was 5.26, indicating that baseline scores were higher than follow up scores. The mean change between openness values for the placebo group was 3.12, indicating that follow up scores were lower than at baseline. In other words, participants receiving placebo were less neurotic, though to a smaller degree than in the MDMA group, and less open at follow up compared to baseline. These findings are summarized in Table 9.

Table 8 NEO scores at baseline and 2-month follow-up

Variable	MDMA group	Placebo group	P value
Neuroticism baseline	67.67 (14.52)	65.88 (11.43)	0.773
Neuroticism follow up	55.833 (15.16)	60.62 (6.65)	0.414
Openness baseline	54.58 (15.88)	63.12 (6.66)	0.170
Openness follow up	57.75 (12.52)	60.00 (8.30)	0.662

Table 9 Analysis of Treatment Efficacy

Variable	Mean Change MDMA	Mean Change Placebo
Neuroticism	+11.837	+5.26
Openness	-3.17	+3.12

DISCUSSION

In the RCT conducted by Mithoefer et al., there was a larger CAPS-IV mean difference for the 125 mg group compared to the 30 mg group, with a statistically significant p-value of 0.004.[7] This indicates symptom improvement was greater for the experimental group than for the control group. Both Mithoefer et al. and Ot'lora et al. found that more participants in the 125 mg groups no longer met CAPS-IV diagnostic criteria after intervention compared to the lower

inactive dose groups, which supports that MAP results in greater symptom improvement for the experimental groups than for the control groups.[6,7]

Although Ot'lora et al. found a greater decrease in CAPS-IV scores for the 125 mg MDMA group than the 40 mg MDMA group, this difference was not statistically significant in the ITT analysis ($p=0.27$). It was significant in the PP analysis ($p=0.01$) once data from four participants was removed.[6] The authors attributed this disparity between sets to the CAPS-IV score of the individual from the 40 mg group who prematurely withdrew from the study after feeling that she had made satisfactory progress after one experimental treatment. When this outlier was removed, the group differences reached significance. However, it is important to recognize that the sample size for the study was initially small, and eliminating data from four additional participants in the PP analysis further reduces the validity of this finding. Wagner et al. found that participants in the MDMA group had higher increases in openness and larger decreases in neuroticism compared to the placebo control group, which would indicate that MAP is correlated to positive changes in these personality traits, but these findings weren't statistically significant and may have been due to chance.[8]

These studies were limited by their small, homogenous samples, making it difficult to generalize these findings across race and gender. Achieving effective blinding is also difficult to maintain when using a psychoactive drug. Many subjects and study staff were able to correctly guess group assignments, which may have introduced bias into the results.

Even if more than one of these studies had been able to demonstrate that MAP improved PTSD symptoms, the feasibility of using this drug as an adjunctive treatment remains questionable. Accessibility and abuse potential must be considered, as it is still a Schedule I drug

in the United States. Even if the drug were readily available, patients must be in relatively good health and have extensive, potentially burdensome monitoring to ensure their safety.

CONCLUSION

Based on the results presented, there is not enough statistically significant data to conclude that MAP improves PTSD symptoms. The small sample sizes, homogeneity of the sample sizes, and outlier data challenge the generalizability and significance of the findings in these studies. Future studies with larger, heterogenous populations should be conducted in order to more definitively conclude whether or not MDMA improves PTSD symptoms. It'd also be important determine how many sessions need to be completed before efficacy is attained, and whether or not MDMA needs to be used long term in order to maintain those effects.

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