

12-2017

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Joey Rudd

Philadelphia College of Osteopathic Medicine

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Rudd, Joey, "Is MDMA-Assisted Psychotherapy an Effective Treatment for Posttraumatic Stress Disorder (PTSD)?" (2017). *PCOM Physician Assistant Studies Student Scholarship*. 421.
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**Is MDMA-Assisted Psychotherapy an Effective Treatment for Posttraumatic
Stress Disorder (PTSD)?**

Joey Rudd, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For
The Degree of Masters of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 16, 2017

ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not MDMA-assisted psychotherapy is an effective treatment for posttraumatic stress disorder (PTSD).

Study Design: Systematic review of three published, randomized controlled trials (double-blind, placebo-controlled) between 2008-2013.

Data Sources: All articles used were published in English, in peer-reviewed journals, and found using PubMed/MEDLINE and Cochrane Review databases.

Outcomes Measured: The primary outcome measure in all three studies was the severity of PTSD symptoms. The primary outcome measure was assessed using the Clinician-Administered PTSD Scale (CAPS) and the Severity of Symptoms Scale for PTSD (SSSPTSD).

Results: All trials demonstrated a larger group mean reduction in CAPS/SSSPTSD scores for the MDMA group compared to the placebo group. One study found these results to be statistically significant ($P = 0.015$) and a considerable clinical response was seen with the MDMA-AP group with a NNT of 2.

Conclusions: Based on the studies, all reported that the use of MDMA-AP reduced group mean scores from baseline to a larger extent than placebo. Although the studies showed a similar outcome, further studies with larger, heterogeneous sample sizes need to be performed to assess the safety and efficacy of MDMA-AP as a treatment for PTSD.

Key Words: MDMA, PTSD

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a highly prevalent and costly mental health disorder that often causes significant impairment in multiple areas of functioning.¹ The lifetime prevalence of PTSD in the United States is approximately 8%, with rates differing between females and males at 10% and 4%, respectively.² Comorbidities are common among PTSD sufferers, with 66% of those diagnosed having two or more psychiatric and/or medical issues, such as depressive disorders, anxiety disorders, and/or substance-related disorders.³ The exact cost and number of healthcare visits due to PTSD have yet to be determined, though a study performed by the Congressional Budget Office found the average costs for the first year of treatment among veterans to be approximately \$8,300 per patient.⁴ In addition, approximately 45-60% of mental health issues are treated in primary care, with primary care typically being the location of the first presentation for those with disturbances due to psychiatric reasons.²

PTSD is a psychiatric illness that commonly manifests in individuals who have witnessed or experienced a traumatic life event, such as death, disastrous injury, or sexual abuse. The development of PTSD does not occur in all individuals who have experienced a traumatic event, though some have certain risk factors and preexisting conditions that make them more susceptible than others. These risk factors, such as being female and the presence of childhood trauma, combined with biological theories suggesting hypothalamo-pituitary-adrenal axis overactivity, autonomic nervous system overactivity, and alterations in norepinephrine levels and receptors, contribute to the evolution of PTSD.¹ Common symptoms that are characteristic of PTSD include flashbacks, nightmares, distressing dreams or memories, sleep disturbances, hypervigilance, exaggerated startle response, and avoidance of thoughts, objects, people, or places that remind the patient of the traumatic event. According to the Diagnostic and Statistical

Manual of Mental Disorders (DSM-5), a diagnosis of PTSD can be given to patients over 6 years of age who meet the following criteria: (a) exposure to actual or threatened death, serious injury, or sexual violence; (b) presence of at least one intrusion symptom; (c) persistent avoidance symptoms; (d) negative alterations in cognitions and mood associated with the traumatic event; (e) marked alterations in arousal and reactivity associated with the traumatic event; (f) duration of the disturbance is more than one month; (g) the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning; and (h) the disturbance is not attributable to the physiological effects of a substance or another medical condition.¹

Current treatment options for PTSD include pharmacotherapy and psychotherapy. Two pharmacotherapeutic agents – sertraline (Zoloft) and paroxetine (Paxil) – have FDA approval for the treatment of PTSD.^{5,6} Cognitive behavioral therapy (CBT) and prolonged exposure therapy (PE) are well known psychotherapeutic options that, although effective, have substantial dropout rates.^{7,8} Patients undergoing CBT or PE are asked to recollect their frightening memories many times within a secure setting with the goal of inducing elimination of the undesirable trauma/fear response. The psychotherapeutic treatment, however, is an arduous process that is psychologically and emotionally taxing and commonly exacerbates symptoms before they meliorate.⁸ Patients often feel overwhelmed during therapy and avoidance behavior – a hallmark symptom of PTSD – often overpowers their ability to persevere through psychotherapy sessions.⁹ Additionally, many PTSD patients have difficulty building interpersonal and trusting bonds – an essential component to successful treatment. Seeing that 70-80% of those with PTSD are unresponsive to pharmacotherapeutics and dropout rates in psychotherapeutic trials range from 20-30%, it is evident that novel therapeutic options must emerge.^{7,8,9}

MDMA (Methylenedioxymethamphetamine)-assisted psychotherapy (MDMA-AP) is a developing method that has shown promise in clinical trials for the treatment of PTSD. MDMA-AP utilizes a psychoactive drug called MDMA as an adjunct to psychotherapy. The subjective psychological effects of MDMA include diminished anxiety, reduced depression, increased relaxation, euphoria, elevated feelings of trust, expanded insight, and mitigated fear response.¹ It is hypothesized that MDMA, when given in a safe context, produces unique psychological effects that allow those with PTSD to engage in, optimize, and endure psychotherapy sessions.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not MDMA-AP is an effective treatment for PTSD.

METHODS

The criteria used in the selection of the three randomized controlled trials (RCTs) for this review were patients 18 years or older who met DSM-III-R, DSM-IV, or DSM-IV-R requirements for PTSD. The intervention that was studied was MDMA-AP. MDMA-AP needed to be compared to psychotherapy with concomitant administration of either active placebo or inactive placebo. Two articles compared psychotherapy with concomitant MDMA administration to the same psychotherapy accompanied by inactive placebo administration. One article compared psychotherapy with concomitant full-dose (125 mg) MDMA administration to the same psychotherapy accompanied by low-dose (25 mg) MDMA administration. The outcomes measured were a reduction in the severity of symptoms associated with PTSD. Studies utilized in this selective EBM review included three randomized, double, placebo controlled clinical trials.

Two databases were used (PubMed/MEDLINE and Cochrane Library) to find all three articles on MDMA-AP. The search included the terms “MDMA” and “PTSD.” All articles were

written in English and published in peer-reviewed journals between the years 2008 and 2013.

The articles were selected based on their relevance to the clinical question and for their focus on patient-oriented outcomes (POEMs). Inclusion criteria comprised studies that were RCTs with publication dates from 2004 to present. Exclusion criteria consisted of patients under the age of 18, as well as pregnant and/or lactating women. The statistics included were mean change from baseline, p-values, and numbers needed to treat (NNT). Table 1 demonstrates the demographics and characteristics of the studies chosen for this review.

Table 1. Demographics and characteristics of included studies

Study	Type	#pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Bouso et al (2008) ⁷	Randomized, double blind, placebo control	6	29 - 49	-Women with chronic, treatment-resistant PTSD secondary to sexual assault - Score > 15 on SSSPTSD	-Pregnant women -Medication usage in the month prior to the start of the study	0	-MDMA 50-75 mg (n=4); placebo (n=2) -MDMA or placebo given during one 6-hour experimental psychotherapy session
Mithoefer et al (2011) ⁸	Randomized, double blind, placebo control	23	21 - 70	Men and women aged 21-70 years who meet DSM-IV-R criteria for the diagnosis of crime or war-related chronic PTSD and have treatment-resistant symptoms, defined as a CAPS score of greater than or equal to 50 following at least 3 months of prior SSRI or SNRI treatment in addition to at least 6 months of psychotherapy.	-Freedom from any major medical conditions -Borderline Personality Disorder or any current Axis I Disorder (exceptions: anxiety disorders, affective disorders other than bipolar disorder type 1, substance abuse or dependence in remission for greater than or equal to 60 days, and eating disorder without active purging)	2	-MDMA 125 mg (n=12); placebo (n=8) -MDMA or placebo given during two 8-hour experimental psychotherapy sessions

Oehen et al (2013) ⁹	Randomized, double blind, active control	14	23 - 67	Men and women who met the DSM-IV-text revision (TR) criteria for PTSD with treatment-resistant symptoms, as indicated by a CAPS score of greater than or equal to 50 and having previously undergone at least 6 months of psychotherapy and 3 months of treatment with an SSRI.	-Significant medical conditions, except for hypothyroidism under hormonal replacement -Psychiatric conditions: hx of psychotic illness, bipolar disorder type I, borderline personality disorder, dissociative identity disorder, and substance abuse or dependence within 60 days of enrollment -Use of MDMA on more than five occasions or less than 6 months prior to enrollment	2	-MDMA 25 mg + 12.5 mg 2.5 hours later (n=4); MDMA 125 mg + 62.6 mg 2.5 hours later (n=8) -MDMA or placebo given during three 8-hour experimental psychotherapy sessions
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OUTCOMES MEASURED

The severity of PTSD symptoms was the primary outcome measure in the selected studies. In the Bouso et al study, outcome measures used were the Severity of Symptoms Scale for Posttraumatic Stress Disorder (SSSPTSD) which assesses the main symptoms of PTSD.⁷ In the Mithoefer et al study, outcome measures used include the Clinician-Administered PTSD Scale (CAPS). The CAPS quantifies PTSD symptoms.⁸ In the Oehen et al study, outcome measures used were a widely-used German version of the CAPS.

RESULTS

The Bouso et al study⁷ performed in 2008 was a double blind RCT consisting of 6 patients with treatment-resistant PTSD (failed at least 1 prior treatment for PTSD) and a baseline SSSPTSD larger than 15. Of these patients, 3 received 50 mg MDMA, 1 received 75 mg MDMA, and 2 received placebo. Each patient endured 7 psychotherapy sessions of 1 hour 30 minutes' duration, with only 1 psychotherapy period coexisting with MDMA or placebo. This

experimental psychotherapy session was the 4th session out of a total of 8 sessions and commenced with either MDMA or placebo ingestion. The experimental session lasted a total of 6 hours. Baseline and post-treatment SSSPTSD scores were calculated and results were reported as a group mean change from baseline. The results from this study showed larger improvements in group mean score for the MDMA group compared to the placebo group, with a mean SSSPTSD score reduction of 9 for the MDMA group vs 4.5 for the placebo group. These changes correspond to a 24.1% average reduction for the MDMA group compared to 10.1% reduction for the placebo group (Table 2). The difference between the mean change from baseline was primarily powered by greater decreases in the reexperiencing and avoidance subdivisions of the SSSPTSD.⁷ It should be noted that the patient receiving 75 mg of MDMA plus psychotherapy achieved a 16 point SSSPTSD score reduction. The results of the 75 mg MDMA group were not considered here because there was only 1 patient in this group. Due to the small size of the study, a statistical analysis between groups was not performed.⁷

Table 2. Mean SSSPTSD scores by group over time (pre-to post treatment)

Group	Baseline	Post-treatment	Mean Reduction from Baseline	Average Reduction (%)
MDMA 50 mg (n=3)	37.3	28.3	9	24.1
Placebo (n=2)	44.5	40	4.5	10.1

The Mithoefer et al study⁸ conducted in 2011 was a double blind RCT consisting of 20 patients with treatment-resistant PTSD (as outlined in Table 1). The study initially enrolled 23 patients, but 1 dropped out due to a relapse of depression, another due to issues with travel expenses, and a 3rd was removed after an assessment revealed he was not treatment-resistant. The 2 experimental psychotherapy sessions (sessions 1 and 5; 8 hours per session) in this study were performed with patients either receiving 125 mg MDMA or inactive placebo. Additionally, all patients underwent 11 nondrug psychotherapy sessions, with each session lasting for 90 minutes. CAPS scores were recorded at baseline (T1), 4 days after each of the 2 experimental sessions

(T2, T3), and 60 days after the final experimental session (T4). The results of this study showed mean CAPS scores improved over time in both groups (group vs time interaction $p < 0.0005$). The MDMA group, however, showed significantly greater improvement compared to the placebo group (group vs time interaction, $p = 0.015$) with a 68% reduction vs 25.2% reduction at 2 months following the second experimental session, respectively (Table 3). A clinically significant response was defined as a $> 30\%$ reduction from baseline in CAPS total severity score.⁸ The results showed that 83.3% (10/12 patients) of the MDMA-AP group and 25% (2/8) of the placebo plus psychotherapy group achieved a clinical response. Furthermore, 10 patients of the MDMA group no longer fulfilled DSM-IV requirements for PTSD compared with 2 patients of the placebo group.⁸ The absolute benefit increase (ABI) was calculated to be 58.3% and the relative benefit increase (RBI) was calculated to be 233%, with a corresponding NNT of 2 (Table 4).

Table 3. Mean CAPS scores by group over time 1 (T1) – time 4 (T4)

Group	Baseline (T1)	T2	T3	T4	Mean Reduction from Baseline	Average Reduction (%)	P-value
MDMA (n=12)	79.2	37.8	29.3	25.5	53.7	68	0.015
Placebo (n=8)	79.6	74.1	66.8	59.1	20.5	25.2	

Table 4. Clinical response and treatment effects of MDMA-AP

Study	EER	CER	ABI	RBI	NNT
Mithoefer et al, 2011	83.3%	25%	58.3%	233%	2

The Oehen et al study⁹ conducted in 2013 was a double blind RCT consisting of 12 patients with treatment-resistant PTSD (as outlined in Table 1). The study initially enrolled 14 patients, but 2 patients withdrew because of adverse events after the first experimental session. The three experimental psychotherapy sessions were 8 hours in duration and were performed

with patients either receiving high-dose MDMA (125 mg + 62.5-mg supplementary dose) or low-dose MDMA (25 mg + 12.5-mg supplementary dose; “active placebo”). The experimental sessions were intermixed with 12 weekly nondrug psychotherapy sessions of shorter duration. CAPS scores were calculated at baseline (T0) and 3 weeks after the second (T1) and third (T2) experimental sessions. CAPS scores were analyzed using 2-way ANOVA.⁹ The results indicated CAPS mean scores increased from T0-T2 for the active placebo group and decreased from T0-T2 for the high-dose MDMA group. Although there was a trend toward larger effects from higher-dose MDMA, these results were not statistically significant ($p = 0.066$, Table 5).

Table 5. Effects of high-dose MDMA-AP vs low-dose MDMA-AP on mean CAPS scores

Group	T0	T1	T2	Mean Change from Baseline	Average Change (%)	P-value
High-dose MDMA (n=8)	66.4	63.0	50.8	- 15.6	- 23.5	0.066
Low-dose MDMA (n=4)	63.4	60.0	66.5	+ 3.1	+ 4.9	

After the clinical trial, an open-label phase was initiated which allowed the 4 patients who had received low-dose MDMA to receive 6 sessions of high-dose MDMA-AP. At one year following completion of the open-label phase, average CAPS scores decreased by 52% (35 points) in these 4 patients. At one year follow-up, 5 of 12 subjects no longer fulfilled diagnostic requirements for PTSD, 4 had moderate PTSD, 2 subjects reduced their PTSD severity level to mild. Furthermore, one patient on disability and three patients on limited employment were able to go back to work as full-time employees by the one year follow-up.⁹

There were no significant drug-related adverse events in any of the studies. Mithoefer et al. did note larger increases in blood pressure, heart rate, and body temperature in the MDMA group, but these effects resolved and returned to baseline in both groups at the end of each experimental session.⁸

DISCUSSION

This systemic review evaluated the three randomized controlled trials evaluated the effectiveness of MDMA-AP as a treatment for PTSD. The study by Bouso et al. demonstrated encouraging indications of efficacy through reductions in SSSPTSD scores for both groups, although there were larger reductions in the MDMA-AP group (24.1%) vs placebo group (10.1%) that were principally fueled by larger decreases in reexperiencing and avoidance. This study, however, has an array of limitations due to its small sample size and enrollment of only female subjects. Additionally, the ethnicity of the subjects was not reported and a statistical analysis was not completed. The Mithoefer et al. study generated clinically and statistically significant improvements in PTSD symptomatology as calculated by CAPS scores and a p -value equal to 0.015 and a NNT of 2. Furthermore, 83.3% of the MDMA-AP group subjects no longer met diagnostic criteria for PTSD. The drawbacks to this study include a small sample size composed solely of Caucasians, with nearly 85% of these being female. The Oehen et al. study showed a reduction in CAPS scores over time, with a trend toward larger effects from higher-dose MDMA, although these results were not statistically significant ($p = 0.066$). Weaknesses in this study include a small sample size composed entirely of Europeans, with most participants being female. An additional pitfall is that all three RCTs in this systemic review exclusively enrolled and treated subjects with chronic, treatment-resistant PTSD.

From a clinical standpoint, safety, affordability, and access are strong considerations when making treatment decisions. Unfortunately, MDMA-AP may miss the mark in all three categories. Although the trials demonstrated no serious drug-related adverse events, MDMA intoxication has been known to cause hyperthermia, hyponatremia, seizures, hepatotoxicity, and life-threatening increases in heart rate and blood pressure.⁶ These serious events, although

uncommon, limit the patient population that could benefit from this type of therapy.

Affordability of MDMA may be another forceful disadvantage considering the 6-8-hour length of the therapy sessions and extended monitoring of patients, which often includes overnight observation.^{7,8,9} Finally, with no current FDA-approved indications and a schedule I drug status, medical access to MDMA is nearly impossible.^{6,7}

CONCLUSION

The studies reviewed demonstrate inconclusive evidence as to whether or not MDMA-assisted psychotherapy (MDMA-AP) is an effective treatment for posttraumatic stress disorder (PTSD). Although all studies demonstrated obvious improvements in CAPS scores for MDMA versus placebo, only one study showed statistical significance. Future studies will need larger sample sizes and a heterogeneous group of patients to apply clinically and statistically significant findings to a more global population. Additionally, future studies need to focus on comparing the effectiveness MDMA-AP to other treatment options, such as the combined gold-standard psychotherapy with SSRI therapy. For many, the use of MDMA-AP greatly reduced debilitating PTSD symptoms, removed a PTSD diagnosis, and/or allowed a return to employment as a full-time employee. These quality of life improvements are patient-oriented outcomes that cannot be overlooked or forgotten. PTSD is a costly condition with the potential for devastating outcomes, and further MDMA-AP studies need to be performed to assess its safety and clarify its effectiveness as a treatment option for this common psychiatric illness.

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