

The Efficacy of MDMA-Assisted Psychotherapy Compared to the Efficacy of Traditional Psychotherapy in Treating Anxiety-Related Symptoms in 18–40-Year-Old Adults Diagnosed With Post-Traumatic Stress Disorder (PTSD)

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Abstract

Post-Traumatic Stress Disorder is a mental health condition brought on by witnessing or experiencing distressing or terrifying events. Both MDMA and SSRIs like fluoxetine have shown to aid in fear extinction and clinical recovery from PTSD. However, recent studies have shown that MDMA used alongside therapy may have longer lasting effects on the anxiety symptoms of PTSD and can result in quicker fear extinction responses compared to current therapeutic methods using SSRIs. This review analyzes the knowledge and studies available comparing the efficacy of MDMA-Assisted psychotherapy to traditional psychotherapy in treating anxiety-related symptoms of PTSD in adults aged 18 to 40.

Introduction

- PTSD**
 - PTSD is a mental health condition brought on by witnessing or experiencing distressing or terrifying events
 - Symptoms of PTSD can be devastating and contribute to increased suicidality
 - Even with treatment, relapse is not uncommon. Of those who continued traditional psychotherapy, 16.4% had relapsed after 24-28 weeks of treatment
- MDMA-Assisted Psychotherapy**
 - MDMA, or 3,4-methylenedioxymethamphetamine, is a psychoactive chemical which stimulates the release of serotonin, oxytocin, prolactin, and cortisol
 - Up until it became a Schedule I drug in 1985, MDMA was used as in therapeutic settings.
 - Researchers have further hypothesized that MDMA-Assisted Psychotherapy has a stronger, longer lasting effect on reducing these symptoms of PTSD than the traditional therapies used today

Methods

- Performed November 2019**
 - EBSCO, Google Scholar, and Google
- Search Terms:** “mdma-assisted psychotherapy” or “mdma assisted psychotherapy for ptsd traditional therapy” or “mdma-assisted psychotherapy randomized controlled trial” or “How does the efficacy of MDMA-Assisted Psychotherapy compare to the efficacy in traditional psychotherapy in treating 18-40 year old adults diagnosed with Post-Traumatic Stress Disorder (PTSD)”
- Inclusion criteria**
 - Peer reviewed and/or Scholarly
 - Published in 2013 or later
 - Discusses at least one of the following:
 - The effects of MDMA-assisted psychotherapy on PTSD
 - The effects of MDMA-assisted psychotherapy on anxiety
 - The pharmacodynamics of MDMA and how it can be used in treatment for mental illness
 - Comparing MDMA-assisted psychotherapy to traditional psychotherapy
- Exclusion criteria**
 - Articles which were not peer reviewed or scholarly
 - Articles which simply support or critique a previously chosen article without providing new information regarding the PICO question
 - Articles which were written before 2013
 - Articles that did not fit any of the inclusion criteria listed above

Results

- Danforth AL, Grob CS, Struble C, et al. Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. Psychopharmacology. 2018;235(11):3137-3148. doi:10.1007/s00213-018-5010-9.**
 - RCT of 12 participants followed by open crossover after 1 month comparing the efficacy of placebo-assisted psychotherapy to MDMA-Assisted psychotherapy in reducing anxiety symptoms
- Wagner MT, Mithoefer MC, Mithoefer AT, et al. Therapeutic effect of increased openness: Investigating mechanism of action in MDMA-assisted psychotherapy. Journal of Psychopharmacology. 2017;31(8):967-974. doi:10.1177/0269881117711712.**
 - RCT of 20 participants followed by open crossover after 2 months comparing the efficacy of placebo-assisted psychotherapy to MDMA-Assisted psychotherapy in treating PTSD
- 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). Journal of Psychopharmacology. 2013;27(1):40-52. doi:10.1177/0269881112464827.**
 - RCT of 14 participants followed by “active placebo condition” comparing the efficacy of placebo-assisted psychotherapy to MDMA-Assisted psychotherapy in treating PTSD
- Amoroso T, Workman M. Treating posttraumatic stress disorder with MDMA-assisted psychotherapy: A preliminary meta-analysis and comparison to prolonged exposure therapy. Journal of Psychopharmacology. 2016;30(7):595-600. doi:10.1177/0269881116642542.**
 - Meta-analysis of RCTs with 712 total participants comparing the efficacy of prolonged exposure therapy to MDMA-Assisted Psychotherapy at treating symptoms of PTSD
- Bousso JC, Doblin R, Farré M, Alcázar MÁ, Gómez-Jarabo G. MDMA-Assisted Psychotherapy Using Low Doses in a Small Sample of Women with Chronic Posttraumatic Stress Disorder. Journal of Psychoactive Drugs. 2008;40(3):225-236. doi:10.1080/02791072.2008.10400637.**
 - RCT of 6 participants comparing the efficacy of placebo-assisted psychotherapy to MDMA-Assisted psychotherapy in treating refractory PTSD symptoms
- Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., ... & Doblin, R. (2018). 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, 5(6), 486-497.**
 - RCT of 26 participants followed by open label crossover after 2nd “experimental session” comparing the efficacy of “active control” assisted psychotherapy to MDMA-Assisted psychotherapy in treating symptoms of PTSD

Table 1. Comparison of study designs. MDMA-AP vs Traditional therapy

Study	Population	Therapy Compared	MDMA Dosing	Outcomes
1	Mean age = 31 +/- 8.8 years, 83.3% male, 16.7% female, 50% White	Placebo-assisted psychotherapy	75 mg during first session, 100 mg during second session	LSAS
2	Mean age = 40.4 +/- 7.2 years, 17 females, 3 males, 100% White	Placebo-assisted psychotherapy	125 mg for each of the two experimental sessions	CAPS scores, NEO-PI-R
3	Mean age = 41.4 +/- 11.2 years, 10 females, 2 males, Ethnicity unlisted	Placebo-assisted psychotherapy	125 mg + 62.5 mg full dose, 25 mg + 12.5 mg “active placebo”	CAPS scores, PDS scores,
4	MDMA-AP: Mean age = 40.9 +/- 9.2 years, 84.4% females, 15.6% males, ethnicity unlisted PE therapy: Mean age = 46.8 +/- 14.3 years, 12.9% females, 87.1% males, ethnicity unlisted	PE therapy	125 mg per session, 62.5 mg per session, 25 mg per session, 12.5 mg per session	CAPS scores, PDS, Cumulative effect size of primary outcomes, Cumulative effect size of secondary outcomes, cumulative dropout rates
5	Ages ranged from 29-49 years old, 100% females, ethnicity unlisted	Placebo-assisted psychotherapy	50 mg experimental session, 75 mg per experimental session	STAI-S, SSSPTSD, BDI, HAM-D, MFS III, MS, SE/R, HRS, HAq
6	Mean age = 37 +/- 2 years old, 27% female, 73% male, 85% white	“Active control” (30 mg MDMA) assisted psychotherapy	30mg for each of the two sessions, 75 mg for each of the two sessions, 125 mg for each of the two sessions	CAPS-IV Score, BDI-II, Mean PSQI, PGTI score, GAF score, DES-II score, NEO-PI-R

Key: RCT = randomized controlled trial; LSAS = Leibowitz Social Anxiety Scale; CAPS = Clinician Administered PTSD scale; NEO-PI-R = The Revised NEO Personality Inventory; PE therapy = Prolonged Exposure Therapy; STAI-S = The State Trait Anxiety Inventory, State Version; SSSPTSD = The Severity of Symptoms Scale for Post-traumatic Stress Disorder; BDI = The Beck Depression Inventory; HAM-D = The Hamilton Rating Scale; MFS III = The Modified Fear Scale; MS = The Maladjustment scale; SE/R = The Rosenberg Self-esteem Scale; HRS = The Hallucination Rating Scale; HAq = The Penn Helping Alliance Questionnaire; CAPS-IV = Clinician-Administered PTSD Scale; BDI-II = Beck Depression Inventory-II; PSQI = Pittsburgh Sleep Quality Index; PGTI = Post-Traumatic Growth Inventory; GAF = Global Assessment of Functioning; DES-II = Dissociative Experiences Scale II

Discussion

5/6 studies reported that MDMA-Assisted psychotherapy was more beneficial in reducing symptoms of PTSD compared to traditional psychotherapy

- Strengths**
 - All studies were based on RCTs
 - 5/6 studies reported statistically significant results ($P \leq 0.05$)
 - 3 studies reported a clinically and statistically significant reduction in CAPS scores when compared to placebo-assisted psychotherapy and prolonged exposure therapy, while 2 studies reported a significant reduction in SSPTSD scores and a significant reduction in Leibowitz Social Anxiety Scale (LSAS) scores compared to placebo-assisted psychotherapy
- Weaknesses**
 - Low number of participants
 - Many of these studies have participant populations that are either over 75% white or fail to list the ethnicities of the population tested → Not a diverse patient population
 - Lack of longitudinal studies
 - MDMA is a Schedule I substance in the United States

Conclusion

Clinically speaking, these studies could support MDMA-Assisted psychotherapy being a suitable option in reducing the anxiety symptoms of PTSD which may be refractory to traditional psychotherapy. However there are several gaps in the research and studies available

With such small patient populations, interpretation of these results simply cannot be generalized to a larger patient population and studies involving larger sample sizes are necessary to support the evidence of efficacy. Also, the differences in population demographics in these studies can make it difficult to support generalizing the evidence and recommending MDMA-Assisted Psychotherapy when working with a diverse patient population.

There is also a lack of evidence in these studies supporting the long term effects of MDMA-Assisted psychotherapy. Finally, MDMA also remains a Schedule I substance in the United States, possessing and prescribing the substance to patients can lead to criminal charges, making large scale, longitudinal randomized controlled studies incredibly difficult to perform and fund legally.

MDMA-Assisted psychotherapy has been showing promise as an alternative breakthrough therapy for patients with refractory anxiety symptoms of PTSD. However, an increase in larger longitudinal studies with more diverse sample populations would be necessary before current practices can be changed and the therapy can be recommended for clinical use.