Efficacy and Safety of MDMA-Assisted Psychotherapy

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Writer's Comment: When I was thirteen years old my mom was diagnosed with breast cancer. Now eight years cancer-free, she continues to face the repercussions of aggressive antibiotics and post-treatment complications. After years struggling to find a solution, my mom began an anti-inflammatory diet, and I watched firsthand the noticeable shift in her mental and physical well-being. It was amazing to watch the positive effects such a seemingly simple solution could have; although, it perplexed me that conventional medicine did not address such preventative and healing methods to combat post-treatment complications and psychological distress. For this reason, I was compelled to write a review addressing alternative treatments to conventional medicine. Thus, I decided to focus on PTSD, since it's known to be a highly treatment-resistant disorder. With conventional methods lacking efficacy for PTSD patients, my paper focalizes on the use of MDMA as an adjunct to psychotherapy. I hope this review excites people about not only the medical value of psychedelics but the possibility of more effective and safe alternatives to conventional, Western medicine.

Instructor's Comment: Even though Kennedy developed a wealth of expertise on the resurging clinical use of an uncommon therapeutic in researching and writing her review paper "Efficacy and Safety of MDMA-assisted Psychotherapy", upon reflection, her learning during the quarter ran much deeper. When preparing to write her personal statement, the brainstorming and drafting process helped her reflect on how her recent personal and academic growth intersected with

her passions, leading Kennedy to a powerful realization. Her interests and passions had changed. She also realized that when she ran into challenges in her classes or work, by applying herself fully she would gain valuable experience and learn new skills, even if things didn't go as planned. These self-reflective moments in Spring Quarter of 2022 helped Kennedy feel confident that she could make choices to listen to herself, follow her passions, and no matter what happened, she would be learning and growing.

This questioning of expectations and willingness to challenge the status quo that resonated so strongly with Kennedy is officially a thing. Not just with the broader societal landscape we find ourselves in right now, but also with the ways in which we approach science. Take MDMA for example, decades ago it was commonly used to support therapy in supervised contexts with success, until the broader war on drugs led the US Government to ban all use. However, beginning in 2010, the surging mental health crises, fueled in part by Veterans suffering from PTSD and a lack of treatment options helped shift policy. Here, Kennedy reviews recent research from clinical studies to highlight that even though MDMA-assisted psychotherapy seems to be effective for treating certain disorders, the small sample sizes, lack of consistency across cohorts and legal red tape suggest a dire need for more in-depth trials to validate and mobilize this much needed therapeutic. This timely, thoughtful and engaging review explores the present and the potential future of an often maligned but potentially potent treatment for PTSD and other disorders.

—Russ Carpenter, University Writing Program

Abstract

Posttraumatic stress is a common psychiatric disorder, typically associated with comorbidities such as depression, substance abuse, and suicide. Even with this disorder's high prevalence, especially in first responders and veteran populations, there fails to be an effective and long-lasting treatment for PTSD

and its common comorbidities. Prior to the criminalization of 3,4-methylenedioxymethamphetamine (MDMA) in 1985, clinical records showed promising results in using MDMA as a catalyst for trauma-focused therapy, especially with PTSD patients [11]. In efforts for a novel treatment, after an almost thirty-year hiatus, a focus on the therapeutic potential of MDMA for PTSD patients has reemerged. The purpose of this review was to evaluate recent studies on the efficacy and safety of MDMA-assisted psychotherapy for PTSD patients. We limited the scope of our research to clinical trial studies from 2010-present. Springer, Taylor & Francis, and PubMed databases were searched for peer-reviewed studies that included "psychotherapy," "MDMA," and/or "3,4-methylenedioxymethamphetamine," and "PTSD" and/or "posttraumatic stress disorder." Precedence was given to phase 2, or ideally phase 3, clinical trial studies. The consistent result found MDMA as an adjunct to psychotherapy to be both effective and safe, with long-lasting PTSD symptom relief. However, recurring limitations across studies included small sample sizes, inconsistent doses and study durations, and stigma around the clinical use of psychoactive drugs. Thus, in order for significant conclusions to be established regarding the clinical use of MDMA-assisted psychotherapy, further efficient studies need to be conducted.

Introduction

Posttraumatic Stress Disorder: Conventional Treatments

Posttraumatic stress disorder affects about 8% of the general population, 17% of military personnel and veterans, and 10-32% of first responders [1]. This psychiatric disorder is

characterized by hypervigilance, re-experiencing phenomena, affect dysregulation, and fear and avoidance associated with traumatic events [10]. While PTSD symptoms alone are debilitating enough, more than 80% of patients with severe or chronic PTSD have associated psychiatric and mental comorbidities such as

depression, substance abuse, and suicide [2,9]. Consistent evidence shows that PTSD patients with comorbidities are more resistant to conventional treatment methods.

Common treatments for PTSD include pharmacotherapy and psychotherapy, both of which have high non-response and dropout rates. Pharmacotherapy is the use of selective serotonin reuptake inhibitors (SSRIs), and there are currently only two FDA-approved SSRIs to treat PTSD: sertraline and paroxetine. These compounds are used as first-line therapeutics for treatment, yet lack efficacy with only a 20-22% higher response rate than a placebo in clinical trials. Psychotherapy is more commonly used to treat PTSD, yet clinical trials have shown a dropout rate of 20-30% and an inconsistent response rate between 60-95% [2,9]. The issue with using psychotherapy treatment for PTSD is that patients commonly experience emotional numbing, retraumatization, dissociation, and anxiety upon revisiting memories of traumatic events [2,6]. Hence, to combat high rates of emergent and treatment-refractory PTSD a surge of research for a novel treatment has led to studying the therapeutic potential of 3,4-methylenedioxymethamphetamine (MDMA).

History of MDMA

MDMA is an illicit psychoactive drug, commonly known for its recreational use under the name 'ecstasy'. In 1914 MDMA was initially synthesized to function as an intermediate for another drug to stop bleeding; it wasn't until later that the psychoactive component of the drug was first studied [2]. Observing the empathogenic effect MDMA has, increasing empathy and prosocial feelings, established the rationale for using it as an adjunct to psychotherapy. By the 1980s it is estimated that 500,000 therapy sessions involved the use of MDMA as a therapeutic catalyst. It was used to treat a variety of psychiatric disorders, yet physicians agreed its most useful effect was in trauma-focused therapy [6]. However, while the drug gained clinical traction it was simultaneously being

used recreationally. The recreational misuse of MDMA caused the DEA to classify the drug as a Schedule I drug in 1985, shutting down all legal use, and halting clinical research [6,11]. However, a need for improved treatments for psychiatric disorders has caused a refocus on exploring MDMA's therapeutic potential.

MDMA's Therapeutic Potential for PTSD

MDMA's unique psychopharmaceutical profile makes it a promising adjunct for trauma-focused psychotherapy. Active dosages of purified MDMA can alter one's consciousness without impairing psychological factors such as visual perception or cognitive process. This ameliorative effect helps participants access traumatic memories with more ease by preventing overwhelming fear and anxiety while simultaneously increasing communication. This aids in maintaining a therapeutic alliance, which is vital for the psychotherapeutic process of treating PTSD [6,10]. PTSD psychotherapy is considered effective when an appropriate level of emotional engagement without overwhelming feelings or dissociation – commonly referred to as working with the 'optical arousal zone'– is achieved [2,13]. MDMA makes reaching this 'zone' more attainable by reducing amygdala activity, which controls fear-and-anxiety behaviors, and increasing connectivity between the hippocampus and prefrontal cortex. This is critical because according to the current neurocirculatory model PTSD is caused by an imbalance of the amygdala and the prefrontal cortex [7, 10]. Additionally, MDMA promotes the release of serotonin, oxytocin, norephedrine, and dopamine. The dynamic interaction of these neurotransmitters and hormones causes acute effects such as euphoria, extroversion, and empathetic social interaction. All of which can facilitate therapeutic effects and create motivation to engage in therapy [10,12]. A growing body of clinical research suggests that MDMA-assisted psychotherapy might be the novel treatment for treatment-refractory PTSD. This review presents the results of recent studies aimed to address the efficacy and

safety of MDMA-assisted psychotherapy to treat PTSD and the comorbidities that typically confer treatment resistance.

MDMA-assisted Psychotherapy: Clinical Trials

Phases of Clinical Trials

To assess the efficacy and safety of new treatments, it is common practice for several clinical trials to be conducted in phases. Phase I trials function to assess the effect the drug has on the body and if it is safe. When a new treatment is found to be safe in phase I trials, phase II trials are conducted to further evaluate what specific disorders/diseases this treatment might benefit. If enough participants benefit from the treatment, without severe side effects, phase III clinical trials are begun.

Phase III trials compare the safety and efficacy of new treatments compared to current standard treatment. Compared to phase II trials, there are a large number of participants, usually around or over 100, and tend to last for longer durations. Placebos are rarely used alone in Phase III trials. Control groups commonly are given a placebo, to begin with, and then endure what is called an 'open-label crossover' where they too receive the standard treatment. The importance of phase III trials is that if a new treatment proves to be safe and more effective than the current treatment a new drug application (NDA) can be submitted to the FDA [3,6,12,13]. Thus, if enough phase III trials prove the efficacy and safety of MDMA as an adjunct to psychotherapy further action can be implemented for its clinical use to treat PTSD.

Therapeutic Methods

Phase 2 clinical trials use therapeutic approaches developed before MDMA was classified as a Schedule I drug in 1985. Psychotherapy methods follow the same manualized supportive therapy modality outlined in 'A Manual for MDMA-assisted Psychotherapy in the Treatment of PTSD'. There is a male and

female co-therapist team provided to ensure an appropriate patient-therapist relationship. Before the administration of MDMA, patients are given three 90-minute preparatory psychotherapy sessions. During the MDMA-assisted psychotherapy session, MDMA is given orally in a capsule form, and the participant wears eyeshades and listens to relaxing music. Therapists encourage discussion of emotions regarding traumatic events. This approach is observational, looking for MDMA's effects such as increased recall ability and reduced emotional numbing or dissociation. After each MDMA-session participants have three additional 90-minute psychotherapy sessions [2,12].

Participants

Clinical trials for MDMA-assisted psychotherapy typically recruit subjects via internet advertisements and letters to psychotherapists. Standard enrollment criteria consist of a CAPS score of 50 or above – meaning the participant has moderate to severe PTSD symptoms. Additionally, participants must have chronic PTSD which is defined by symptom duration of at least six months and non-response to at least one first-line treatment. Since PTSD is commonly associated with several psychiatric and mental comorbidities studies permitted comorbidities such as anxiety disorders, affective disorders (expect bipolar disorder), substance abuse, and eating disorders without active purging [1,2,8,9,13].

Phase 2 Clinical Trials of MDMA-assisted Psychotherapy

After almost thirty years since MDMA was classified as a Schedule I drug, in 2010 Micheal C Mithoefer was the first to publish a randomized, controlled clinical trial testing MDMA as a therapeutic catalyst. After one course of MDMA-assisted psychotherapy, 85% of the patients no longer met the criteria for PTSD. The participants that received an active dose of MDMA had a significant decrease in CAPS scores from baseline compared to the

placebo group [2]. To ensure long-term effects, a follow-up study of the same cohort concluded no substance abuse or harmful effects. Four years later and that same 85% of the cohort remained free of PTSD symptoms [3]. These promising results from Mithoefer et al clinical trial and follow-up catalyzed further clinical research on the therapeutic potential of MDMA.

Dose-Response Effects

With Phase I clinical trials establishing the safety of MDMA as an adjunct to psychotherapy for PTSD treatment, further Phase II trials were conducted to find the best level of sporadic dosages of MDMA. However, dose-response studies failed to provide consistent results of efficacy. In efforts to secondarily confirm Mithoefer et al study in 2010, a study by Oehen et al attempted to address the question of if an active control, 25mg of MDMA, could optimize the blinding of the double-blind experiment. The experimental group received a full dose of 125mg followed by a 62.5mg dose 2.5 hours later; the active placebo dose consisted of a 25mg dose followed by 12.5mg 2.5 hours later. There were subjective clinical and patient reportings of improvements in PTSD symptoms. However, Oehen and colleagues did not find statistically significant reductions in CAPS scores. Since conclusions did not align with Mithoefer et al 2010, it was predicted that three MDMA sessions would have more effective in decreasing CAPS scores [7].

Whereas, in 2018, Mitoefer et al conducted a dose-response clinical trial to test the efficacy and safety of MDMA-assisted psychotherapy for PTSD, specifically in military personnel and first responders. Mithoefer found that active doses of MDMA, 75mg and 125mg, had significant decreases in PTSD symptoms compared to the active control of 30mg. Furthermore, the open-label crossover administration of 100-125mg of MDMA, in all three experimental groups, showed a significant decrease in PTSD symptoms in the active control group. This proved that a full dose

of MDMA had a difference compared to the active control. After a twelve-month follow-up, PTSD symptoms had significantly improved compared to baseline after all groups had received active dosages of MDMA [1]. Ot'alora et al study in 2018 found dose-response differences that aligned with Mitoefer et al 2018 study findings. The groups that received active doses of MDMA, 125mg and 100mg, had significant improvements in PTSD symptoms compared to the low dose of 40mg. Additionally, a twelve-month follow-up post-open-label crossover found that 76% of participants no longer met PTSD criteria [8].

Phase 2 Trials: Common Limitations

Phase 2 trials pose limitations of small sample sizes and between-study variabilities, such as inconsistent doses and study durations. The stigma around the use of psychoactive drugs has also created limitations. For example, in 2006, a clinical trial in Madrid published data that included only 6 participants because political and social pressure terminated the study prematurely [6]. Additionally, with the limited literature on the benefits of MDMA, clinicians and psychiatrists might stray from exploring clinical use. Findings from phase 3 trials will be able to validate and further expand upon the results of MDMA-assisted psychotherapy found in phase 2 trials [1,2,5,6,9].

Phase 3 Clinical Trials: Creating A Generalized Effect

With the recent approval of phase 3 clinical trials, the safety and efficacy of MDMA-assisted psychotherapy have been further validated, and additionally have shown a generalization of MDMA's therapeutic benefit in simultaneously aiding common PTSD comorbidities. Oehen et al prediction that three active dosages of MDMA would be more effective was validated in the 2020 study by researchers at the University of San Francisco. It was demonstrated that the administration of MDMA in three dosages significantly improved PTSD symptomology and decreased rates of withdrawal

and non-response to treatment. This study also found that MDMA treatment was equally effective in patients with comorbidities often associated with higher treatment resistance. Comparing BDI-II scores from baseline to study termination, a decrease in depressive symptoms was found [9].

As noted in the previous paragraph, clinical trials have been able to generalize the effect of MDMA-assisted psychotherapy to also decrease depression symptoms; a study by Nicholas et al in 2021 explored additional outcomes of MDMA-assisted psychotherapy by examining changes in alcohol and substance abuse. Alcohol and substance abuse disorders (ASUDs) have a 17-46% co-occurrence with PTSD. ASUDs are commonly comorbid with PTSD, particularly because PTSD patients rationalize the abuse as a way to alleviate PTSD symptoms. Participants that received MDMA-assisted psychotherapy had significant decreases in alcohol consumption and risk for hazardous use compared to the placebo group [5].

Conclusion

In this review, we examined the findings of notable modern studies on the efficacy and safety of MDMA-assisted psychotherapy for treating PTSD. The review detailed information on MDMA's therapeutic potential and its relevance to PTSD and the comorbidities that typically confer treatment resistance. This elucidated the current state of research on this topic, and while it is expanding, the literature on the clinical use of MDMA remains rather limited. However, phase 2 and 3 trials found harmonious results which leads us to the conclusion that MDMA as an adjunct to psychotherapy might be the novel treatment needed for treatment-resistant PTSD.

The scheduling of MDMA, and the stigma around the use of psychoactive drugs, have made it difficult to validate findings due to limited clinical studies on the therapeutic benefit of MDMA. Now with fewer regulations on clinical research for MDMA, it

is important for more phase 3 trials to be conducted in order to assess larger sample sizes and help educate physicians on MDMA's therapeutic potential in psychotherapy, especially trauma-focused therapy [7]. MDMA's unique psychopharmacological profile gives it an advantage over conventional treatments for PTSD. As previously discussed, pharmacotherapy uses SSRIs, which target the neurotransmitter serotonin, while MDMA is able to target multiple neurotransmitters: serotonin, dopamine, and norepinephrine [10,13]. MDMA's ability to decrease amygdala activity, increase prefrontal cortex activity, and release specific neurotransmitters and hormones makes it a promising psychotherapeutic adjunct [2,10].

In efforts to create a more effective psychotherapy, recent studies have tested the efficacy and safety of administering MDMA during psychotherapy sessions in order to catalyze the psychotherapeutic process. In doing so, significant reductions in PTSD symptoms compared to placebo groups were found. Only one study did not report a statistically significant reduction in CAPS scores in participants that received active dosages of MDMA. However, this study did report clinical and patient reports of symptom relief. Dose-response trials found additional significant evidence in the effect active dosages of MDMA had compared to a low dosage.

Phase 3 trials were able to generalize MDMA's therapeutic effect to also reduce depressive symptoms and substance abuse. Further studies should be conducted on the efficacy and safety of MDMA-associated psychotherapy regarding other specific comorbid conditions for PTSD patients. Thus, MDMA's empathogenic qualities have been proven to be an effective catalyst for psychotherapy to treat PTSD, yet to establish significant conclusions for clinical use additional phase III trials need to be conducted.

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