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MDMA-Assisted Psychotherapy for Treatment of Posttraumatic Stress Disorder: A Systematic Review With Meta-Analysis

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Abstract

This article discusses current literature on the use of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in the treatment of posttraumatic stress disorder (PTSD). MDMA, the intended active ingredient in illicit Ecstasy or Molly products, is a psychedelic that causes an elevated mood, feeling of bonding, and increased energy. In MDMA-assisted psychotherapy, patients are subjected to 2 or 3 multihour sessions of therapy with a team of psychiatrists. The dosing of MDMA is used to allow the therapist to probe the underlying trauma without causing emotional distress. The use of MDMA-assisted psychotherapy treatment reduced patient's Clinician-Administered PTSD Scale (CAPS) scores from baseline more than control psychotherapy (–22.03; 95%CI, –38.53 to –5.52) but with high statistical heterogeneity. MDMA-assisted psychotherapy enhanced the achievement of clinically significant reductions in CAPS scores (relative risk, 3.65; 95%CI, 2.39-5.57) and CAPS score reductions sufficient to no longer meet the definition of PTSD (relative risk, 2.10; 95%CI, 1.37-3.21) with no detected statistical heterogeneity. While therapy was generally safe and well tolerated, bruxism, anxiety, jitteriness, headache, and nausea are commonly reported. While MDMA-assisted psychotherapy has been shown to be an effective therapy for patients with PTSD with a reasonable safety profile, use of unregulated MDMA or use in the absence of a strongly controlled psychotherapeutic environment has considerable risks.

Keywords

clinical pharmacology, (CPH), drug abuse, drug development, psychiatry (PSY), psychopharmacology (PSP)

Posttraumatic stress disorder (PTSD) is a debilitating mental health disorder characterized by avoidance, hypervigilance, and flashbacks where patients are re-experiencing aspects of a traumatic event.[1] It can be further confounded by comorbid anxiety, depression, substance abuse, and suicidal ideation and actions.[1] PTSD affects nearly 7% of the population in the United States and causes those impacted to lose an average of 3.6 days of work per month. While there are several pharmacologic and nonpharmacologic treatment options available, many people with PTSD do not adequately respond.[2]

3,4-Methylenedioxymethamphetamine (MDMA) can increase the feeling of energy via norepinephrine release, elevate mood via serotonin release, increase bonding with strangers via oxytocin release, and provide a psychedelic effect from its methylenedioxy molecular component.[3] MDMA is a substance of abuse and the active ingredient sought by purchasers of Ecstasy and Molly, although many of these illicit products contain a variable amount of MDMA and adulterants ranging from methamphetamine, lysergic acid, and synthetic cathinones that amplify the adverse event potential. Users of illicit MDMA-containing products are at risk of hyperthermia and hyponatremia with resultant rhabdomyolysis and renal damage, elevated blood pressure and tachycardia with cardiovascular events including arrhythmias, a period of anhedonia after the elevated mood due to depletion of serotonin, bruxism (jaw clenching) with tooth damage, and compromised objectivity with an elevated risk of physical or sexual assault.[3]

The increases in energy, elevated mood, feelings of closeness with psychologists/psychiatrists, and the surreal aspect of the psychedelic effects that the MDMA provides were proposed to enhance psychotherapy sessions where patients with PTSD are reluctant or unable to tap into the traumatic events due to acute panic

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or anxiety reactions.[3,4] MDMA appears to bilaterally reduce activity in the amygdala, the brain structure that acquires and stores fearful memories.[5] The reduction of amygdala activity with concomitant serotonin release has been experimentally found to increase cognitive flexibility, diminishing responses to negative stimuli while enhancing responses to positive emotions that could be useful when working through the event(s) that led to PTSD.

The Drug Enforcement Agency designation as a Schedule I drug (no therapeutic uses, high abuse potential) made it very difficult to study MDMA-assisted psychotherapy for many years. Early studies provided enough promising safety and efficacy data on the controlled use of MDMA-assisted psychotherapy that in 2017, the Food and Drug Administration (FDA) granted breakthrough therapy designation and the ability to conduct more extensive clinical studies.[6] Since then, there have been several clinical studies assessing the efficacy and safety of MDMA-assisted PTSD psychotherapy including phase II clinical trials and a phase III clinical trial.

There are 2 common outcome scales for PTSD. The most common outcome measure is the Clinician-Administered PTSD Scale (CAPS), which was recently adapted as the Diagnostic and Statistical Manual of Mental Disorders (DSM) moved from the fourth edition to the fifth edition.[7–9] An aggregate CAPS score $\geq$50 units constitutes a severe case of PTSD.[8] Another outcome measure for PTSD symptoms is the Severity of Symptoms Scale for PTSD (SSSPTSD) but it is used less often.[10,11] An aggregate SSSPTSD score of $\geq$46 is considered severe PTSD.

This article will provide an general overview of guideline-suggested pharmacologic options for PTSD and then provide an in-depth assessment of the clinical trials assessing MDMA-assisted psychotherapy with its possible place in therapy.

Current FDA- or Guideline-Recommended Pharmacologic Options

Numerous medications have been assessed for use in the treatment of PTSD, but sertraline and paroxetine are the only 2 FDA-approved treatment options.[12,13] These agents and fluoxetine and venlafaxine are recommended by the American Psychological Association's and the Veterans Administration Department of Defense PTSD guidelines.[12,13]

Sertraline was assessed in 4 phase III trials of similar design in patients with severe PTSD (CAPS-II scores >50 units) with a 12-week flexible daily dose between 50 and 200 mg.[14] Two of the 4 studies failed to find a significant difference between the sertraline- and placebo-treated groups for CAPS-II scores. Of the trials that found significant benefits at 12 weeks, the first (n = 208) reported that the change in CAPS-II scores from baseline was –6.8 units greater in the sertraline than the placebo group ($P = .043$), while the difference between groups in the second study (n = 183) was –9.8 units ($P = .016$). Importantly, 29% of participants in trial 1 and 28% in trial 2 withdrew during the study.[14] A combined analysis of 2 sertraline studies showed that CAPS-II scores were –8.3 units lower in the sertraline group and placebo group but were only significantly improved in female subjects.[14]

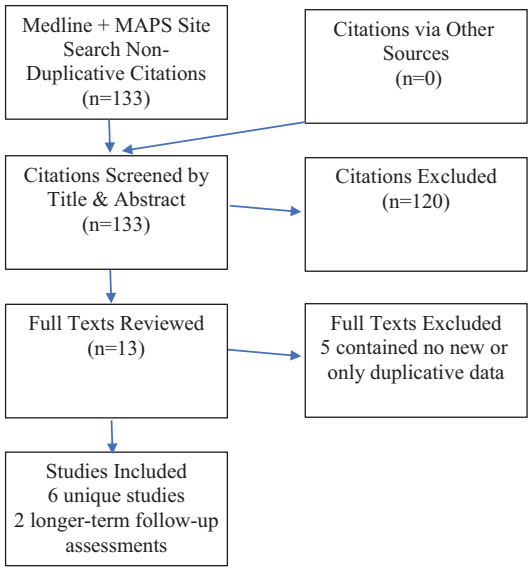
Paroxetine was assessed in three 12-week phase III clinical trials in patients with PTSD with doses between 20 and 50 mg/day.[14] In the first, second, and third clinical trials, the differences in CAPS-II scores were –14 units ($P < .001$), –11 units ($P < .001$), and –6 units ($P = .047$). No sex-based differences in efficacy was found in these paroxetine trials. Similarly, 36%, 39%, and 33% of participants withdrew from the 3 trials, respectively.[14]

Fluoxetine was assessed in 2 trials, 1 open prospective trial and 1 randomized double-blind placebo-controlled trial, in patients with severe PTSD (CAPS scores >45 units) with daily doses between 20 and 80 mg over 5 to 10 weeks and the change in CAPS score was the primary outcome.[15,16] Both trials reported a statistically significant decrease in CAPS scores. The open prospective trial (n = 19) reported a decrease of 21.8 units ($P < .001$) from baseline in CAPS-II scores after 10 weeks of fluoxetine titrated up to 80 mg daily.[15] Similarly, the double-blind placebo-controlled trial (n = 47) reported a 12.59-unit ($P = .0106$) decrease in total CAPS scores relative to placebo after 5 weeks, with a max daily fluoxetine dose of 60 mg.[16] Of note, 47% of participants in the open prospective trial and 27% in the double-blind trial withdrew during the study.[15,16] Additionally, it was reported that 37% of participants did not benefit at all from fluoxetine in the prospective trial (37% had a good response and 26% had a partial response).[16]

Venlafaxine extended release was assessed in 1 randomized double-blind, placebo-controlled trial (n = 329) with a 24-week flexible daily dose between 37.5 to 300 mg also in patients with severe PTSD (17-item Clinician-Administered PTSD Scale [CAPS-SX_{17}] score of at least 60).[17] At study end, venlafaxine extended release showed significantly greater reduction in the CAPS-SX_{17} score vs placebo, –51.7 units and –43.9 units, respectively ($P = .006$). A difference in CAPS-SX_{17} from baseline between groups was reported as –8.9 ($P = .006$). This study reported no significant difference in withdrawal rates between placebo and venlafaxine group, 33.3% vs 30.4%, respectively.[17]

MDMA-Assisted Psychotherapy Trial Selection and Analysis Methods

We (K.S., D.S., C.W.) searched PubMed from inception to September 20, 2021, using the search strategy:



Legend: MAPS – Multidisciplinary Association for Psychedelic Studies

Figure 1. Preferred Reporting Items for Systematic Review and Meta-analyses diagram for 3,4-methylenedioxymethamphetamine search.

([MDMA OR 3,4-methylenedioxymethamphetamine] AND [PTSD OR posttraumatic stress disorder]) and the website for the Multidisciplinary Association of Psychedelic Studies with backward citation tracking.[18] Citations were included if they represented unique studies of MDMA in patients with PTSD or if they provided information from the studies that were nonduplicative of the published constitutive studies. Figure 1 is a Preferred Reporting Items for Systematic Review and Meta-analyses diagram for the citations found to the final trials included. Data were dually extracted by 2 investigators (D.S., K.S.) with any discrepancies reconciled by a third investigator (C.W.).

We assessed the impact of MDMA vs control for the change in CAPS scores from baseline, the percentage of people in each group receiving a clinically significant CAPS score reduction, and the percentage of people no longer meeting the CAPS score criteria for PTSD at the follow-up period using meta-analysis. For 3-arm trials, where there were 2 active MDMA dosing groups and 1 control (placebo or low-dose MDMA); means, standard deviations, and numbers from the 2 active MDMA dose arms were combined (A.H.) into 1 arm using https://www.statstodo.com/CombineMeansSDs.php.

Random effects meta-analyses (A.H.) were used to compare MDMA to control therapy, with the inverse variance method. The restricted maximum likelihood method was used to calculate between-study variance tau,[2] and the Hartung-Knapp method of adjustment of 95%CIs was used. Effects of MDMA vs control (placebo or very low MDMA dose) on dichotomous outcomes were expressed as relative risk with its 95%CI, and on continuous outcomes as mean difference with its 95%CI. High heterogeneity of effects among studies was defined as $I^2>75\%$. All meta-analyses were performed using the meta package from R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed P value $<.05$ was considered statistically significant.

Results when patients were crossed over to alternate therapy, adverse events, and long-term follow-up data were described narratively without statistical pooling because the data were not deemed amenable for meta-analysis.

Demographic Overview of MDMA-Assisted Psychotherapy Trials

Table 1 provides methodological and demographic information for all included trials.[8,10,19–22] All trials were randomized and double-blinded. Three studies (Bouso et al, Mithoefer et al 2011, Mitchell et al)[10,19,20] used placebo control, although given the psychedelic effects associated with MDMA, the placebo was likely inadequate for maintaining double blinding. Most of the trials were very small ranging from 6 (Buoso et al) to 90 subjects (Mitchell et al) with the rest having 12 (Oehen et al)[8] or 20 to 27 subjects (Mithoefer et al 2011, Ot'alora et al, Mithoefer et al 2018).[10,19–22]

One trial (Bouso et al),[10] used the SSSPTSD scale for their primary end point, while the others used the more commonly used and better validated CAPS-IV (4 studies) or CAPS-V scales (1 study).[8,19–22] The trial by Bouso et al was pre–phase II, Mitchell was phase III, and the rest were phase II trials.[8,10,19–22]

All of the trials had specific safeguards to minimize the adverse effects of MDMA therapy.[8,10,19–22] None of the trials used illicit sources of MDMA, which could contain variable amounts of MDMA and may be contaminated or adulterated. Subjects taking MDMA or placebo were kept in a supportive environment for an extended period (6-8 hours) in each experimental session so the pharmacologic effects of MDMA were abolished before they left. Subjects were not allowed to exercise to prevent amplifying the amphetamine-like effects of the drugs. Subjects at high risk of cardiovascular events were excluded.[8,10,19–22]

MDMA-Assisted Psychotherapy Efficacy

The trial by Bouso et al[10] was not amenable to meta-analysis. Bouso et al used moderate 50- to 75-mg MDMA doses, did not allow a second subsequent MDMA dose to be administered, and used the SSSPTSD scale instead of the CAPS scale. While no statistical analyses were provided, the average scores on the SSSPTSD were reduced 27% for MDMA-assisted

Table 1. Method and Demographic Overview of MDMA-Assisted Psychotherapy Trials[8,10,12-15]

Study Name/Year/Sample Size	% Female	Predominant Trauma	Primary Measure	Original + Supplemental Dose Regimen	Experimental Sessions	Baseline CAPS Scores	End Point Assessment After Last MDMA Session
Placebo controlled trials							
Bouso (2008) n = 6 R, DB, PC	100%	Sexual Assault	SSSPTSD	MDMA 50–75 mg (n = 4) Placebo (n = 2)	One 6-hour psychotherapy session	MDMA Moderate: N/A Placebo: N/A	1 mo (n = 4) 3 mo (n = 2) 6 mo (n = 1)
Mithoefer (2011) n = 20 R, DB, PC	85%	Crime	CAPS-IV	MDMA 125 mg + 62.5 mg (n = 12) Placebo (n = 8)	Two 8-h psychotherapy sessions	MDMA High: 79.2 ± 23.6 Placebo: 79.6 ± 22.0	2 mo
Mitchell 2021 n = 90 R, DB, PC	66%	Developmental	CAPS-V	MDMA 80 mg + 40 mg (Session 1) 80 mg + 40 or 120 mg + 60 mg (Sessions 2 and 3) (n = 46) Placebo (n = 44)	Three 8-h psychotherapy sessions	MDMA Variable: 44.0 ± 6.0 Placebo: 44.2 ± 6.2	2 mo
Dose response trials							
Oehen (2013) n = 12 R, DB, AC	83%	Sexual assault	CAPS-IV	MDMA 125 mg + 62.5 mg (n = 8) MDMA 25 mg + 12.5 mg (n = 4)	Three 8-h psychotherapy sessions	MDMA High: 66.4 ± 13.6 MDMA Low: 63.4 ± 7.9	3 wks
Ot'alora (2018) n = 27 R, DB, AC	67%	N/A	CAPS-IV	MDMA 125 mg + 62.5 mg (n = 12) MDMA 100 mg + 50 mg (n = 9) MDMA 40 mg + 20 mg (n = 6)	Two 8-h psychotherapy sessions	MDMA High: 93.5 ± 20.2 MDMA Moderate: 94.4 ± 20.2 MDMA Low: 84.8 ± 8.0	1 mo
Mithoefer (2018) n = 26 R, DB, AC	27%	Occupational (war/first responders)	CAPS-IV	MDMA 125 mg + 62.5 mg (n = 12) MDMA 75 mg + 37.5 mg (n = 7) MDMA 30 mg + 15 mg (n = 7)	Two 8-h psychotherapy sessions	MDMA High: 89.7 ± 17.3 MDMA Moderate: 82.4 ± 17.3 MDMA Low: 87.0 ± 14.1	1 mo

CAPS, Clinician Administered PTSD Scale; DB, double blinded; MDMA, 3,4-methylenedioxymethamphetamine; N/A, not available; PC, placebo controlled; R, randomized; SSSPTSD, Severity of Symptoms Scale for Post-Traumatic Stress Disorder.

MDMA high ≥125 mg; MDMA moderate = 50-100 mg; MDMA low = 30-49 mg; MDMA variable = loading and supplemental doses change between sessions.

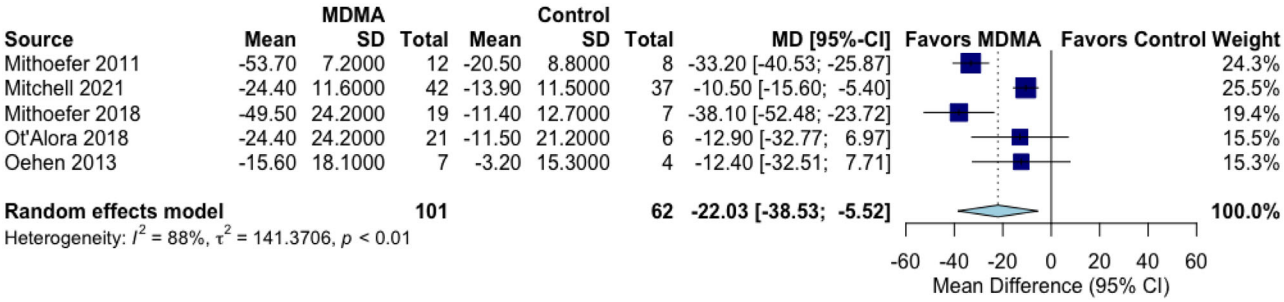


Figure 2. Pooled comparison of differences of CAPS scores from baseline for MDMA-assisted psychotherapy versus control. CAPS, Clinician-Administered PTSD Scale; MD, mean difference; MDMA, 3,4-methylenedioxymethamphetamine.

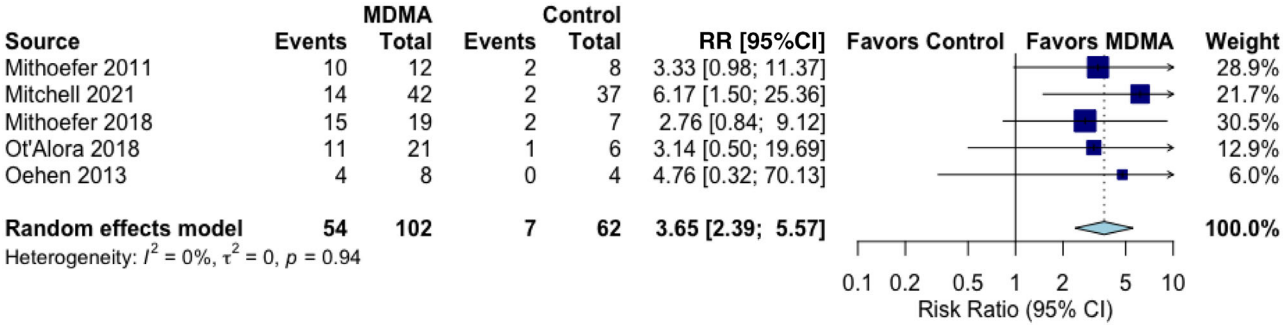


Figure 3. Pooled comparison of the percentage of patients experiencing a clinically significant reduction in baseline CAPS scores for MDMA-assisted psychotherapy vs control. CAPS, Clinician-Administered PTSD Scale; MDMA, 3,4-methylenedioxymethamphetamine; RR, relative risk.

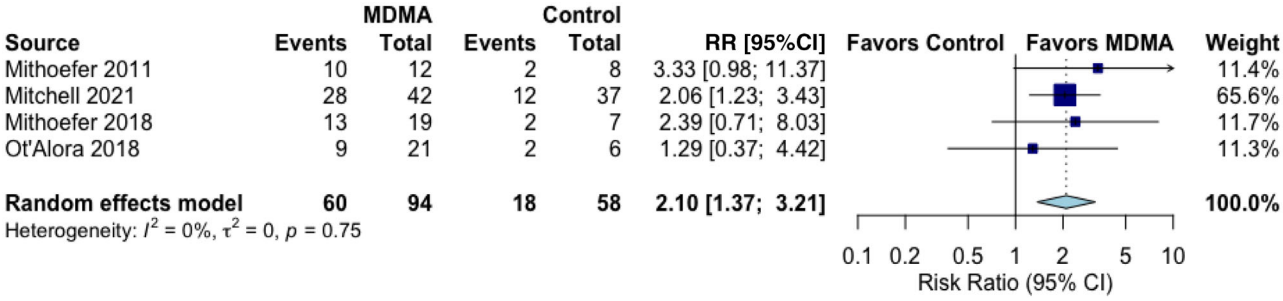


Figure 4. Pooled comparison of the percentage of patients no longer meeting CAPS score criteria for PTSD with MDMA-assisted psychotherapy versus control. CAPS, Clinician-Administered PTSD Scale; MDMA, 3,4-methylenedioxymethamphetamine; RR, relative risk.

psychotherapy sessions compared to a 10% reduction in the placebo group.[10]

Figure 2 provides the pooled change in CAPS score results for MDMA-assisted psychotherapy vs control therapy.[8,19–22] The reduction in CAPS scores from baseline were 22 points greater than that seen with control (mean difference, –22.03; 95%CI, –38.53 to –5.52). Even though the direction of effect was consistent across all trials, the magnitude of effect varied substantially with high resulting statistical heterogeneity.

Figure 3 shows that patients receiving MDMA-assisted psychotherapy were more likely to achieve clinically significant reductions in CAPS scores than control, while Figure 4 shows that more patients no longer met the CAPS criteria for PTSD at follow-up in the MDMA-assisted psychotherapy group vs control.[8,19–22] Statistical heterogeneity was not detected in either of these analyses.

There were several possible sources of heterogeneity. The average patient in Mitchell et al[20] had a baseline CAPS score of 44 units, just under the cutoff for severe disease, while in all other trials, the average patient had average CAPS scores of ≈65 (Oehen et al[8]), ≈79 (Mithoefer et al[19]), ≈87 (Mithoefer et al[22]), and ≈90 units (Ot'alora et al[21]). Among placebo controlled trials, Mitchell et al[20] had a less robust reduction in CAPS score than Mithoefer[19] with MDMA-assisted psychotherapy (Figure 2). Among active controlled trials, Oehen et al[8] has a less robust reduction in CAPS scores from baseline with high dose MDMA-assisted

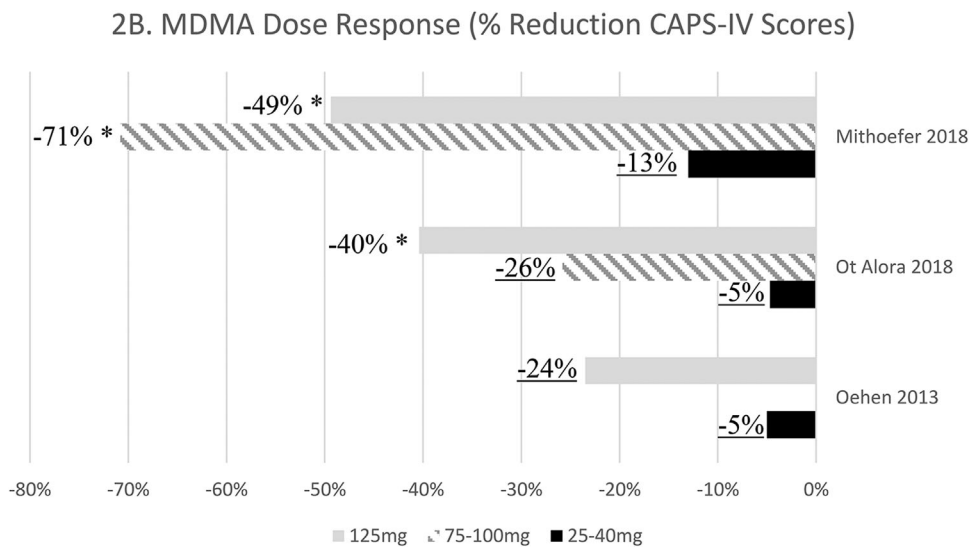


Figure 5. Impact of MDMA dose on CAPS response in active control trials. * $P < .05$ vs 25- to 40-mg doses of MDMA. CAPS, Clinician-Administered PTSD Scale; MDMA, 3,4-methylenedioxymethamphetamine.

psychotherapy than the Mithoefer et al[22] or Ot'alora et al[21] trials (Figure 5).

The time from the last experimental session to assessment of MDMA's impact on the primary endpoint is not as likely a cause of heterogeneity.[8,19–22] While Oehen et al[8] had 3 weeks of follow-up after the last experimental session and less robust effects than other active control trials (Ot'alora et al,[21] 1 month; and Mithoefer et al,[19] 2 months), Mitchell et al[20] had 2 months of follow-up and less robust results vs placebo than Mithoefer et al,[22] which had 1 month of follow-up.

The initial MDMA doses in placebo controlled trials varied from high 125 mg (Mithoefer et al[19]) to variable (80 mg in session 1 and then 80 or 120 mg in sessions 2 or 3) (Mitchell et al[20]) in placebo-controlled trials. The other studies (Oehen et al,[8] Ot'alora et al,[21] Mithoefer et al[22]) assessed 2 or 3 different groups who all received a different initial MDMA dose ranging from high (>125 mg) or medium (50-100 mg) doses compared to low dose (30-49 mg) control therapy. However, there were not major differences in CAPS score reductions in trials with moderate and high dose MDMA-assisted psychotherapy arms vs control (Figures 2 and 5).[8,19–22]

All the placebo or active controlled trials allowed a second subsequent MDMA or placebo dose to be given part way through each assisted psychotherapy session to maintain the MDMA effects.[8,19–22] Mithoefer et al[19] allowed a supplemental MDMA or placebo dose but only if both the therapist and subject agreed. Twenty-two of the 23 MDMA sessions where a supplemental dose was offered, it was accepted. However, it was never used in placebo sessions, raising questions about the adequacy of blinding for the therapist and patient.[19] High (Mithoefer et al,[19] Mitchell et al,[20] Oehen et al,[8] Ot'alora et al,[21] and Mithoefer et al[22]), moderate (Ot'alora et al,[21] Mithoefer et al[22]), and low (Oehen et al,[8] Ot'alora et al,[21] and Mithoefer et al[22]) dose MDMA regimens received different supplemental doses of 60 to 62.5, 37.5 to 50, or 12.5 to 20 mg, respectively. These differences do not seem to explain the statistical heterogeneity.

Mithoefer et al 2018 was conducted primarily in men while all the others were conducted primarily in women.[8,19–22] Sexual assault was the primary cause of PTSD in 2 trials (Bouso et al,[10] Oehen et al[8]), veteran/first responder occupational trauma in 1 trial (Mithoefer et al[22]), crime-related trauma in 1 trial (Mithoefer et al[19]), developmental trauma in one trial (Mitchell[20]), and the cause was not broken out in 1 trial (Ot'alora[21]). There were not enough data to assess these factors as possible causes of statistical heterogeneity.

Low-dose MDMA sessions in the active control trials did not reduce CAPS-IV scores more than the placebo sessions did in the placebo-controlled trials suggesting the benefits are negligible.[8,19–22] This was actually the intent of investigators, who were hoping to have the low-dose MDMA comparator provide some MDMA-like effects to help maintain double-blinding without providing much therapeutic benefit. As such, this is not a likely explanation for the statistical heterogeneity.[8,19–22]

The size of the newest clinical trial by Mitchell et al[20] allowed additional insight from subgroups within the PTSD population. Participants with the dissociative subtype of PTSD who received MDMA-assisted therapy had symptom reductions in CAPS-V scores versus placebo (30.8 ± 9.0 vs 12.8 ± 12.8 points), which was similar to those with nondissociative PTSD (23.6 ± 11.7

vs 14.3 ± 11.2 points). The beneficial impact MDMA therapy on CAPS-V scores was similar, even in people with a history of alcohol use disorder, substance use disorder, or severe childhood trauma.[20]

Efficacy of MDMA in Placebo or Low-Dose MDMA-Treated Patients

In several trials, after the primary end point was assessed, participants in the placebo or low-dose MDMA groups were offered the ability to receive open label high-dose MDMA-assisted psychotherapy. These results were not amenable to meta-analysis but are discussed narratively. In Oehen et al,[8] the 4 participants originally in the low-dose MDMA group responded to open-label high-dose MDMA treatment, with a 52% decrease in CAPS-IV score over the course of treatment, and 50% of them no longer meeting criteria for PTSD diagnosis. In Mithoefer et al 2011,[19] the open-label phase of the study included 7 of the 8 participants from the original placebo group. All subjects showed clinically meaningful reductions in CAPS-IV score after MDMA therapy was used, which averaged 48% lower than baseline. The eighth participant was satisfied with the progress made during the placebo-controlled therapy and chose not to join the open-label session.[19] In Ot'alora et al,[21] the participants who originally received low-dose MDMA were switched to open-label high-dose MDMA therapy and achieved a 47% reduction in CAPS scores from the end of the blinded portion of the study. In Mithoefer et al,[22] the participants who originally received low-dose MDMA were switched to open-label high-dose MDMA therapy and achieved a reduction in CAPS-IV score of 27 units, and 33% of 6 participants no longer met PTSD diagnostic criteria.

Durability of MDMA-Assisted Psychotherapy's Impact

Jerome et al[23] assessed the 4 aforementioned phase II studies, including 12-month posttreatment follow-up analyses from these trials, along with 2 unpublished phase II studies to perform a pooled analysis of efficacy and harm from MDMA-assisted psychotherapy. Participants (n = 107) received 2 to 3 active sessions where moderate- or high-dose MDMA (75-125 mg) was administered during the blinded or open-label portions of the trials, and 91 participants had long-term outcome data. The CAPS-IV scores were analyzed 1 to 2 months after the last active MDMA session, and at least 12 months after the final MDMA session. There was a significant reduction in CAPS-IV scores from baseline to 1 to 2 months after the last MDMA assisted session (−44.8 units; standard error, 2.8; $P < .0001$). CAPS-IV scores continued to decrease from the last session out to 12 months of follow-up (−5.2 units; standard error, 2.3; $P < .05$). Fifty-six percent of participants no longer met PTSD criteria 1 to 2 months after the last MDMA session, and this increased to 67.0% of subjects at the end of 12 months after treatment. While the data from 2 of the trials are not published and cannot be directly assessed, the pooled 1- to 2-month effects are aligned with those of the individual studies and shows that the benefits of MDMA-assisted psychotherapy are durable out to 12 months.[23]

Table 2. Common Adverse Events With MDMA or Placebo-Assisted Psychotherapy[13,16]

Adverse Event	Placebo or Low-Dose MDMA, %	Moderate or High-Dose MDMA, %
Aggregate of phase II trials		
Anxiety	48	72
Jaw clenching	19	64
Reduced appetite	23	49
Dizziness	19	40
Nausea	19	40
Depressed mood	3	8
Irritability	0	6
Panic attack	0	6
Mitchell et al 2021 (phase III)		
Muscle tightness	11	63
Reduced appetite	11	52
Nausea/Vomiting	11/0	30/9
Excessive sweating	2	20
Restlessness	0	15
Jaw clenching	2	13
Dizziness	5	13
Jittery	0	11
Pyrexia	2	7
Anxiety	0	7
Blurred vision	2	9

MDMA, 3,4-methylenedioxymethamphetamine.

Safety of MDMA-Assisted Psychotherapy

In a pooled analysis by Mithoefer et al,[6,] using the same constituent trials as in Jerome et al,[23] the safety of MDMA-assisted psychotherapy was assessed but not statistically analyzed. These events could have occurred from the time of enrollment through the 1- to 2-month follow-up period after the last MDMA or placebo session.[6] Table 2 provides the comparison of adverse events occurring in >3 individuals in an experimental group.[6,20] The adverse events were predominantly mild to moderate in severity. Among rare but serious adverse events, there was 1 patient receiving high-dose MDMA who experienced ventricular extrasystoles, and 1 person who received low-dose MDMA experienced suicidal ideation. Patient attrition was 7.6% in these trials which is comparably lower than the 17% to 36% rates in other PTSD treatment trials, suggesting that patients felt the benefits outweighed the risks.[6]

Mitchell et al[20] was a phase III clinical trial and not included in the pooled safety analysis by Mithoefer et al.[6] Like the Mithoefer et al[6] assessment, Mitchell

et al found increases in anxiety, dizziness, jaw clenching, lack of appetite, and nausea (Table 2). In their hemodynamic assessment, systolic (146 ± 19 vs 118 ± 16 mm Hg), diastolic blood pressure (87 ± 10 vs 76 ± 10 mm Hg), and pulse (92 vs 66 beats per minute) were elevated in the MDMA session vs the placebo session 3 with similar comparative changes after experimental sessions 1 and 2.[20] Since patients with hypertension, advanced age, or those at high risk of cardiovascular events can have muted baroreceptor buffering capacity, they could experience accentuated blood pressure increases and adverse cardiovascular events over what was seen in these clinical trials.[24] Overall, 37% of MDMA participants and 32% of placebo participants reported suicidal ideation at baseline.[20] The prevalence of suicidal ideation during the study never exceeded baseline and was not exacerbated in the MDMA group.[20] While some of these adverse events were likely directly related to MDMA use (jaw clenching), the others could have occurred in part due to discussing the traumatic PTSD-causing events.[3]

Jerome et al[23] reported on the results of a questionnaire sent to the participants in the constituent phase II trials 12 months after their last MDMA session. On a 5-point scale, with 1 being slight and 5 being large or severe, 86% of participants said their benefits were a 4 or 5, and no one said they received a benefit of 1. Conversely, no one reported experiencing a 5, 2% of participants reported a 4, 3% reported a 3, 2% reported a 2, and 5% reported a 1 for adverse events, so most people did not report adverse events from MDMA-assisted psychotherapy. Participants receiving MDMA-assisted psychotherapy reported the following benefits: 84% had improved feelings of well-being, 72% had less excess vigilance, 71% had fewer nightmares, 69% had less avoidance, 69% had less anxiety, and 66% had improved sleep. Only 1.2% of participants reported feeling worse or having worse sleep, while 2.4% of participants reported increased nightmares, avoidance, excessive vigilance, and anxiety.[23] The short-term adverse events from MDMA therapy need to be weighed against these long-term benefits after the few MDMA-assisted psychotherapy sessions have ended.

MDMA's Place in Therapy and Future Directions

The Veterans Administration Department of Defense guidelines for systematic review specifies that trauma-focused psychotherapy is preferable to pharmacotherapy if it is available and the patient is able to access this care and is amenable to this treatment modality.[13] Pharmacotherapy, preferably with selective serotonin reuptake inhibitors (SSRIs) or venlafaxine, is an option for those without access to trauma-focused psychotherapy or those unwilling to engage in it.[13]

MDMA is being used in patients with PTSD who were not sufficiently responsive to unenhanced trauma-focused psychotherapy and would likely be tried before patients would be offered SSRI or venlafaxine therapy.[13] An advantage of trying MDMA-enhanced psychotherapy before moving to other pharmacotherapeutic options is that the MDMA benefits are long lasting, but MDMA exposure is only intermittent and is ingested in the presence of health professionals.[8,10,19–23] The need for chronic use of SSRIs or venlafaxine may be a contributing factor in the high patient withdrawal rate from the available studies.[15–17] There is no evidence that the use of MDMA in the absence of trauma-focused psychotherapy would provide benefits and would not be a monotherapeutic option like the SSRIs or venlafaxine.

While the trials assessing MDMA-assisted psychotherapy yielded consistent directions of effect that were superior to that of psychotherapy alone, the sample sizes of these trials were small and statistical heterogeneity was high for the comparison of the difference in CAPS scores between groups. However, there were other limitations as well.[8,10,19–22] One of the limitations with the trials assessing MDMA-assisted psychotherapy is that the psychotherapy provided in both groups was structured to fit what would likely work best for those receiving MDMA. Future studies comparing MDMA-assisted psychotherapy vs proven trauma-focused psychotherapy regimens would have much better applicability to the clinical situation even though it would eliminate the ability to blind the patients and investigators. As it is, there is evidence that the psychotherapists and patients in the current trials were able to determine who was receiving MDMA, taking away some of the internal validity benefits of blinding.[19] Another limitation is that when world experts in an area pioneer a treatment modality, the benefits and the risks in those studies may not reflect what is seen when the therapy is widely available and being conducted by frontline practitioners. Future studies in which MDMA-assisted psychotherapy is assessed vs other modalities by frontline practitioners will be important. A final limitation is that the patients in the available trials had more severe PTSD as evidenced by their high baseline CAPS scores.[8,10,19–22] Future studies assessing MDMA in patients with less severe PTSD is needed.

Conclusion

Current pharmacologic therapies for PTSD must be taken daily and have modest efficacy. MDMA-assisted psychotherapy is a novel experimental therapy that is only given in 2 or 3 sessions. The reductions in CAPS-IV or CAPS-V scores are pronounced, the benefits

may be seen within a few weeks of the last session, and the impact may last for a year after the sessions are completed. Long-term improvements in sleep, nightmares, and general well-being were commonly reported. When MDMA was cautiously used in these clinical trials, they were generally well tolerated, but anxiety, nausea, vomiting, and jaw clenching are commonly reported. The literature base is hampered by small sample sizes within the clinical trials and a lack of direct comparison to other drugs in treatment of PTSD. Blood pressure is transiently increased during MDMA sessions, so the risk-benefit balance is not as clear for those with underlying hypertension or cardiovascular disease. Additionally, illicit MDMA sources have not been studied and may have additional risks due to adulteration and contamination and these sessions used many safeguards to reduce risks from both MDMA and reliving the traumatic event that must be in place before this therapy is tried in a patient.

Conflicts of Interest

The authors declare that they have no conflicts of interest to disclose.

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