Evaluating the Efficacy and Safety of MDMA for the Treatment of Posttraumatic Stress Disorder: A Systematic Review

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Abstract

BACKGROUND: Posttraumatic stress disorder (PTSD) affects approximately 5-7% of the population, with conventional treatments often proving inadequate for some patients. Recent studies suggest that methylenedioxymethamphetamine (MDMA) combined with psychotherapy may offer a novel therapeutic approach. This systematic review evaluates the efficacy and safety of MDMA-assisted psychotherapy for the treatment of PTSD in individuals with chronic, treatment-resistant forms of the disorder.

METHODS: A comprehensive search was conducted in PubMed, OVID, Scopus, Cochrane databases, and select reference lists for randomized controlled trials (RCTs) evaluating MDMA as a treatment for PTSD. Eligibility criteria included RCTs with participants with confirmed PTSD diagnoses using standardized clinical assessments.

RESULTS: In the RCT studies, there are significant reductions in PTSD symptoms ($p<0.05$) in those with MDMA-assisted psychotherapy compared to those with placebo and psychotherapy; dose-dependent improvements were observed in various measurements scales (specifically in CAPS-IV/CAPS-5 scores). Open-label trials further demonstrated improvements in PTSD symptoms when given MDMA-assisted therapy ($p<0.05$) and long-term analyses of studies demonstrated that effects of MDMA-assisted therapy were maintained for a minimum of 12 months post-intervention($p<0.05$). Adverse effects were transient and mild to moderate, including anxiety, headache, fatigue, muscle tension, and insomnia.

CONCLUSION: Extant data suggests that MDMA-assisted psychotherapy for PTSD demonstrates significant symptom reduction, with sustained efficacy up to 12 months post-treatment. Functional unblinding is a major methodological challenge, which makes it difficult to interpret the magnitude of the effect MDMA has in the treatment of treatment-resistant PTSD. Future research should refine methodologies and explore long-term safety and efficacy in diverse populations.

Introduction

Posttraumatic stress disorder (PTSD) is a mental disorder that occurs in approximately 5-7% of the population, with higher rates in women than in men (1). Individuals can develop PTSD post-experiencing/witnessing a traumatic event, and their symptoms include, but are not limited to, hypervigilance, increased startle response, avoidance of traumatic triggers, anxiety, depression, and sleep disturbances (2). Conventional treatment for PTSD consists of psychotherapy (e.g., trauma-focused psychotherapy) and/or pharmacotherapy, which consists of therapy and medications (1,2). Currently, selective serotonin reuptake inhibitors (SSRIs), specifically paroxetine and sertraline, are FDA-approved treatments for PTSD; other medications such as venlafaxine, a serotonin-norepinephrine reuptake inhibitors, are used to treat PTSD off-label (2). However, extant literature indicates that monoamine-based pharmacotherapy is suboptimal in facilitating fear extinction emotional processing (3). Exposure-based psychotherapy is efficacious in improving PTSD symptoms broadly; however, patient adherence is low and is not generally accessible and/or available (3).

Methylenedioxymethamphetamine(MDMA) modulates serotonin, dopamine, and norepinephrine signaling (4). MDMA primarily acts by increasing the synaptic release and blocking the reuptake of serotonin, which is associated with feelings of euphoria, increased sociability, and decreased anxiety (5). In addition to the effects on serotonin, MDMA also increases levels of dopamine and norepinephrine in the brain (4). These neurotransmitters are involved in regulating mood, motivation, and attention, and MDMA-induced synaptic release of dopamine and norepinephrine can contribute to the drug's effects of elevated mood, decreased fear, altered perception of surroundings, and impaired memory (4). The foregoing points

provide the impetus to investigate the efficacy of MDMA-assisted psychotherapy as an alternative and novel treatment for PTSD. Herein, we aim to conduct a systematic review to comprehensively evaluate published clinical trials investigating MDMA for the treatment of PTSD. Notably, we delimited our search to studies that investigated MDMA-assisted psychotherapy as previous studies have reported additional therapeutic benefits of psychotherapy when integrated with MDMA compared to standalone MDMA treatment (6).

Materials and Methods

ELIGIBILITY CRITERIA

Any clinical trial that evaluates MDMA-assisted psychotherapy as an adjuvant or standalone treatment for PTSD. Only English-language articles were included. Studies must have included participants with a confirmed diagnosis of PTSD based on standard clinical assessments or structural interviews (i.e. Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) and Sheehan Disability Scale (SDS)) were included. Studies were excluded if they 1) described unpublished data sets, case reports, crossover studies, and observational studies, 2) did not have a clinical assessment of PTSD, 3) did not have MDMA as the treatment intervention, and 4) were animal studies. Papers were further divided based on whether they were randomized controlled trials (RCTs), open-label trials, and follow-up studies. Qualitative analyses were conducted on RCTs, open-label trials, and follow-up studies.

SEARCH STRATEGY

MK, HC, and CC conducted a search on PubMed, OVID, Scopus, and Cochrane databases for English-language articles published between database inception to June 15 2024, using the following search string: ((“MDMA” OR “Methylenedioxymethamphetamine” OR “Ecstasy” OR “Molly”) AND (“PTSD” OR “Post-traumatic stress disorder” OR “Combat disorder” OR “Post-traumatic stress syndrome” OR “Trauma stress disorder”)). Subsequent searches through previous systematic reviews were conducted manually. Zotero was used to conduct screening and remove duplicate papers. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and checklist was used to assess the reliability of included studies and the reporting of study methods and results. The titles, abstracts, and full text of the studies were screened by 3 reviewers (MK, HC, and CC) independently based on the eligibility criteria. The consensus for papers to include was based on follow-up discussions.

DATA EXTRACTION AND MANAGEMENT

The data to be extracted from studies was predetermined and included sample size, ethnicity, gender, mean age, clinical presentation, type of MDMA and psychotherapy intervention, PTSD assessment, endpoints (primary and secondary), study design, Quality Rating Scheme for Studies and Other Evidence, and main study findings. Missing data was noted in the tables. Data extraction was performed independently by MK and AA, and later reviewed and confirmed by HC and CC.

ASSESSMENT OF BIASES

Study quality assessments (i.e. risk of bias) were performed by HF and MK. Study quality was assessed using the revised Cochrane risk-of-bias tool for randomized trials (RoB2 tool). All the RCTs involved in the quantitative assessment would be assessed according to the six domains that evaluated the risk of bias, including randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported result and other biases.

Results

SEARCH RESULTS

A total of 3363 studies were identified from the search on PubMed, OVID, Scopus, and Cochrane databases and previous systematic reviews. There were 2704 studies remaining after 659 duplicates were removed, of which 2677 were excluded following title and abstract screening. 27 studies were assessed in the full-text evaluation stage, of which 1 was removed for being a symposium abstract and 3 were removed for reporting on data from original studies already being assessed. A total of 23 studies were included in this review - 8 studies were found to be follow-up/long-term follow-up studies, 5 studies were open-label studies, and 10 studies were original RCTs. See supplementary materials for the PRISMA flow diagram.

RISK OF BIAS IN STUDIES

The Cochrane risk of bias assessment is displayed in Table 4. All included studies had minimal biases except for Bouso et al. (2008) which included more significant biases in the domains: randomization process, measurement of the outcome, and selection of the reported result. This study was halted due to political pressures, the original objective of the paper was altered and the reported data was only recorded from 6 individuals with variable follow-up times (7).

STUDY CHARACTERISTICS AND EFFICACY OF MDMA IN RCTS

The total sample of all the included RCTs included in the quantitative analysis (k=10) consisted of 530 participants. 335 participants received an active dose of MDMA (between 75-125 mg +/- optional half-dose) and psychotherapy, and 215 participants received a placebo/control dose (between 0-40 mg) of MDMA and psychotherapy.

A summary of all the major factors of each RCT is displayed in Table 1. Some studies included pooled data from multiple studies (8,9) or were conducted over multiple sites (8,10,11). One study was halted prior to full completion (7). Mean sample ages ranged between 35-45 years. All participants presented with chronic, treatment-resistant PTSD with CAPS-IV/CAPS-5 scores greater than 50. Evaluation of PTSD was conducted with CAPS-IV/CAPS-5 for the majority of studies, except for one study (7). The study designs also differed, some were randomized, double-blind, dose-response trials (6,12), others were randomized, double-blind, controlled trials (7–11,13–15), and one paper was a prospective, double-blind, crossover-design study (14). Some studies further included a placebo run-in component where the participants were unblinded to treatment allocation following the collection of outcome variables and prior to open-label trials (6,8,9,12–15). All studies, except one (7), consisted of a primary endpoint of change in CAPS-IV/CAPS-5 score from baseline (prior to MDMA administration) to at least a month after the 2nd/3rd treatment session. The secondary endpoint of the studies included changes in other domains of psychopathology (eg. depression, sleep, alcohol consumption, etc.).

Across the included RCTs, reductions in PTSD-related symptom severity scores were dose-dependent. The foregoing studies reported significant improvements in PTSD symptoms across various measurement scales, primarily focusing on CAPS-IV scores. In Mithoefer et al. (2018), the mean change in CAPS-IV total scores was –11.4 (standard deviation (SD) 12.7) for the 30 mg group, –58.3 (SD 9.8) for the 75 mg group, and –44.3 (SD 28.7) for the 125 mg group, with the 75 mg and 125 mg MDMA groups showing significantly greater improvements than the 30 mg group (6). Mithoefer et al. (2019) reported that the active group (75–125 mg) had a mean decrease of –30.4 (standard error (SE) 3.20) in CAPS-IV scores compared to the control group's drop of –10.5 (SE 4.46) ($P < 0.0001$) (8).

Mithoefer et al. (2019) reported a greater improvement in BDI-II scores in the active group, with a mean change of –12.4 (SE 1.84) versus –6.5 (SE 2.69) in the control group ($P = 0.053$) (8). Ponte et al. (2021) highlighted significant treatment effects in CAPS-IV scores (active group mean change –34.0, SD 26.46; control group mean change –12.4, SD 16.38, $p = .003$) and Pittsburgh Sleep Quality Index (PSQI) scores (mean change –3.53, SD 5.03, active group vs. 0.56, SD 3.05, control group, $p = .003$) (9). Mithoefer et al. (2011) found that the active group had a mean CAPS-IV change of -53.7 points compared to -20.5 points in the placebo group, with a higher response rate in the active group (14). In Ot'alora et al. (2018), it was observed that active dose groups had mean CAPS-IV reductions of –26.3 (SD 29.5) for 125 mg, –24.4 (SD 24.2) for 100 mg, and –11.5 (SD 21.2) for 40 mg (12). Oehen et al. (2013) demonstrated that the full-dose group, given 125mg of MDMA, had significantly greater reductions in CAPS-IV scores by -15.6 (18.1) compared to the active placebo group which only reduced by -3.2 (15.3); this study unlike others did not find a significant reduction in CAPS-IV score in the placebo group (15). The group that received full-dose MDMA also had reductions in CAPS scores (35% reduction) at the 12-month follow-up assessments compared to baseline. Changes in Posttraumatic Diagnostic Scale (PDS) scores were -8.6 (13.0) in the full MDMA dose group and +7.3 (6.2) in the active placebo group, an increases in the PDS score in the placebo group was not expected (15).

Mitchell et al. (2021) reported a mean change in CAPS-5 scores of -24.4 (SD 11.6) for the MDMA group and -13.9 (SD 11.5) for the placebo group, indicating the superior efficacy of MDMA-assisted therapy (10). Mitchell et al. (2023) revealed a mean CAPS-5 score change of -23.7 for the MDMA group compared to -14.7 for the placebo group (effect size 0.91, $p < 0.001$) (13). Bouso et al. (2008) suggested a dose-response relationship in PTSD symptom reduction, with low doses of MDMA showing promising efficacy compared to placebo, despite the study's small sample size of 6 individuals (7). Finally, Nicholas et al. (2022) reported that the MDMA treatment group demonstrated a greater improvement in Alcohol Use Disorders Identification Test (AUDIT) scores from baseline to study termination, although changes were not statistically significant (11).

STUDY CHARACTERISTICS AND EFFICACY OF MDMA IN OPEN-LABEL TRIALS

The specific information for each study is displayed in Table 2. Ching et al. (2022) reported mean adjusted changes in CAPS-IV scores in the MDMA group of –25.65 (SD 14.54) for Black, Indigenous, and people of color (BIPOC) participants and –25.95 (SD 13.16) for non-Hispanic White participants (16). In the Placebo group, the mean changes were –16.77 (SD 10.08) for BIPOC participants and –9.59 (SD 11.96) for non-Hispanic White/Caucasian participants (16). There was a greater mean improvement between treatment and placebo groups among Caucasian participants compared to BIPOC participants (16). This suggests that ethnicity may modulate MDMA treatment efficacy in persons with PTSD. Consistent with the foregoing trends, Jardim et al. (2021) observed that MDMA-assisted psychotherapy significantly reduced CAPS-IV scores, with all reductions greater than 30%, indicating clinically significant improvement (17). The baseline scores of 90, 78, and 72 dropped to 61, 27, and 8 at the primary endpoint, with reductions of 29, 51, and 64 points, respectively (Jardim et al., 2021). Wang et al. (2021) demonstrated a significant mean change in CAPS-5 scores of –29.89 (SD 13.45) at the primary endpoint, indicating an improvement in PTSD symptoms ($p < .0001$) (18). At the primary endpoint (Visit 19), 91.89% of participants had a clinically meaningful reduction (10 points or greater) in their CAPS-5 scores, and 75.68% no longer met PTSD criteria ($p < .001$) (18). Lewis et al. (2023) reported that in a sub-study sample, the MDMA group had a baseline CAPS-5 score of 44.2 (SD 6.16) and a final score of 17.94 (SD 14.28), with a mean

difference of 26.26 (SD 15.55) (19). The placebo group had a baseline score of 46.6 (SD 7.03) and a final score of 30.77 (SD 11.02), with a mean difference of 15.83 (SD 13.07) (19).

In addition, MDMA-assisted psychotherapy was evaluated for its effects on secondary outcomes. Specifically, MDMA treatment was significantly associated with both lower Beck Depression Inventory (BDI-II) scores and higher Post-Traumatic Growth Inventory and Global Assessment of Functioning scores (17). Christie et al. (2022) focused on chronic pain rather than PTSD (20). Significant reductions in Chronic Pain Grade Scale (CPGS) subscales for pain intensity and disability scores among participants in the highest pain cluster, and for pain intensity in the medium pain cluster post-treatment were reported, however, the small sample size limited the power of the analysis (20).

STUDY CHARACTERISTICS AND EFFICACY OF MDMA IN FOLLOW-UP STUDIES

The specific information for each study is displayed in Table 3. Jerome et al. (2020) reported a mean change in CAPS-IV total scores from baseline to the primary endpoint of -44.8 (SE 2.82) (21). Scores continued to decrease from the primary endpoint to the long-term follow-up of 12 months by -5.2 (SE 2.29) (21). The percentage of participants who no longer met PTSD criteria increased from 56.0% at treatment exit to 67.0% at long-term follow-up (LTFU) (21). Comparatively, Mithoefer et al. (2013) found no statistically significant change in mean CAPS-IV and IES-R scores at LTFU for the 16 study completers compared to their 2-month (short-term) mean scores (22). Barone et al. (2019) reported that all participants experienced lasting personal benefits and enhanced quality of life beyond quantifiable symptom reduction (23). Fifteen participants (79%) had prolonged therapeutic efficacy from MDMA therapy, but there were no changes in PTSD symptom severity at the one-year follow-up compared to the end of the study (23).

A secondary analysis of the study conducted by Wang et al. (2021), done by Godes et al. (2023), indicated that all seven participants reported a range of benefits during and at the end of treatment, including tolerance of conflict, processing trauma, positive emotions, interpersonal connections, and connection (24). The change in CAPS-5 from baseline to termination, after approximately 1 month after the last treatment session, for these seven participants was -34 (SD 8) (24). Van Der Kolk et al. (2024) considered data from the original study done by Mitchell et al. (2023) (25). They found significant improvements in alexithymia, self-compassion, and most IASC factors compared to the placebo group. Higher baseline alexithymia was associated with greater reductions in PTSD symptoms, with a notable decrease in CAPS-5 scores (-16.16; 95% CI: -28.80, -7.52) (25).

Zeifman et al. (2024) reported that therapeutic alliance, the relationship between a healthcare professional and a patient, significantly increased the explained variance in post-treatment PTSD severity, with session 4 adding 29% and session 9 adding 24% (26). Self-reported PTSD severity showed that therapeutic alliance at session 4 explained an additional 40% of the variance, and at session 9 it explained an additional 26% of the variance (26). Corey et al. (2016) did a further analysis of the study conducted by Mithoefer et al. (2011) and investigated the correlation between utterances, which were when patients initiated topics that were empathic, entactic, or ensuic, during psychotherapy sessions and change in their CAPS-IV score (27). Corey et al. (2016) observed that the MDMA treatment group produced significantly more utterances than the placebo group, and a higher number of scored utterances correlated with a lower post-treatment CAPS-IV score ($r = -0.506$, $p = 0.023$, $n = 20$) (27). The correlation remained significant when utterances were grouped into "many" (nine or more) and "few" (six or fewer) categories ($r = -0.596$, $p = 0.006$, $n = 20$) (27). The sub-group utterances correlated with an overall change in CAPS-IV scores ($r = 0.513$, $p = 0.021$, $n = 20$) (27). Wagner et al. (2017) observed a significant interaction between changes in Openness and CAPS-IV scores, with those showing the greatest increase in Openness also demonstrating the greatest decreases in PTSD symptom severity (28).

ADVERSE EFFECTS DUE TO MDMA THERAPY

The main adverse effects that were noted to have occurred or been contributed to by MDMA therapy compared to placebo in the RCTs are displayed in Table 5. The adverse effects did not significantly vary based on the dose of active MDMA individuals received (6). Most adverse events were transient with rates decreasing 7-10 days after treatment cessation (6,8,14). MDMA therapy did not increase in suicidal behavior, participants with pre-existing suicidal thoughts would report thoughts of suicide after sessions but this was not increased from baseline (10,12,13).

Discussion

Our synthesis of extant literature of MDMA-assisted psychotherapy in the treatment of PTSD demonstrates a significant reduction in PTSD psychopathology as measured by CAPS-5 score up to 1-month post-treatment as well as sustained efficacy with maintenance treatment for 12-months. All of the included RCTs were double-blinded until the end of the second/third treatment session, and all the RCTs (even if a placebo run-in trial component was incorporated) reported similar levels of efficacy of MDMA for treatment-resistant PTSD, through various measurement modalities. The RCTs demonstrated that MDMA-assisted therapy reduced PTSD symptoms more than placebo with psychotherapy ($p<0.05$) and did so in a dose-dependent manner. Open-label trials further demonstrated the benefits of MDMA-assisted therapy in

reducing PTSD symptoms. Moreover, Follow-up/Long-term trials observed that the beneficial effects of MDMA-assisted therapy on symptoms of PTSD are maintained for a minimum of 12 months post-treatment ($p<0.05$).

Our results reported herein align with previous reviews and research into this field (29). The implications of this review indicate that MDMA may be a useful therapy for treatment-resistant PTSD only after first and second-line treatments have been exhausted.

Notwithstanding the observed benefit, there are several methodological limitations that affect the interpretation of our findings. An overarching limitation is functional unblinding in the clinical trials investigating MDMA. Functional unblinding refers to the lack of concealment of group assignment as a consequence of the subjective effects of the intervention (6,8,10,12–15). In addition to participants knowing they were assigned to MDMA in most cases, they also reported a high level of confidence that they were taking this treatment. As MDMA has been combined with psychotherapy, it is not possible to discern the relative therapeutic contribution of MDMA. The aforementioned methodologic concerns have also been identified by an FDA Advisory Panel who were evaluating the efficacy of MDMA for PTSD (30).

Further limitations include the differences in the studies when it comes to the different dosages of MDMA used (the doses for the control groups ranged between 0-40 mg and in the treatment groups 70-180 mg), the number of therapy sessions (2 or 3 sessions) and the study design utilized (some studies included a placebo run-in trial). Other limitations mentioned from the RCT trials include: small sample sizes, study populations mainly consisting of Caucasians, study populations consisting predominantly of one gender, studies including a cross-over component at the end without a control group which prevented long-term results from being assessed, participants being on other psychotropic medications during trials, including subjective measures (questionnaire) for symptom measurement, evaluation of symptoms after a short assessment period and lack of long-term follow-up (although some studies are currently undergoing long-term follow-up), disclusion of those with imminent suicide risk, and placebo group drop-outs.

The implications of our analysis suggest that MDMA may have therapeutic benefits in the treatment of PTSD when combined with psychotherapy. There is, however inadequate, long-term data as well as suboptimal evaluation of the safety of this agent. The methodological aspects discussed above also hinder the ability to accurately evaluate the relative contribution of MDMA.

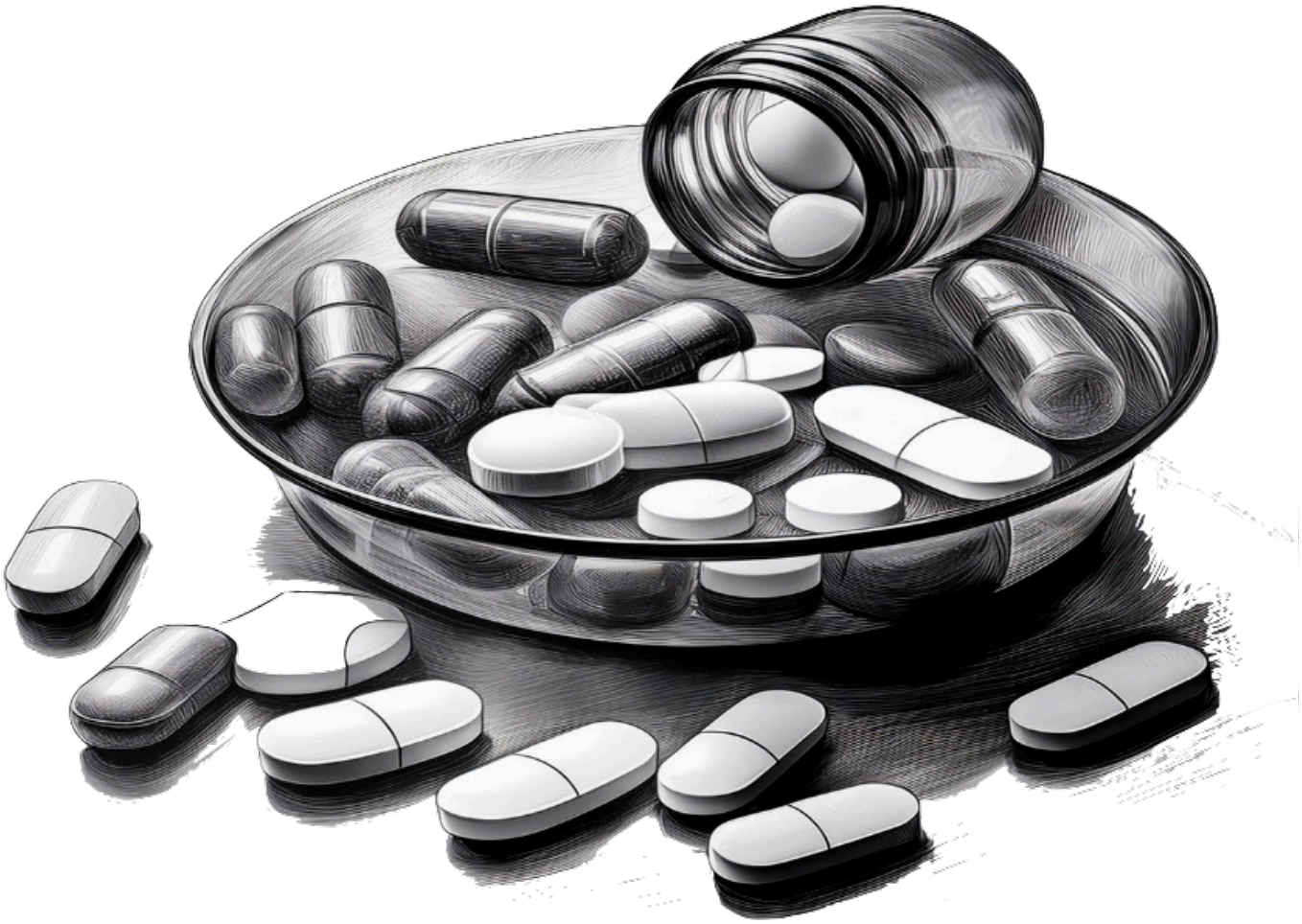

Table 1: RCTs

Source	Sample Size	Ethnicity	Gender	Mean Age (SD)	Clinical Presentation	Intervention	PTSD Assessment	Endpoints - Primary (P), Secondary (S)	Study Design	Quality Rating	Findings
Mithoefer et al. 2018.	26	85% Caucasian; 8% Hispanic/Latino; 4% Native American; 4% Mixed	73% M, 26% F	37.2 (10.3)	Chronic, treatment-resistant PTSD resulting from traumatic experiences during their service as military veterans, firefighters, or police officers	2× 8h MDMA-assisted psychotherapy sessions (30, 75, 125 mg) + optional half-dose; 2–3 weekly integration sessions; open-label phase followed	CAPS-IV	P: CAPS-5 change at 1 mo post-2nd session. S: BDI-II, PSQI, PTGI, NEO-PI-R, DES-II, GAF	RCT, double-blind, dose-response + open-label	1	Mean CAPS-IV change: –11.4 (30 mg), –58.3 (75 mg, p=0.0005), –44.3 (125 mg, p=0.004). 75 & 125 mg > 30 mg; no diff. 75 vs 125. Secondary outcomes also improved. Placebo group improved after open-label high-dose.
Mithoefer et al. 2019	105	87.6% White; 2.9% Hispanic; 1.9% Native Am.; 1.9% Middle Eastern; 5.7% Other	42% M, 58% F	40.5 (10.6)	Chronic, treatment-resistant PTSD related to various causes (e.g., combat, abuse, assault, accidents)	2× 8h MDMA-assisted sessions (0–40 mg vs 75–125 mg) + optional half-dose; 2–3 integration sessions; open-label crossover	CAPS-IV	P: CAPS-5 change after 2nd session. S: BDI-II change; CAPS-5 at 2 mo post-blind	6 RCTs, double-blind + open-label	1	Active (75–125 mg) group improved more than control (Δ –30.4 vs –10.5; p<0.0001). BDI-II change trended toward significance. Further gains in open-label active dose.
Nicholas et al. 2022	82	80% White; 6% Asian; 4% Native Am.; 2% Black; 7% Mixed	35% M, 65% F	41.42 (12.22)	Severe PTSD + alcohol/substance use disorder	3× 8h MDMA (80→120 mg + optional half-dose) or placebo; 3× 90-min integration sessions	CAPS-5	P: AUDIT, DUDIT change. S: CAPS-5, SDS, BDI-II, C-SSRS	RCT, double-blind	1	MDMA group had greater AUDIT improvement vs placebo (p=0.0436, g=0.45). No sig. DUDIT difference. MDMA also reduced PTSD severity, functional impairment, and depression.
Ponte et al. 2021	63	85% Caucasian; 4% Hispanic; 2% Native Am.; 9% Other	54% M, 46% F	40.80 (11.49)	Chronic, treatment resistant PTSD	3× 8h MDMA (75–125 mg) or placebo (0–40 mg) + half-dose option; integration; open-label	CAPS-IV	P: PSQI & CAPS-5 at 1–2 mo. S: 12-mo follow-up	RCT, double-blind + open-label	1	Significant treatment effect of change in CAPS scores (–34.0 vs –12.4; p=0.003) and PSQI (–3.53 vs +0.56; p=0.003). More pts in the active group improved ≥3 PSQI points than in the control group (53% vs 13%). Open-label active doses gave further benefit
Mitchell JM, Bogenschutz M, et al. 2021	90	77% White; 9% Mixed; 8% Asian; 3% Native Am.; 2% African	34% M, 66% F	41.0 (11.9)	Severe PTSD incl. commorbidities such as dissociation, depression, substance use, childhood trauma	3× 8h MDMA (80→120 mg + half-dose) or placebo; 3 integration sessions	CAPS-5	P: CAPS-5 at 8 wks post-3rd session. S: SDS at 18 wks	RCT, double-blind	1	CAPS-5 reduction greater with MDMA (–24.4 vs –13.9). SDS also improved (–3.1 vs –2.0). Equally effective in comorbid subtypes.
Mithoefer et al. 2011	20		15% M, 85% F	40.4 (7.2)	Chronic, treatment-resistant PTSD.	2× 8h MDMA (125 mg + half-dose) or placebo; integration; open-label	CAPS-IV	P: CAPS-5 at 2 mo post-2nd session. S: IES-R, SCL-90-R	RCT, double-blind + open-label	1	Active MDMA reduced CAPS more than placebo (–53.7 vs –20.5; p=0.015) and had a higher response rate (83% vs 25%). Open-label higher doses gave further benefit.
Mitchell JM, Ot'alora GM, et al. 2023	104	66% White; 11% Asian; 8% Black; 2% Native Am.; 1% Hawaiian; 12% Other	33% M, 67% F	39.1 (10.3)	Moderate–severe PTSD (mean CAPS 52.5)	3× 8h MDMA (80→120 mg + half-dose) or placebo; integration (CBT, psychodynamic, mindfulness)	CAPS-5	P: CAPS-5 change at 18 wks. S: SDS change at 18 wks	RCT, double-blind + open-label	1	CAPS-5 improvement greater with MDMA (–23.7 vs –14.7; ES=0.91, p<0.001). 67% vs 32% no longer met PTSD criteria (p=0.02). Also improved depression/anxiety.
Ot'alora et al. 2018	28	93% White; 4% Hispanic; 4% Native Am.	32% M, 68% F	42.0 (12.9)	Chronic, treatment resistant PTSD	2× 8h MDMA (40, 100, 125 mg) + half-dose option; placebo; integration; open-label	CAPS-IV	P: CAPS-5 at 1 mo. S: BDI-II, DES-II, PSQI at 1 mo	RCT, double-blind, dose-response + open-label	1	CAPS reduction larger in active dose groups (–26.3 at 125 mg; –24.4 at 100 mg; –11.5 at 40 mg). Placebo improved in open-label; 12-mo follow-up confirmed 125 mg benefit. 40 mg ≈ placebo. Well tolerated.
Oehen et al. 2013	12	Not reported	17% M, 83% F	41.4 (11.2)	Chronic, treatment-resistant PTSD (CAPS ≥50)	3× 8h MDMA (125 mg) or active placebo (25 mg) + half-dose; integration; open-label	CAPS-IV	P: CAPS at 3 wks post-2nd & 3rd sessions. S: PDS at same timepoints	RCT, double-blind + open-label	1	CAPS reduction greater with MDMA (–15.6 vs –3.2). 12-mo follow-up: 35% CAPS reduction in full-dose MDMA group. PDS improved with MDMA (–8.6 vs +7.3). 50% full-dose pts had clinical response.
Bouso et al. 2008	6	Not reported (All participants from Madrid)	100% F	35.6 (7.3)	Chronic, treatment resistent PTSD	6× 6h MDMA (50–75 mg) or placebo; pre/post non-drug therapy	SSPTSD, STAI, BDI, HAM-D, MSF III, Maladjustment Scale, RSE	P: safety of low-dose MDMA. S: alliance, side effects, subjective & physiological effects	Planned RCT (underpowered)	1	Low-dose MDMA were psychologically and physiologically safe. Signs of efficacy in reducing PTSD symptomatology: 75 mg > 50 mg > placebo. Too small for significance; larger/higher-dose studies needed.

Abbreviations: AUDIT = Alcohol Use Disorders IdentificationTest, BDI-II = Beck's Depression Inventory, C-SSRS = Columbia Suicide Severity Rating Scale, DES-II = Dissociative Experiences Scale, DUDIT = Drug Use Disorders Identifiction Test, GAF = Global Assessment of Functioning, HAM-D = Hamilton Rating Scale, IES-R = Impact of Event Scale, MSF II = Modified Fear Scale, NEO-PI-R = Revised NEO Personaility Inventory, PDS = Posttraumatic Diagnostic Scale, PSQI = Pittsburg Sleep Quality Index, PTGI = Posttraumatic Grwoth Inventory, RSE = Rosenberg Self-Esteem Scale, SCL-90-R = Symptom Checklist - 90 - Revised, SDS = Sheehan Disability Scale, SSSPTSD = Severity of Symptoms Scale for Post-traumatic Stress Disorder, STAI = State-Trait Anxiety Inventory

Table 2: OPEN LABEL TRIALS

Source	Sample Size	Race/Ethnicity Breakdown	Gender Breakdown	Mean Age (SD)	Clinical Presentation	MDMA and Psychotherapy Intervention	PTSD Assessment	Study Design	Quality Rating Scheme for Studies and Other Evidence	Study Findings
Ching et al. 2022	127	2.9% Native American, 9.5% Asian, 2.9% African American, 11.7% Hispanic, 65.7% White, and 7.3% Multiracial.	37% M, 63% F	40.0 (12.6)	Chronic, treatment resistant PTSD (CAPS-5 score 35<)	3x MDMA sessions and 9x integrative sessions. 80/40 mg for the first dosing session and increased to 120/60 mg for the second and third dosing sessions.	CAPS-IV	Secondary analysis of two Phase 2 open-label trials and a Phase 3 randomized, blinded placebo-controlled trial	2	In the MDMA-assisted psychotherapy group, both BIPOC and non-Hispanic White participants showed similar reductions in PTSD symptoms, with recovery rates of 65% and 71%, respectively. In contrast, the placebo group showed smaller improvements overall, though BIPOC participants trended toward greater symptom reduction than non-Hispanic White participants (p = 0.054), with recovery rates of 29% and 26%.
Wang et al. 2021	37	2.7% Native American, 16.2% Asian, 2.7% African American, 73.0% White, and 5.4% Mixed.	40.5% M, 59.5% F	35.6 (10.8)	Chronic, treatment resistant PTSD with associated suicidal ideation in most	3x sessions, with each session being 3 to 5 weeks apart. Initially were given 80 mg MDMA initial + 40 mg MDMA supplemental (United States) or 100 mg MDMA initial + 50 mg MDMA supplemental (Canada). The second and third experimental sessions utilized slightly higher divided doses of 120 mg MDMA + 60 mg MDMA (United States) and 125 mg MDMA + 62.5 mg MDMA (Canada).	CAPS-5	Multisite Open-Label Clinical Trial of MDMA-Assisted Therapy for Severe PTSD, conducted across 14 investigative sites	2	At the primary endpoint, there was a significant mean change in CAPS-5 scores of −29.89 (13.45), p < .0001 indicating improvement in PTSD symptoms. At the primary endpoint (Visit 19), 91.89% (n = 34) of all participants had a clinically meaningful reduction (10 points or greater) in their CAPS-5 scores (p < .0001) and 75.68% (n = 28) no longer met PTSD criteria (p < .001).
Jardim et al. 2021	3	Not provided	33% M, 64% F	40.3 (5.0)	Severe, chronic, treatment resistent PTSD resulting from sexual abuse	Multidisciplinary Association for Psychedelic Studies (MAPS) protocol consisting of 15 weekly therapy sessions: 3x with orally administered MDMA with concurrent psychotherapy and music, spaced approximately 1 month apart. Initially was 75 mg, and 75 or 125 mg in the second and third sessions. A supplemental dose of 50% the initial dose was offered 90 to 120 minutes after the initial dose.	CAPS-IV	The study design was an open-label pilot study.	2	The study found that MDMA-assisted psychotherapy could become a viable treatment in Brazil for PTSD. CAPS-IV reductions were 29, 51, and 64 points (z = 1.604, r = 0.924 and p = 0.108) for the participants, which is indicative of clinically significant improvement. Secondary outcomes included lower BDI-II scores, higher PTGI, and GAF scores.
Christie et al. 2022	32	72% Caucasian, 3% Native American, 16% Asian, 3% African American, 6% Mixed	41% M, 59% F	37.5 (IQR = 30.5–46.5).	Severe, chronic, treatment resistent PTSD and chronic pain.	3x experimental sessions 3 to 5 weeks apart. Initially given 80 mg MDMA, followed by a supplemental dose of 40 mg MDMA. In the second and/or third study drug sessions, participants received an increased dose of 120 mg MDMA followed by a supplemental dose of 60 mg MDMA.	CAPS-5	Exploratory data analysis of a subset of participants who completed chronic pain measures drawn from a Phase 2 open-label study	2	Significant reductions in CPGS subscales for pain intensity and disability score, and overall CPGS severity grade were observed among participants in the highest pain cluster (n = 9, p < 0.05), and for pain intensity in the medium pain cluster (n = 11, p < 0.05) post- vs. pre-treatment. However, the small sample size limited the power of the analysis, and further research with a larger sample in randomized, controlled trials is needed to investigate the role of MDMA-assisted psychotherapy as a treatment for chronic pain.
Lewis et al. 2023	23	Not provided	48% M, 52% F	42.4 (12.7)	Severe, chronic, treatment-resistent PTSD	Each experimental session was followed by three 90-min integration sessions that were spaced ~1 week apart to allow the participant to understand and incorporate their experience. The first integration session always occurred on the morning after the experimental session, and the remaining two integration sessions occurred over the following 3–4 weeks. Participants received a single divided dose of 80–180 mg MDMA or placebo.	CAPS-5	Pilot sub-study to the parent clinical trial (Phase 3). The study utilized a subsample of patients from the larger clinical trial who consented to participate in the epigenetic sub-study.	2	Baseline mean difference CAPS-V score in the MDMA group of the sub-study sample was 44.2 (6.16), and the final CAPS-V score was 26.26 (15.55). Baseline mean difference CAPS-V score in the placebo group of the sub-study sample was 46.6 (7.03), and the final CAPS-V score was 15.83 (13.07). Changes in DNA methylation of the NR3C1 and FKBP5 gene were associated with treatment response, with greater methylation changes associated with greater reductions in PTSD symptoms.

Abbreviations: BDI-II = Beck's Depression Inventory, BIPOC = Black, Indigenous, People of Colour, CPGS = Chronic Pain Grade Scale, C-SSRS = Columbia Suicide Severity Rating Scale, DES-II = Dissociative Experiences Scale, GAF = Global Assessment of Functioning, PSQI = Pittsburg Sleep Quality Index, PTGI = Posttraumatic Growth Inventory

Table 3: LONG TERM FOLLOW-UP AND ADDITIONAL FOLLOW-UP OF RCTS OF MDMA AND PTSD

Source	Sample Size	Ethnicity Breakdown	Gender Breakdown	Mean Age (SD)	Clinical Presentation	PTSD Assessment	Endpoints of Interest (Primary, Secondary)	Study Design	Quality Rating Scheme for Studies and Other Evidence	Study Findings	Extra Notes
Wagner et al. 2017	20	100% Caucasian	15% M, 85% F	40.4 (7.2)	Crime or war-related, chronic, treatment-resistent PTSD (CAPS score of ≥ 50)	CAPS-IV	**P**: NEO PI-R 2 months after blinded trials ended. **S**: CAPS score 2 months after blinded trials ended.	Randomized, double-blind, controlled trial followed by open-label sessions.	1	At two-month follow-up, increases in Openness and decreases in Neuroticism were significantly associated with greater reductions in PTSD symptoms, though the effect of MDMA-assisted therapy on CAPS scores was not significant after adjusting for Openness. Long-term data showed lasting changes in both traits, with Openness increasing and Neuroticism decreasing in the MDMA group, and an inverse correlation observed between the two traits.	Additional analysis and Follow-up of **Mithoefer et al. 2011**
Jerome et al. 2020	105	87.6% White, 2.9% Hispanic/Latino, 1.9% Native American, 1.9% Middle Eastern, and 5.7% Other/Biracial.	42% M, 58% F	40.5 (10.6)	Chronic, treatment resistent PTSD lasting more than 6 months with a CAPS-IV score of ≥50 (except for one study with ≥60). Average duration of PTSD at baseline was 214.1 months.	CAPS-IV	**P**: CAPS-5 score **S**: LTFU Questionnaire at least 12 months after final MDMA session, C-SSRS (n=68) at all visits	Long-term follow-up of six randomized, blinded with open-label crossover sessions, phase 2 trials	1	The mean change in the CAPS-IV total score from baseline to the primary endpoint was - 44.8 (SE 2.82). Scores continued to decrease from primary endpoint to LTFU by -5.2 (SE 2.29). Number of participants who no longer met PTSD criteria increased from treatment exit (56.0%) to LTFU (67.0%).	Follow-up of **Mithoefer et al. 2019**
Mithoefer et al. 2013	20	100% Caucasian.	15% M, 85% F	40.4 (7.2)	Chronic, treatment-resistant PTSD mostly resulting from sexual abuse or assault	CAPS-IV	**P**: CAPS-5 and IES-R score from 2-month follow-up to LTFU. **S**: LTFU questionnaire 10–74 months after final MDMA session	Long-term follow-up Randomized, double-blinded with open-label cross-over sessions	1	This study focused on long term follow up (LFTU) of participants in the original treatment group. No statistically significant change in mean CAPS-5 and IES-R scores at LTFU for the 16 study completers compared to 2-month (short-term) mean scores.	Follow-up of **Mithoefer et al. 2011**
Corey et al. 2016	20	100% Caucasian	15% M, 85% F	40.4 (7.2)	Chronic, treatment-resistant PTSD from crime or combat with CAPS score of ≥50.	CAPS-IV	**S**: Correlation between number of scored utterances and bimodal categories with overall change in CAPS score.	Additional evaluation of randomized, double-blind study	1	Participants in the MDMA group produced significantly more scored utterances, which were associated with lower posttreatment CAPS scores and greater overall symptom reduction when categorized as “many” vs. “few.” While the total number of utterances alone did not correlate with overall CAPS score change, the bimodal grouping showed a significant relationship with symptom improvement.	Additional analysis of **Mithoefer et al. 2011**
Barone et al. 2019	19	90% Caucasian, 5% Caucasian/Native American, 5% Native American	68% M, 32% F	24-56 years old. Original study reported Mean (SD) = 37.2 (10.3)	The study included military veterans, police, and firefighter with treatment-resistant PTSD with a CAPS-IV total score of ≥50.	CAPS-IV	**P**: Interpretative Phenomenological Analysis to semi-structured interviews to examine the meaning participants make of their experiences in the trial.	Long-term follow-up qualitative study of semi-structured interviews conducted one year post ending of randomized, double-blind, crossover phase 2 clinical trial.	1	All participants reported experiencing lasting personal benefits and enhanced quality of life that extend beyond quantifiable symptom reduction. 15 participants (79%) showed clinically significant decreases in PTSD symptoms at one-year follow-up (>30% reduction in CAPS-IV total scores from baseline), with average change in CAPS-IV total scores of 68% from baseline.	Follow-up of **Mithoefer et al. 2018**
Godes et al. 2023	7	85.7% Caucasian and 14.3% Asian	57.1% M, 42.9% F	36.3 (9.19)	The study included participants who met criteria for severe PTSD. Baseline CAPS-5 of 46.28 (5.72). Cause of PTSD development trauma (71.4%), veteran (28.6%), combat exposure (28.6%), and multiple trauma (57.1%).	CAPS-5	**P**: Interpretative phenomenological analysis. **S**: Change in CAPS-5 from baseline to termination.	Part of phase 2 open-label clinical trial - qualitative analysis of patients' experiences.	2	All seven participants reported experiencing a range of benefits during the course and at the end of the treatment. Coding scheme included tolerance of conflict, processing trauma, positive emotions, interpersonal, and connection. Change in CAPS-5 from baseline to termination for 7 participants −34 (8).	Additional analysis of **Wang et al. 2021**
van der Kolk et al. 2024	90	3.3% American Indian, 7.8% Asian, 2.2% African American, 76.7 % Caucasian, 8.9& Mixed, 1.1% Unknown	34.4% M, 65.6% F	41.0 (11.9)	Chronic (over 6 monthes) and severe PTSD (CAPS score of > 35)	CAPS-5, IASC, TAS-20, SCS	**P**: changes IASC score, TAS-20 score, and SCS score 2 monthes afetr last experimental session from baseline	Analysis of a multi-site double-blind, placebo-controlled randomized Phase 3 study	1	Reductions in alexithymia were significant, and participants with higher baseline alexithymia showed greater PTSD symptom improvement, especially in the MDMA-assisted therapy group. Notably, those with high alexithymia receiving MDMA had significantly larger reductions in CAPS-5 scores compared to the placebo group, suggesting MDMA therapy may enhance emotional regulation and self-awareness.	Additional analysis of **Mitchell JM, Ot'alora GM, et al. 2023**
Zeifman et al. 2024	22	100% Caucasian	28.7% M, 77.3% F	57.5 (7.5)	Chronic, treatment resistent, and severe/moderate PTSD (CAPS score of > 50)	WAI score for therapeutic alliance, CAPS-IV, IES-R	**P**: relationship between thearpautic alliance and cliniation and patient obsevred changes in PTSD symptoms.	Double-blind randomised controlled phase (Phase 1) followed by an open-label phase (Phase 2)	1	Therapeutic alliance at sessions 4 and 9 significantly predicted reductions in both clinician- and self-reported PTSD severity, explaining up to 40% of the variance in outcomes. No gender differences were found in alliance scores, and Bayesian analyses confirmed the strong predictive value of therapeutic alliance in MDMA-assisted therapy.	Additional analysis of **Mithoefer et al. 2011**

Abbreviations: C-SSRS = Columbia Suicide Severity Rating Scale, IASC = Inventroy of Altered Self Capacities, IES-R = Impact of Event Scale, LTFU = Long term follow-up, NEO-PI-R = Revised NEO Personaility Inventory, SCS = Self-Compassion Scale, TAS-20 = Toronto Alexithymia Scale, WAI = Work Ability Index

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