MDMA-assisted psychotherapy in the treatment of PTSD: A Systematic Review and Meta-Analysis

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Introduction

Post-traumatic stress disorder (PTSD), formerly known as battle fatigue syndrome or shell shock, is defined as a psychiatric condition that develops when an person experiences or is exposed to a terrifying circumstance, such as war, abuse, a terrorist attack, sexual assault or a natural catastrophe (American Psychiatric Association, 2013). It can also occur in individuals that are menaced by death, harassment or injury. According to the DSM-5, the principal symptoms observed in PTSD patients are intrusion, avoidance, mood fluctuations, changes in cognitive abilities and shifts in arousal. In pursuance of a way to treat PTSD and the emerging symptomatology, two drugs (sertraline and paroxetine) have been licensed in the last decades, but both of them have shown limited effectiveness (Cipriani et al., 2018; Hoskins et al., 2015). In this way, exposed-based psychotherapy has now been specified as the main approach to follow in order to treat PTSD (National Institute for Health and Care Excellence, 2018). Nevertheless, recent studies have demonstrated that PTSD symptoms persist despite following numerous sessions of psychotherapy (e.g., Bryant et al., 2016).

In order to find an adequate medication for PTSD, many researchers and clinicians have been testing the efficiency of 3,4-methylenedioxymethamphetamine (MDMA), a psychoactive molecule that provokes cortical serotonin, oxytocin, cortisol and prolactin release (Feduccia et al., 2018). The aim of this systematic review and meta-analysis is to assess, using the most recent evidence, whether MDMA-assisted psychotherapy can ameliorate PTSD symptoms in controlled psychotherapeutic conditions and whether the results are consistent across sample sizes and clinical trials.

We would also like to determine whether the effect of MDMA-assisted psychotherapy is moderated by the proportion of women in the sample. Indeed, gender is known to be associated with emotional intelligence (Cabello et al., 2016), which may mediate the efficacy of the treatment. Furthermore, gender may correlate with the cause of the trauma, which could also be an important predictor of response to treatment. Similarly, we will investigate the potential moderating effect of age, as it is also associated with emotional intelligence (Cabello et al., 2016) and it could be a useful proxy to when the traumatic event took place.

Methods

Search strategies

To identify studies evaluating the effect of MDMA-assisted psychotherapy, we systematically searched in the PubMed database, the search engine Google scholar and the website Connected Papers. We used the following search terms: “MDMA + PTSD”. We also conducted a backward citation search in every systematic review or meta-analysis we identified through our initial screening to identify the original clinical trials the articles mentioned.

To prevent biases, we made sure to select relevant papers independent of the number of citations. Furthermore, papers were searched for independently by every member of the group. None of us were familiar with the authors of these papers and made our selection exclusively on our inclusion/exclusion criteria.

Inclusion/Exclusion criteria

The PRISMA flow diagram of the included studies is listed in Figure 1. We identified 66 records in our initial search, and we then screened these articles over two stages.

In the first screening phase, we looked at the title and abstract of the selected articles. We only retained papers reporting original data about the quantitative effects of MDMA-assisted psychotherapy on PTSD symptoms in a clinical trial.

In our secondary screening phase, we read the whole text of the article. We only included studies with randomized controlled trials (RCTs) with a control group receiving either a placebo or low doses of MDMA. We only included papers that were original clinical trials and for instance we did not include follow-ups of previous studies.

As our secondary screening phase yielded a total of 5 papers only, we also searched the database ClinicalTrials (https://clinicaltrials.gov/ct2/home) in a second time, although this was not part of our initial strategy. We applied the exact same inclusion criteria we listed above to the reviewed clinical trials. This allowed us to include two additional, unpublished clinical trials corresponding to our inclusion criteria. The general characteristics of the included studies are shown in Table 1.

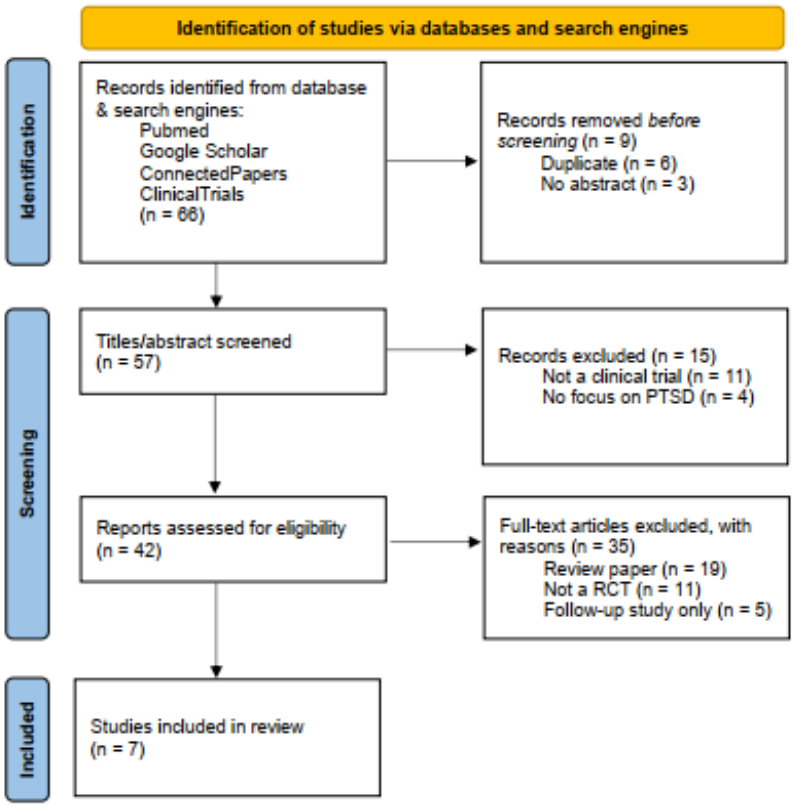

Figure 1. PRISMA chart of the included studies.

Statistical analyses

Most papers use the Clinician Administered PTSD Scale (CAPS) to evaluate the impact of the therapy in a standardized fashion. We first extracted for each paper the decrease of CAPS score from baseline separately for the treated and the control groups, and then we computed the difference of these two scores in absolute values ($CAPS_{treated}$ - $CAPS_{control}$). Hence, a positive value favors MDMA (i.e., indicates a greater decrease in CAPS score from baseline in the MDMA group), and a negative value favors placebo.When there were 2 MDMA-treated groups, we combined means and standard deviations into one group using https://www.statstodo.com/CombineMeansSDs.php (following Smith et al., 2022).

As a measure of effect size, we used Hedges' g to account for the small sample sizes included in our analysis (Hedges, 1981). We used the *metafor* package in R to conduct our analyses (Viechtbauer, 2010). Our code and data can be found at the following link: drive.google.com/1QcADn4Ull4R.

Author	Journal	Year	Study location	Mean age (SD)	Proportion of women (%)	Placebo	Treatment duration (Nb of sessions)
Mithoefer et al.	J. Psychopharmacol.	2011	USA	40.4 (7.2)	85%	Inactive (lactose)	Approx. 4 months (2)
Oehen et al.	J. Psychopharmacol.	2013	Switzerland	41.4 (11.2)	83%	Active (25mg of MDMA)	Approx. 4 months (5-6)
Ot'alora et al.	J. Psychopharmacol.	2018	Boulder Colorado, USA	42 (12.9)	68%	Active (40mg of MDMA)	Approx. 5 months (6)
Mithoefer et al.	Lancet	2018	Charleston, SC, USA	37.2 (10.3)	27%	Active (30mg of MDMA)	Approx. 5 months (6)

Author	Journal	Year	Study location	Mean age (SD)	Proportion of women (%)	Placebo	Treatment duration (Nb of sessions)
Kotler et al.	Unpublished	2016	Israel	NA	38%	Active (25mg of MDMA)	Approx. 2 months (2)
Pacey et al.	Unpublished	2021	NA	47.7 (8.82)	5%	Inactive	NA

Table 1. Characteristics of included studies.

Results

Efficacy of MDMA-assisted psychotherapy

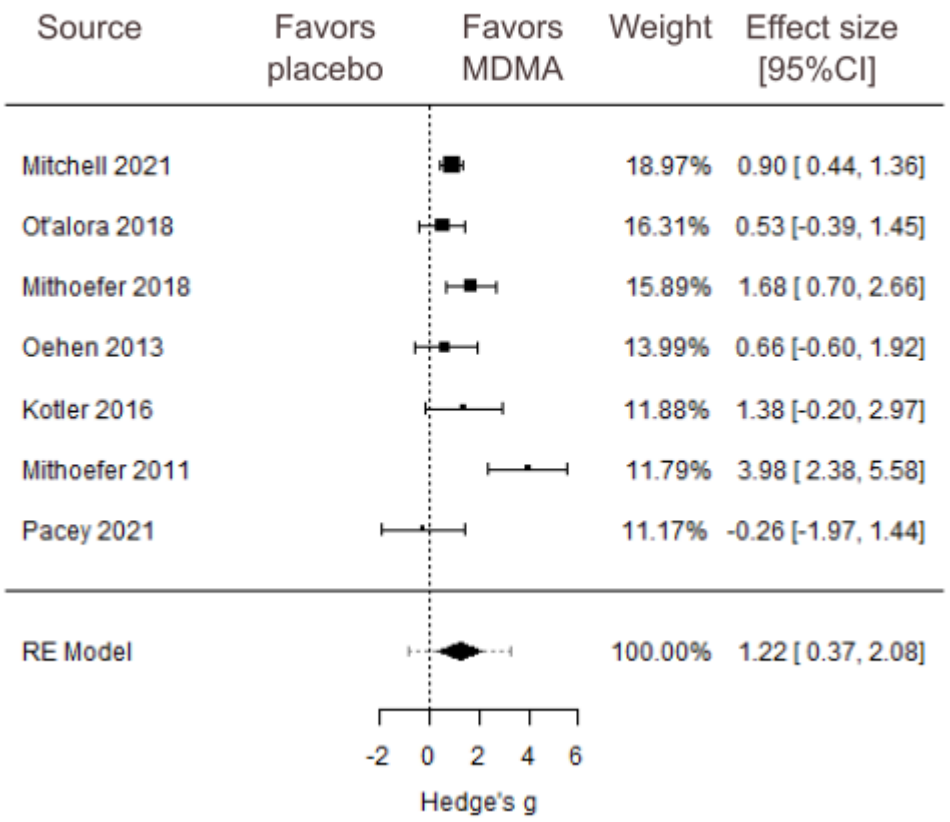

Figure 2. Forest plot of the effect sizes across the different studies. The black diamond represents the 95% confidence interval of the estimated pooled effect size, while the overlaid dotted line shows the 95% prediction interval.

As studies may vary in several important ways (e.g., type of trauma), we used a random-effects model to take into account this inter-study variability (Schwarzer et al., 2015).

Figure 2 shows the pooled effect size for MDMA-assisted psychotherapy vs control therapy (placebo/low-dose). The results indicate a significant benefit of MDMA-assisted psychotherapy compared to control, g = 1.22, z = 2.8, p = .005, 95%CI [0.37, 2.08]. Note that a Hedge's g superior to 0.8 is usually deemed large (Cohen, 2013). For completeness, we also report the raw mean CAPS-score difference. Remember that the total CAPS score can range from 0 to 80. The mean reduction in CAPS scores from baseline was 19.32 points greater for the treated group than for the control group (95%CI [8.29, 30.35]).

The percentage of variability in the effect sizes not caused by sampling error was high (I^2 = 77.7%), indicating a substantial between-study heterogeneity (Higgins, 2003). In addition, the 95% prediction interval: [-0.87, 3.31] stretched well below zero, indicating that the overall positive effect found for the interventions might not be robust in every context.

Moderation analyses

Unaccounted between-study moderators might explain this between-study variability. To investigate this issue, we performed meta-regressions to study the impact of publication (published vs unpublished), proportion of women in the sample as well as mean age of the sample on the overall effect size[1]. All analyses failed to reach significance (publication : p =.44; women proportion : p = .66; age : p = .15; However, note that these results should be interpreted with caution, as we only included a small number of studies in our sample (n = 7), thus resulting in a very low statistical power.

Assessment of publication bias

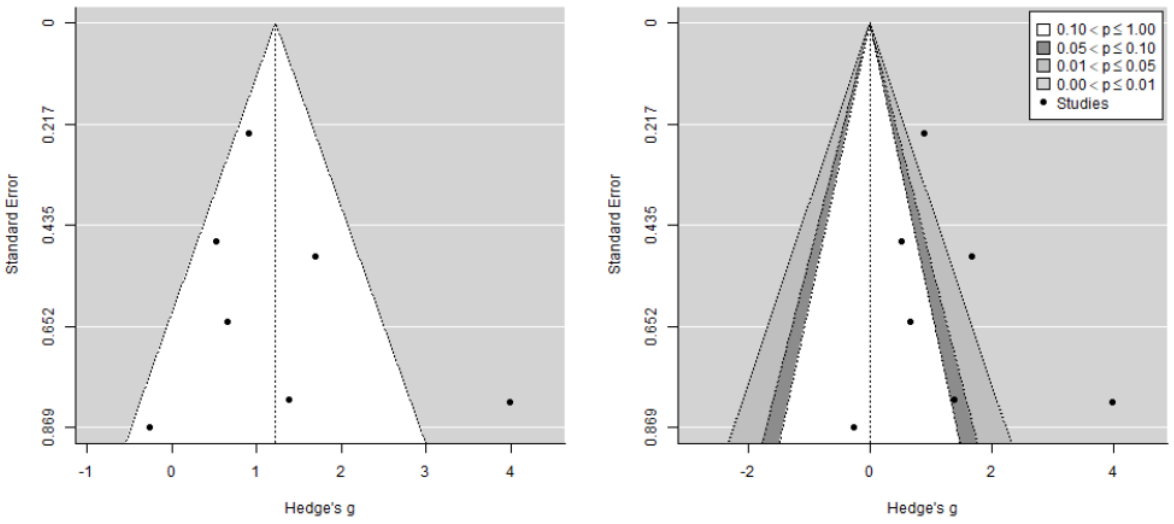

Figure 3. Funnel plots of the effect size of each individual study (Hedge's g; x-axis) as a function of its precision (Standard Error; y-axis). A higher value on the y-axis indicates a higher precision. **Left:** traditional funnel plot centered on the random-effects model estimate, where the white region represents the 95% pseudo confidence interval. **Right:** contour-enhanced funnel plot centered on 0 and showing the estimated significance level of each study.

[1] Although we said we would also use duration of treatment as a moderator, this variable proved difficult to extract from the different studies as it was not always reported in a precise and straightforward way.

The left panel of Figure 3 shows the funnel plot of the studies included in the analysis. A visual inspection of the figure did not reveal any obvious publication bias. Egger's regression test (Egger et al., 1997) further confirmed the absence of a significant asymmetry, as the intercept of the model did not significantly differ from 0, b = 0.55, 95% CI [-2.1, 3.2], z = 0.53, p =.6. Once again, the absence of a significant asymmetry should be taken with caution because of our low statistical power (Sterne et al., 2011). In addition, the right panel of Figure 3 shows a contour-enhanced funnel plot displaying the significance level of each study in the plot (Peters et al., 2008). Here again, there was no visible evidence of publication bias. Note that these results were expected as we mainly deal with registered medical clinical trials for which a publication bias is unlikely to happen.

Side effects

We assess the side effects of MDMA-assisted psychotherapy compared to placebo without analyzing them quantitatively. The majority of adverse events were of mild or moderate severity. The most common adverse events that articles reported for MDMA-assisted psychotherapy were anxiety, nausea, jaw clenching, reduced appetite and dizziness. Serious adverse events were very rare, and patient attrition was lower than in other traditional PTSD trials.

Quality of included studies

We used the NIH quality assessment tool to assess the quality of each included study. Among the included studies, 4 were deemed of Good quality, 2 of Fair quality and 1 of Poor quality.

Discussion

Findings

The current meta-analysis supports the idea that MDMA-assisted psychotherapy is superior to psychotherapy alone. We included a total of 7 studies in our quantitative analysis (total n = 179) and we compared the difference in reduction of CAPS scores from baseline between the MDMA and the placebo/low dose groups. Overall, we found a large positive effect size of g = 1.22 (95%CI [0.37, 2.08]), corresponding to an additional reduction of 19.32 in CAPS scores from baseline compared to the control group (95%CI [8.29, 30.35]). In addition, a qualitative review of the included studies showed no evidence for serious side effects of the supervised MDMA intake.

We found no evidence of publication bias in our analysis, but the between-study statistical heterogeneity was high. This may be due to the small sample sizes used in the studies (M = 25.6 participants). We tried to investigate this between-study heterogeneity by conduction moderation analyses. However, neither the mean proportion of women in the sample nor the mean age of the sample significantly moderated the effect of MDMA-assisted psychotherapy[2]. Note that these non-significant results should be taken with caution as our small set of studies (k = 7) did not allow us to reach sufficient statistical power to find meaningful differences between studies (Higgins & Thompson, 2004).

[2] There may be several other reasons for this statistical heterogeneity, such as the care team running the study, the symptoms severity or the event responsible for the PTSD for instance.

Although only one study was found to be of Poor quality, the studies we included suffered from two main limitations. First, although we only selected RCTs with double-blind procedures in our studies, both participants and therapists seem to be able to guess almost perfectly who received MDMA (Mithoefer et al., 2011). This is likely to bias the behavior of both the participants and the health workers, and may explain a part of the effect we observed. Unfortunately, there appears to be no possible solution to this blinding problem. Second, the therapy received by both the MDMA and the control groups has been tailored to the needs of participants receiving MDMA (e.g., Mithoefer et al., 2008), questioning the validity of the comparison with the control group. This makes it necessary to compare MDMA-assisted psychotherapy to other tried and tested forms of psychotherapy and/or drugs in treatment of PTSD (Smith et al., 2022)[3].

Limitations

First, because MDMA-assisted psychotherapy only came back into the spotlight during the 2010s, our set of studies was quite small (k = 7). This resulted in a very low statistical power which undermines the robustness of our results, and in particular the meta-regression analysis we conducted.

In addition, although the random-effects model we used allows to take heterogeneity into account, one of its drawbacks is that it gives more weight to small studies when pooling the overall effect in a meta-analysis compared to a fixed-effect model (Schwarzer et al., 2015). Our pooled estimate may thus overweight the very small studies we included in our analysis, which are more likely to be flawed/biased than published studies with high sample size. For instance, one of the clinical trials we used had a final sample size of n = 6. Therefore, our estimate may not necessarily be conservative.

Furthermore, although we initially said that we would use an inter-rater agreement for the secondary screening phase (by asking a second coder if they agree about the exclusion of papers), we did not implement this eventually. This may increase the risk of potential biases in our meta-analysis.

Finally, a very recent meta-analysis (Smith et al., 2022) on the exact same topic was published as we were working on this project, thus limiting the originality of our work. Although we included two additional unpublished clinical trials in our meta-analysis (which accounted for 23% of the weight in our random-effects model), our findings were quite consistent with the ones they obtained.

Conclusion

MDMA-assisted psychotherapy appears to be a safe and promising candidate in the treatment of PTSD. However, studies with larger sample sizes and more valid comparison groups are needed to fully assess the benefits of this breakthrough psychotherapy.

[3] Note that one of the main advantages of MDMA-assisted psychotherapy is that one has only 2 or 3 sessions with MDMA, whereas other drugs require a daily intake.

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