Introduction

Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is a psychiatric disorder triggered by exposure to a psychologically traumatic event, and is characterised by anxiety, sleep disturbance, hypervigilance, avoidance behaviour, and intrusive thoughts and memories about the trauma. To satisfy diagnostic criteria, symptoms must continue at least 1-month after exposure and cause significant distress and social, occupational or other dysfunction (American Psychiatric Association, 2013). Newer diagnostic criteria (DSM V) have also included changes in mood and cognition as part of this disorder (American Psychiatric Association, 2013). Examples of commonly associated traumatic events include sexual assault, particularly at a young age, and witnessing or being the victim of violence, particularly in conflict-zones (Kessler et al., 1995).

PTSD is a disabling condition and inflicts a large individual and societal burden. It is reported to have a lifetime prevalence of between 1.0–9.2% in the general population (based on DSM criteria), with more robust epidemiological data placing the estimated figure at 3.64–3.9% worldwide (Creamer et al., 2001; Karam et al., 2010; Koenen et al., 2017; Van Ameringen et al., 2008). PTSD is particularly prevalent in conflict-affected populations such as refugees (mean: 30.6%) (Steel et al., 2009).

Abstract

Rationale: Novel, evidence-based treatments are required for treatment-resistant post-traumatic stress disorder (PTSD). 3,4-Methylenedioxymethamphetamine (MDMA) has beneficially augmented psychotherapy in several small clinical trials.

Objective: To review the use of MDMA-assisted psychotherapy in treatment-resistant PTSD.

Methods: Systematic searches of four databases were conducted from inception to February 2020. A meta-analysis was performed on trials which were double-blinded, randomised, and compared MDMA-assisted psychotherapy to psychotherapy and placebo. The primary outcomes were the differences in Clinician Administered PTSD Scale (CAPS-IV) score and Beck's Depression Inventory (BDI). Secondary outcome measures included neurocognitive and physical adverse effects, at the time, and within 7 days of intervention.

Results: Four randomised controlled trials (RCTs) met inclusion criteria. When compared to active placebo, intervention groups taking 75 mg (MD −46.90; 95% (confidence intervals) CI −58.78, −35.02), 125 mg (MD −20.98; 95% CI −34.35, −7.61) but not 100 mg (MD −12.90; 95% CI −36.09, 10.29) of MDMA with psychotherapy, had significant decreases in CAPS-IV scores, as did the inactive placebo arm (MD −33.20; 95% CI −40.53, −25.87). A significant decrease in BDI when compared to active placebo (MD −10.80; 95% CI −20.39, −1.21) was only observed at 75 mg. Compared to placebo, participants reported significantly more episodes of low mood, nausea and jaw-clenching during sessions and lack of appetite after 7 days.

Conclusion: These results demonstrate potential therapeutic benefit with minimal physical and neurocognitive risk for the use of MDMA-assisted psychotherapy in TR-PTSD, despite little effect on Beck’s Depression Inventory. Better powered RCTs are required to investigate further.

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Keywords
MDMA, 3,4-Methylenedioxymethamphetamine, PTSD, post-traumatic stress disorder, psychotherapy, treatment-resistance, novel therapies
It is estimated that PTSD tends to remit in only about half of individuals after a period of more than 3 years (Morina et al., 2014). The definition of treatment-resistance varies across the literature and between the studies analysed within this review, though it is often considered as failure to respond to at least two evidence-based therapies. Further complexity arises because of inconsistency in the definition of ‘treatment response’, for example one commonly used and validated benchmark is a 10-point reduction in CAPS-IV, however many others exist (Sippel et al., 2018). Because of this heterogeneity in the literature, for the purposes of this review all trials describing their subjects as ‘treatment resistant’ were included, regardless of the criteria used to determine said treatment resistance.

**Co-morbidity and disease burden**

There are close links between PTSD and physical health: not only are those who have had life-threatening illnesses, such as strokes and heart attacks, more likely as a result to develop PTSD (Davydow et al., 2008; Edmondson et al., 2012, 2013), those with PTSD are also at greater risk of future morbidity and mortality from a range of physical medical conditions (Remch et al., 2018; Sareen et al., 2007; Spitzer et al., 2009).

PTSD populations also have higher rates of psychiatric co-morbidity than non-affected populations (Perkonigg et al., 2000). Rates of self-harm and suicide in those with PTSD are significantly higher than those in the general population (Bernal et al., 2016; Bernal et al., 2018; Sareen et al., 2007; Spitzer et al., 2009).

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**Current treatment options and their efficacies**

Management of PTSD generally consists of pharmacological treatments, primarily serotonin reuptake inhibitors (Hoskins et al., 2015; Stein et al., 2006), as well as psychotherapies that involve exposure to and processing of traumatic events. Many types of psychotherapy are used in the management of PTSD including exposure therapies, trauma-focused cognitive behavioural therapy (CBT), interpersonal therapy (IPT) and eye-movement desensitisation and reprocessing (Althobaiti et al., 2020; Powers et al., 2010). Of these, IPT is notable in that it does not require exposure to, or processing of, traumatic experiences (Bleiberg and Markowitz, 2019). Psychotherapy is first line management in the UK (National Institute for Health and Care Excellence (NICE), 2019). There is good evidence for the efficacy of a range of psychotherapies for the treatment of PTSD (Bisson and Andrew, 2007; Institute of Medicine, 2008; Schnurr et al., 2007). Of the pharmacotherapy options, the strongest evidence is for selective serotonin reuptake inhibitors (SSRIs) and venlafaxine, a serotonin and norepinephrine reuptake inhibitor (SNRI) (Bisson et al., 2020; Hoskins et al., 2015; Stein et al., 2006).

Psychotherapy alone appears to be more effective than pharmacotherapy alone although methodological difficulties, for example with blinding and sampling, in trials of psychotherapies means their effectiveness may be overestimated (Bisson et al., 2020; Lee et al., 2016). On the whole, pharmacotherapy has not been shown to be effective at augmenting psychotherapy in clinical trials, however the two treatment modalities are nonetheless frequently used in combination (Hetrick et al., 2010; Rothbaum et al., 2006; Schneier et al., 2012; Simon et al., 2008). Despite this, a significant proportion (33–60%) of patients do not achieve remission regardless of the regimen used (Bisson et al., 2009, Bradley et al., 2005).

Because of its chronicity and the number of patients who do not achieve satisfactory response with currently available therapies, there is a pressing need for new treatment options for PTSD.

**Proposed benefits of MDMA for augmentation of psychological therapies**

3,4-methylenedioxymethamphetamine (MDMA) is a psychoactive drug that has been widely used as a recreational drug for its entactogenic (promoting feelings of empathy and relatedness), pro-social and euphoric effects (Cami et al., 2000; Harris et al., 2002; Winstock et al., 2001). It may elicit these effects through modulation of monoamine neurotransmitter systems (Green et al., 2003). Administration of MDMA also results in increased circulating concentrations of oxytocin, which may mediate interpersonal bond-forming and trust, and prolactin, thought to be responsible for relaxation and receptivity to novel ideas and experiences (Dumont et al., 2009; Green et al., 2003; Harris et al., 2002). Reductions in fear and negative emotions, as well as increases in empathy, extroversion and confidence are among the other positive subjective effects of MDMA (Baylen and Rosenberg, 2006). Similar effects have been demonstrated in SSRIs in the context of PTSD (MacNamara et al., 2016, Seedat et al., 2002).

Because of these subjective and appreciable effects of MDMA, active placebo is frequently the comparator of choice in trials. Active placebos are control interventions that mimic some of the psychophysiological effects but not therapeutic effects of the intervention under investigation, in an attempt to reduce the risk of unblinding. Examples include using an alternative medication that produces similar side effects or alternatively using a lower dose of the drug under investigation.

In those affected by PTSD, excess fear and aversion may impair access to traumatic memories. If they are accessed, associated states of hyper-arousal or dissociation may prevent psychological resolution. By moderating fear responses, MDMA may have utility in positively augmenting psychotherapy for PTSD by inducing a psychological state more conducive to accessing and processing trauma.

**Side-effect and toxicity profile**

Side effects of MDMA include, but are not limited to, dry mouth, nausea, anxiety, inability to urinate, bruxism, restless-ness and increases in heart rate, blood pressure and body temperature (Baylen and Rosenberg, 2006). Higher doses can cause a potentially fatal serotonin syndrome (Francescangeli et al.,
Summary of intervention

The intervention investigated in this review is the administration of MDMA in an expertly supervised clinical setting as an adjunct to a limited number of psychotherapy sessions. The feasibility of administering MDMA during supervised psychotherapy has been demonstrated in phase 1 (Cami et al., 2000; Harris et al., 2002; Liechti et al., 2001; Tancer and Johanson, 2001) and phase 2 clinical trials (Mithoefer et al., 2010, 2013; Oehen et al., 2013; Ot’alora et al., 2018). Further phase 3 trials are planned or ongoing in the USA (Identifier NCT03537014) (Mithoefer et al., 2019) and Europe.

There have been previous systematic reviews in this area published in 2016 (Amoroso and Workman, 2016) and 2019 (Bahji et al., 2019). This present review has several notable differences, updating and complementing this previous research.

Amoroso and Workman (2016) used robust statistics to compare the effect sizes of MDMA assisted psychotherapy and prolonged exposure (PE) therapy, finding both treatments had comparable outcomes. However, PE effect sizes were based on several studies comparing PE to wait-list controls, while MDMA assisted psychotherapy was compared to equivalent psychotherapy plus active placebo. As a result, the effect-sizes for MDMA assisted psychotherapy were considered more in-depth analysis of adverse events (AE) and secondary outcomes.

Methods

The protocol was registered on PROSPERO: International Prospective Register of Systematic Reviews. The registration number is CRD42019109132 and is available online (www.crd.york.ac.uk/prospero).

We followed the reporting guidelines for meta-analyses and systematic reviews of randomised controlled trials, as outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. We searched PUBMED, PsychINFO, EMBASE and MEDLINE from September 2018 to February 2020 to identify published double-blinded, randomised controlled trials evaluating the efficacy and safety of MDMA-assisted psychotherapy treatment in TR-PTSD patients (search terms: MDMA; 3,4-methylenedioxymethamphetamine; psychotherapy; PTSD; post-traumatic stress disorder). Two review authors (BJGI and DJL) independently screened titles and abstracts. They critically reviewed the full text of selected randomised trials to assess eligibility. We included studies where participants had been diagnosed with PTSD and were treated with MDMA and psychotherapy. We only included randomised control trials. In all studies included for analysis in this review where the intervention was compared to placebo, ‘active placebo’ should be taken to mean a lower dose of MDMA than used in the intervention arm. An inactive placebo should be taken to mean a substance with no psychoactive effects. Trials conducted in inpatient or outpatient settings were considered eligible.

Two review authors (BJGI and DJL) independently extracted study characteristics including trial design, setting, participants and outcomes. We extracted all relevant data from each randomised trial report. Two review authors (BJGI and DJL) independently assessed the risk of bias for each study using the Cochrane Risk of Bias tool. Each trial was evaluated based on its approach to minimizing selection, performance, detection, attrition, and reporting bias.

Two review authors (BJGI and DJL) independently extracted data from each randomised trial report related to pre-specified primary and secondary outcomes. The primary outcomes were Clinician Administered PTSD Scale (CAPS-IV) score at greater than 3 weeks and the Beck Depression Inventory (BDI). Secondary outcomes included episodes of anxiety and low mood and physical adverse effects (jaw clenching, insomnia, nausea, headache and anorexia), reported both during the session and at 7-day follow-up. We contacted authors to seek clarification and requested missing data or additional data to complete our analysis. Discrepancies between the reviewers were resolved through discussion, by contacting the authors, or by consultation with a third reviewer (JMND).

Review Manager 5.3 (Cochrane Collaboration, UK) was utilised to analyse results. We used a random-effects model (inverse variance) to calculate the summary estimates given the statistical heterogeneity of our data. For secondary outcomes, we used a fixed-effects (Mantel–Haenszel method) to calculate summary estimates. When there were few or no events we used the peto odds ratio (POR) as this is a less biased and more powerful method when comparing studies with low event rates (Higgins et al., 2019). For secondary outcomes where events were reported as both per session and per patient in different studies at the same dosage, we calculated separate summary estimates because these denominators are not directly comparable.
Results

We imported 688 references for screening. After excluding 573 duplicate records, 115 titles and abstracts were screened which identified 13 potentially relevant studies. Six randomised controlled trials reporting data from 109 participants met our inclusion criteria. Of these trials one was excluded for not containing appropriate follow up times (Bouso et al., 2008) another was excluded as the participant data was previously used in another trial included in the analysis (Mithoefer et al., 2010, 2013). Four trials using 85 participants were used in the final analysis (Figure 1).

Included randomised trials evaluated the reduction of PTSD symptoms in subjects with treatment-resistant PTSD. The included randomised trials were relatively small, ranging from 12 to 28 participants. (The authors’ judgments regarding the risk of bias for the included studies are detailed in Figure 2)
Primary outcomes

One primary outcome was the change in CAPS-IV score from baseline to greater than 3 weeks after the blinded sessions. When compared to active placebo, the intervention groups taking 75 mg and 125 mg of MDMA in conjunction with psychotherapy had significant decreases in CAPS-IV scores (Figures 3, 4 and Table 1). The decrease in CAPS-IV score at 100 mg, however, did not reach significance (MD = −12.90; 95% CI [−36.09, +10.29], p = 0.28) (Figure 5). When compared to inactive placebo, a statistically significant reduction in PTSD symptoms was also noted in the intervention groups taking 125 mg of MDMA in conjunction with psychotherapy (Figure 6 and Table 2) (MD = −33.20; 95% CI [−0.53, −25.87], p < 0.00001). As the 150mg dose was only administered in open-label sessions we have not included the data in our analysis of the primary outcome.

The other primary outcome measurement was the Beck’s Depression Inventory (BDI). When compared to active placebo,
there was no significant difference noted in BDI at higher strengths of MDMA (100 and 125 mg) when taken in conjunction with psychotherapy and only the intervention group taking 75 mg MDMA in conjunction with psychotherapy saw a significant improvement in BDI (MD $-10.80$; 95% CI $(-20.19, -1.41)$, $p = 0.02$), (Figures 7, 8, 9 and Table 1).

**Secondary outcomes**

We calculated risk ratios and PORs for both physical (jaw clenching, headache, loss of appetite, nausea) and psychological adverse effects (anxiety, low mood, insomnia) at intervention and within the 7 days subsequently (Tables 3 and 4).

Jaw clenching occurred significantly more often when compared to inactive placebo (RR 4.22; 95% CI 1.49, 11.95) and active placebo when taken at 75 mg (POR 13.46; 95% CI 1.44, 125.80), 125 mg (per patient) (POR 7.34; 95% CI 1.98, 27.71), 125 mg (per session) (POR 4.08; 95% CI 1.04, 15.99), 150 mg (RR 8.67; 95% CI 1.21, 61.91) but not 100 mg (RR 1.67; 95% CI 0.47, 5.96). Nausea during the session and lack of appetite within 7 days occurred significantly more often when taking therapeutic doses of MDMA at 125 mg when compared to inactive but not active placebo (RR 4.00; 95% CI 1.03, 15.53) (POR 8.14; 95% CI 1.03, 76.80) (Figure 6).

![Figure 6. CAPS IV scores in MDMA-assisted psychotherapy versus psychotherapy with inactive placebo: 125 mg MDMA versus inactive placebo.](image)

![Figure 7. Beck’s depression index scores in MDMA-assisted psychotherapy versus psychotherapy with active placebo: 75 mg MDMA versus active placebo.](image)

| Table 1. Primary outcome: MDMA-assisted psychotherapy versus psychotherapy with active placebo. |
|---|---|---|
| Outcomes and outcome measures | Effect size estimate (MD (95% CI)) | $p$ |
| Difference in CAPS-IV scores | | |
| 75 mg MDMA versus active placebo | $-66.90$ (−58.78, −35.02) | $<0.00001$ |
| 100 mg MDMA versus active placebo | $-12.90$ (−36.09, 10.29) | 0.28 |
| 125 mg MDMA versus active placebo | $-20.98$ (−34.35, −7.61) | 0.002 |
| Difference in Beck’s Depression Index | | |
| 75 mg MDMA versus active placebo | $-10.80$ (−20.39, −1.21) | 0.03 |
| 100 mg MDMA versus active placebo | 1.60 (−9.10, 12.30) | 0.77 |
| 125 mg MDMA versus active placebo | $-9.85$ (−29.93, 10.24) | 0.34 |

CI: confidence interval; MD: mean difference.

| Table 2. Primary outcome: MDMA-assisted psychotherapy versus psychotherapy with inactive placebo. |
|---|---|---|
| Outcomes and outcome measures | Effect size estimate (MD (95% CI)) | $p$ |
| Difference in CAPS-IV scores | | |
| 50 mg MDMA versus inactive placebo | N/A | N/A |
| 75 mg MDMA versus inactive placebo | N/A | N/A |
| 125 mg MDMA versus inactive placebo | $-33.20$ (−40.53, −25.87) | $<0.00001$ |

CI: confidence interval; MD: mean difference.
CI 1.82, 36.33) respectively. Low mood in session was noted to be significantly more prevalent when taking therapeutic doses of MDMA than in the active placebo group at 100mg only (POR 10.31; 95% CI 1.24, 85.66).

**Discussion**

**Main findings**

The results of this meta-analysis suggest that the use of MDMA in conjunction with psychotherapy is associated with a significant decrease in CAPS-IV scores at greater than 3 weeks when compared to both active (except at 100 mg) and inactive placebo groups in the treatment of treatment-resistant PTSD. MDMA-assisted psychotherapy showed no significant decreases in BDI except for at 75 mg. Subjects in these trials experienced significant physical side effects from the intervention. These included nausea (58% of sessions), low mood (17% of sessions) and jaw clenching in session (30% of sessions) and also lack of appetite within 7 days of intervention (25% of sessions). Jaw clenching was more prevalent at higher doses (67% of 150 mg sessions). Four serious adverse effects (SAE), including suicidal ideation, were recorded during one study (Mithoefer et al., 2018).

**Strengths and limitations**

The strengths of this prospectively registered systematic review include its comprehensive search strategy, methodological design and statistical analysis. All the studies included reported the primary outcome, reduction in CAPS-IV score after 3 weeks of intervention. Another strength of this paper as compared to other reviews and the pooled analysis performed by Mithoefer et al. (2019), is that it looks in-depth at the secondary outcomes and adverse events. This paper has attempted to compare the intervention arm against active and inactive placebos separately. It has also assessed the dose differences on effect size. Pooling of data, as used by previous studies, may be inappropriate as it assumes that different MDMA doses or inactive and active placebos are comparable or interchangeable.

| Outcomes and outcome measures | Effect size estimate (RR or POR (95% CI)) | p |
|-------------------------------|------------------------------------------|---|
| **Anxiety in session**        |                                          |   |
| 125 mg MDMA versus inactive placebo | RR 0.72 (0.48, 1.08) | 0.11 |
| 75 mg MDMA versus active placebo | RR 1.50 (0.74, 3.05) | 0.26 |
| 100 mg MDMA versus active placebo | RR 2.00 (0.59, 6.79) | 0.27 |
| 125 mg MDMA versus active placebo | RR 1.61 (0.87, 2.97) | 0.08 |
| 125 mg MDMA versus active placebo | RR 1.76 (0.44, 6.99) | 0.47 |
| 150 mg MDMA versus active placebo | RR 1.08 (0.12, 9.75) | 0.94 |
| **Anxiety within 7 days of session** |                                          |   |
| 125 mg MDMA versus inactive placebo | RR 1.24 (0.64, 2.41) | 0.53 |
| 75 mg MDMA versus active placebo | RR 1.25 (0.56, 2.77) | 0.58 |
| 100 mg MDMA versus active placebo | RR 2.67 (0.84, 8.46) | 0.10 |
| 125 mg MDMA versus active placebo | RR 1.76 (0.94, 3.28) | 0.08 |
| 125/150 mg MDMA versus active placebo | RR 1.66 (0.42, 6.56) | 0.47 |
| **Low mood in session**       |                                          |   |
| 125 mg MDMA versus inactive placebo | RR 1.33 (0.28, 6.44) | 0.72 |
| 75 mg MDMA versus active placebo | N/A | N/A |
| 100 mg MDMA versus active placebo | POR 10.31 (1.24, 85.66) | 0.03 |
| 125 mg MDMA versus active placebo | POR 4.70 (0.22, 101.04) | 0.32 |
| 125 mg MDMA versus active placebo | RR 1.41 (0.17, 11.46) | 0.75 |
| 150 mg MDMA versus active placebo | RR 0.67 (0.03, 14.35) | 0.80 |
| **Low mood within 7 days of session** |                                          |   |
| 125 mg MDMA versus inactive placebo | RR 0.83 (0.42, 1.65) | 0.60 |
| 75 mg MDMA versus active placebo | POR 0.09 (0.01, 1.10) | 0.06 |
| 100 mg MDMA versus active placebo | RR 2.00 (0.59, 6.79) | 0.27 |
| 125 mg MDMA versus active placebo | RR 1.12 (0.52, 2.40) | 0.66 |
| 125/150 mg MDMA versus active placebo | RR 1.01 (0.52, 1.97) | 0.98 |
| **Insomnia within 7 days of session** |                                          |   |
| 125 mg MDMA versus inactive placebo | RR 0.67 (0.34, 1.31) | 0.24 |
| 75 mg MDMA versus active placebo | RR 0.60 (0.23, 1.59) | 0.30 |
| 100 mg MDMA versus active placebo | RR 1.56 (0.65, 3.72) | 0.32 |
| 125 mg MDMA versus active placebo | RR 1.07 (0.65, 1.76) | 0.79 |
| 125/150 mg MDMA versus active placebo | RR 1.01 (0.52, 1.97) | 0.98 |

CI: confidence interval; POR: peto odds ratio; RR: risk ratio.
This study has several limitations. The comprehensive search strategy only identified four randomized trials that reported data from a relatively small number of participants. The sample sizes that were included in the trials were low. As numbers within a sample decrease, so the magnitude of chance variation within the sample increases, which may lead to errors of inference and comparison. Our results should, therefore, be treated with caution.

A further limitation is that outcome measures (such as BDI) are not reported consistently throughout all the papers. To address this, and to ensure that there is adequate evidence in order to inform clinical practice, a core outcome set for use in all future PTSD trials would be helpful. This might include measures such as the BDI, PHQ-9 and Generalised Anxiety Disorder 7 score (GAD-7), intervals at which the CAPS IV should be measured (1 month, 2 months, 12 months), and a set of ‘adverse events of special interest’, occurring up to 12 months after treatment.

The doses used in these studies were large enough to produce noticeable psychoactive and physical effects. This implies

| Table 4. Physical adverse events across all studies (active and inactive placebo). |
|---------------------------------|---------------------------------|----------------|
|                                  | Outcomes and outcome measures   | Effect size estimate (RR or POR (95% CI)) |
| **Jaw Clenching in session**    |                                 | p            |
| 125 mg MDMA versus inactive placebo | RR 4.22 (1.49, 11.95)           | 0.007        |
| 75 mg MDMA versus active placebo  | POR 13.46 (1.44, 125.80)        | 0.02         |
| 100 mg MDMA versus active placebo | RR 1.67 (0.47, 5.96)           | 0.43         |
| 125 mg MDMA versus active placebo | POR 7.34 (1.98, 27.71)         | 0.003        |
| 125 mg MDMA versus active placebo | POR 4.08 (1.04, 15.99)         | 0.04         |
| 150 mg MDMA versus active placebo | RR 8.67 (1.21, 61.91)          | 0.03         |
| **Headache in session**         |                                 | p            |
| 125 mg MDMA versus inactive placebo | RR 1.04 (0.60, 1.80)           | 0.90         |
| 75 mg MDMA versus active placebo  | RR 1.00 (0.52, 1.94)           | 1.00         |
| 100 mg MDMA versus active placebo | RR 0.67 (0.26, 1.68)           | 0.39         |
| 125 mg MDMA versus active placebo | RR 0.66 (0.38, 1.14)           | 0.14         |
| 125 mg MDMA versus active placebo | RR 0.77 (0.33, 1.80)           | 0.55         |
| 150 mg MDMA versus active placebo | RR 0.87 (0.23, 3.26)           | 0.83         |
| **Headache within 7 days of session** |                                 | p            |
| 125 mg MDMA versus inactive placebo | RR 1.00 (0.33, 2.99)           | 1.00         |
| 75 mg MDMA versus active placebo  | RR 1.50 (0.35, 6.40)           | 0.58         |
| 100 mg MDMA versus active placebo | RR 0.50 (0.17, 1.48)           | 0.21         |
| 125 mg MDMA versus active placebo | RR 1.04 (0.51, 2.14)           | 0.92         |
| 150 mg MDMA versus active placebo | RR 0.76 (0.28, 2.01)           | 0.58         |
| **Nausea in Session**           |                                 | p            |
| 125 mg MDMA versus inactive placebo | RR 4.00 (1.03, 15.53)          | 0.05         |
| 75 mg MDMA versus active placebo  | RR 1.75 (0.48, 6.43)           | 0.40         |
| 100 mg MDMA versus active placebo | RR 0.30 (0.05, 1.83)           | 0.66         |
| 125 mg MDMA versus active placebo | RR 1.05 (0.24, 4.59)           | 0.94         |
| 150 mg MDMA versus active placebo | RR 2.17 (0.39, 11.92)          | 0.37         |
| **Lack of appetite within 7 days of session** | | p            |
| 125 mg MDMA versus inactive placebo | POR 8.14 (1.82, 36.33)        | 0.006        |
| 75 mg MDMA versus active placebo  | RR 1.75 (0.48, 6.43)           | 0.40         |
| 100 mg MDMA versus active placebo | RR 0.76 (0.05, 8.73)           | 0.40         |
| 125 mg MDMA versus active placebo | RR 2.17 (0.72, 6.21)           | 0.18         |
| 125/150 mg MDMA versus active placebo | RR 0.42 (0.16, 1.11)           | 0.08         |

CI: confidence interval; POR: peto odds ratio; RR: risk ratio.

Figure 8. Beck’s depression index scores in MDMA-assisted psychotherapy versus psychotherapy with active placebo: 100 mg MDMA versus active placebo.
suboptimal blinding of both participants and investigators in all of the studies included. This failure of the blind is supported by evidence from Mithoefer et al. (Mithoefer et al., 2010), where 95% of participants were able to guess which treatment arm they were in after receiving a 125 mg dose of MDMA. Therapists in this trial were also able to identify which treatment arm the patients were on with complete accuracy.

**Interpretation**

MDMA-assisted psychotherapy has been shown to have a largely favourable safety profile and have some effect in reducing CAPS-IV scores in participants with treatment-resistant PTSD in phase 2 trials. Ongoing phase 3 trials will provide further evidence on whether efficacy and safety parameters are sufficiently favourable to warrant an application for a marketing authorisation. Certain symptomatology clusters or trauma aetiologies (such as combat or domestic violence) may be more amenable to MDMA-assisted psychotherapy. Sub-group analysis may identify those most likely to respond, although this has proven challenging with other treatments (Sullivan and Neria, 2009).

This meta-analysis adds to a literature that shows that MDMA-assisted psychotherapy may have a role in the reduction of symptoms of PTSD, although our results also highlight that MDMA-assisted psychotherapy may have only limited effects on depressive symptoms. Our analysis shows, overall, that patients undergoing MDMA-assisted psychotherapy did not experience an increase in reported depressive or anxious episodes in the week following the session, in either the active or inactive arms of the trial.

Some participants experienced a transient increase in suicidal ideation and one participant was admitted to hospital because of suicidal thoughts 13 days after their second 30mg session (Mithoefer et al., 2018). Transient increases in suicidal ideation were more common in the active MDMA group, although no suicidal behaviour was reported (Mithoefer et al., 2019). Larger trials will be required to investigate this phenomenon more definitively. To an extent, the emergence of low mood and suicidal ideation may be interpreted as a necessary part of engaging with and re-processing long-avoided traumatic experiences. On the other hand, such processes could be understood as a biological effect of MDMA itself. The truth likely lies in-between, bringing the skilled management of such processes by the attending therapist and psychiatrist into necessary focus. This treatment is not just drug, nor is it just psychotherapy. In this sense, it is rather more complex and ‘real world’ than current paradigms of clinical trial design are able to interrogate.

Part of the purpose of phase 2 trials is dose finding. Doses of MDMA as low as 75mg had a significant effect on the symptoms of TR-PTSD when compared to active placebo and were as effective as 125mg. Some somatic side effects were more prevalent at lower doses of MDMA; however, our analysis detected no significant difference. At higher doses, some physical adverse events such as jaw clenching were significantly more prevalent in the experimental group and followed a dose-response relationship, suggesting a causative aetiology. On this basis it would be difficult to justify increased doses of MDMA (Brun et al., 2012; Kalant, 2001; Morefield et al., 2011), however it may be fruitful to examine the effects of lower doses, particularly in individuals who otherwise appear sensitive to the effects of MDMA (Bouso et al., 2008).

**Conclusion**

In summary, this meta-analysis has demonstrated that use of MDMA-assisted psychotherapy is associated with significant decreases in CAPS-IV scores but little effect in BDI in subjects with TR-PTSD, indicating a potential therapeutic benefit with minimal physical and neurocognitive risk. Care must be taken when interpreting these results due to the small sample sizes involved and data from larger scale studies are needed to provide further evidence on whether efficacy and safety parameters are sufficiently favourable to warrant use in a clinical setting.

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**Contributorship**

Study concept and design: BJGI, DJL. Acquisition of data: BJGI, DJL. Analysis and interpretation of data: BJGI, DJL, DCH, KS and JMND. Drafting of the manuscript: BJGI, DJL, ATL. Critical revision of the manuscript for important intellectual content: BJGI, DJL, ATL, KS, DCH, JMND, LAJ, JR. Study supervision: JMND, LAJ and JR.

**Declaration of conflicting interests**

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**Supplemental material**

Supplemental material for this article is available online.

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