Optimizing Active Placebo Dose for MDMA randomized controlled trials for Post-Traumatic Stress Disorder

Lauren M. Ranney[1], Brian J. Gully[1], Christy Capone[1], Erica Eaton[1], Robert M. Swift[1], Carolina L. Haass-Koffler[1]

[1]Center for Alcohol and Addiction Studies, School of Public Health, Brown University, RI

Overview

In light of the U.S. Food and Drug Administration (FDA) 10-1 decision to not approve MDMA-Assisted Therapy for Post-Traumatic Stress Disorder (PTSD) due to concerns over lack of effective blinding, we aim to address a specific request to optimize an active placebo dose for future MDMA randomized controlled trials.

Background

- The empathogen 3,4-methylenedioxymethamphetamine (MDMA) is a psychoactive substance that has been studied in recent years in conjunction with assisted therapy (AT) to treat psychiatric disorders.
- Within many studies utilizing MDMA-AT, blinding procedures have served as a challenge in compromising outcomes.
- Transient increases in blood pressure in the MDMA condition were indicative of patient assignment, potentially compromising blinding.
- The goal of this study was to optimize low doses of MDMA to be utilized as an active placebo in future MDMA randomized controlled trials (RCT).

Study Design

- We first conducted a scoping review of published RCTs that used different doses of MDMA in conjunction with therapy on patients with post-traumatic stress disorder (PTSD) and healthy volunteers.
- Inclusion:
  - RCT with low dose MDMA (30-60 mg)
  - RCT with hemodynamic response
- Exclusion:
  - RCT with lowest dose MDMA above 60 mg
- We extracted data on systolic (SBP) and diastolic (DBP) blood pressure to monitor the change of multiple doses of MDMA from baseline.
- Data were analyzed to determine which dose was required to increase by 10 mmHg for SBP and 5 mmHg for DBP.

Results

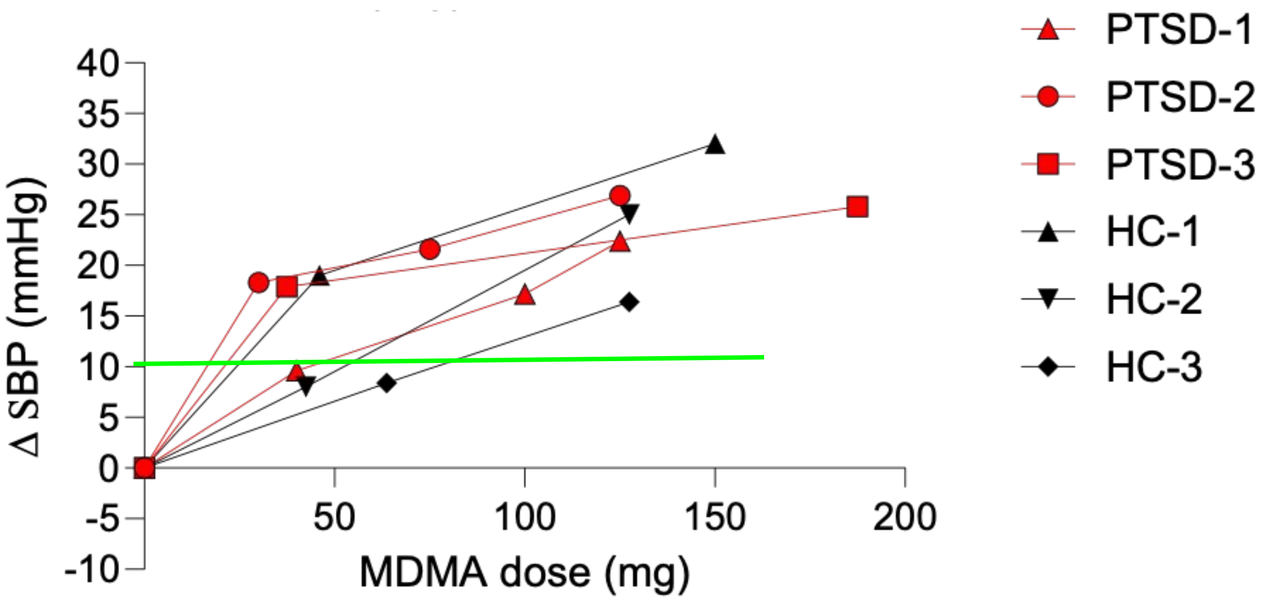

Figure 1. MDMA dose (mg) on SBP. 40 mg of MDMA is sufficient to increase SBP by 10 mmHg in patients with PTSD (*n*= 66). Healthy controls (*n*= 81) require doses up to 75 mg to increase by 10 mmHg.

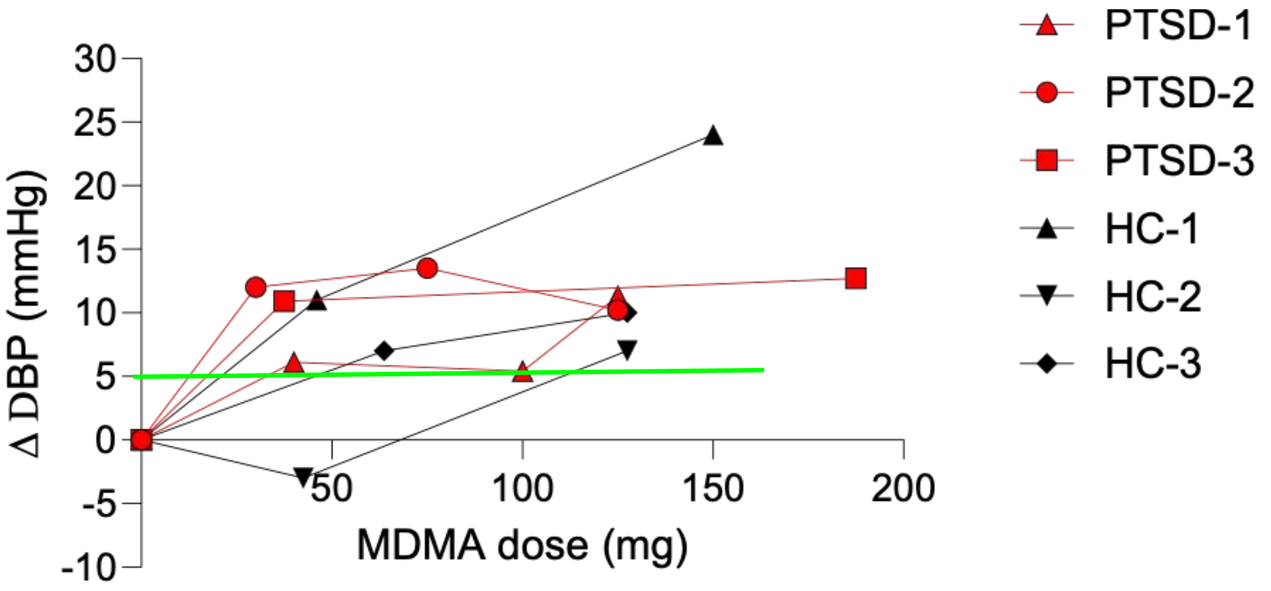

Figure 2. MDMA dose (mg) on DBP. 40 mg of MDMA is sufficient to increase DBP by 5 mmHg in patients with PTSD (*n*= 66). Healthy controls (*n*= 81) require doses up to 120 mg to increase by 5 mmHg.

- Six studies were included that collected data on changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP).
- Three studies consisted of individuals with PTSD (*n*=66) and three of healthy volunteers (*n*=81) with prior MDMA use.
- All studies showed a dose-response increase on hemodynamics parameters after MDMA administration.
- In individuals with PTSD, doses between 30-40 mg were sufficient to increase SBP above 10 mmHg. In healthy volunteers, doses between 38-75 were needed to increase SBP by 10 mmHg.
- In individuals with PTSD, doses between 15-38 mg were sufficient to increase DBP above 5 mmHg. In healthy volunteers, doses between 37.5-120 mg were needed to increase DBP above 5 mmHg.

Conclusion

- These findings indicate that low-dose MDMA (40 mg) can serve as an active placebo for future RCTs examining MDMA-AT in patients with PTSD by transiently increasing blood pressure and improving the integrity of the blinding procedures for patients, therapists, and clinicians.

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