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Publication Date

2022-04-01

DOI

10.1016/j.drugalcdep.2022.109356

Peer reviewed

HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2022 December 14.

Published in final edited form as:

Drug Alcohol Depend. 2022 April 01; 233: 109356. doi:10.1016/j.drugalcdep.2022.109356.

THE EFFECTS OF MDMA-ASSISTED THERAPY ON ALCOHOL AND SUBSTANCE USE IN A PHASE 3 TRIAL FOR TREATMENT OF SEVERE PTSD

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Abstract

Background—Post-traumatic stress disorder (PTSD) is commonly associated with alcohol and substance use disorders (ASUD). A randomized, placebo-controlled, phase 3 trial demonstrated the safety and efficacy of MDMA-assisted therapy (MDMA-AT) for the treatment of severe PTSD. This analysis explores patterns of alcohol and substance use in patients receiving MDMA-AT compared to placebo plus therapy (Placebo+Therapy).

Methods—Adult participants with severe PTSD (n = 90) were randomized to three blinded trauma-focused therapy sessions with either MDMA-AT or Placebo+Therapy. Eligible participants met DSM-5 criteria for severe PTSD and could meet criteria for mild (current) or moderate (early remission) alcohol or cannabis use disorder; other SUDs were excluded. The current analyses examined outcomes on standardized measures of hazardous alcohol (i.e., Alcohol Use Disorder Identification Test; AUDIT) and drug (i.e., Drug Use Disorder Identification Test; DUDIT) use at baseline prior to randomization and at study termination.

Results—There were no treatment group differences in AUDIT or DUDIT scores at baseline. Compared to Placebo+therapy, MDMA-AT was associated with a significantly greater reduction in mean (SD) AUDIT change scores (Δ = −1.02 (3.52) as compared to placebo (Δ = 0.40 (2.70),

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CRediT authorship contribution statement

CRN and JBW had full access to the study data and take responsibility for the integrity of those data and accuracy of the data analysis. BY-K, AE, and RD conceived and designed the clinical trial. AE and BY-K carried out sponsor oversight of data collection in the clinical trial. JBW carried out statistical analysis and interpretation of data in the present study. CRN, JBW, AC, JM, SK, and RB drafted the paper. All authors contributed to the critical review and final version of the manuscript.

F (80, 1) = 4.20, p = 0.0436; Hedge's g= .45). Changes in DUDIT scores were not significantly different between treatment groups.

Conclusions—MDMA-AT for severe PTSD may also lead to subclinical improvements in alcohol use. MDMA-AT does not appear to increase risk of illicit drug use. These data provide preliminary evidence to support the development of MDMA-AT as an integrated treatment for co-occurring PTSD and ASUD.

Keywords

MDMA; post-traumatic stress disorder; alcohol use; substance use

1. INTRODUCTION

Post-traumatic stress disorder (PTSD) has a lifetime prevalence of 7–8% in the United States and is strongly associated with the co-occurrence of alcohol and substance use disorders (ASUDs) with estimates between 17% and 46% (McCauley et al., 2012). This co-occurrence is often attributed to self-medication, since PTSD symptoms typically precede the onset of substance use (Hawn et al., 2020; Khantzian 1997; Saladin et al., 1995) and patients report PTSD-symptom relief as rationale for substance use (Flanagan et al., 2016). However, there also may be a more nuanced interaction given the evidence for active ASUDs increasing risk of trauma and reciprocal reinforcement between the disorders (Hien et al., 2021, Logrip et al., 2012). Importantly, the individual impact of PTSD and ASUD on health, psychosocial functioning, and service utilization is only further compounded when these conditions are comorbid (Boudreaux and Murdoch 2019; Bowe and Rosenheck, 2015; Tate et al., 2007).

3,4-Methylenedioxymethamphetamine (MDMA) in combination with therapy was found to be efficacious and safe in a multi-site, randomized, placebo-controlled, Phase 3 trial, demonstrating a substantial decrease in symptoms associated with severe PTSD (Mitchell et al., 2021). The overall rate for a clinically significant response for the MDMA-assisted therapy (MDMA-AT) was 88% (versus 60% for Placebo+Therapy), with 67% in the MDMA-AT arm no longer meeting criteria for clinical diagnosis of PTSD by study termination. Outcome measures of functional impairment and depression symptoms showed a robust decrease, indicating the potential for generalized effects of MDMA-AT on relevant comorbidities and clinical sequelae. The aim of the current analysis was to explore additional outcomes associated with MDMA-AT by examining differential changes in measures of alcohol and substance use from baseline to study termination.

2. METHODS

2.1. Study design

The present analysis assessed exploratory data on alcohol and substance use from a two-arm, randomized, double-blind, placebo-controlled study of the efficacy and safety of MDMA-assisted therapy for PTSD. The study was conducted across 15 study sites in the US, Canada, and Israel with the ethics approval of local institutional review boards. The complete study methods have been described in Mitchell et. al (2021), and the study protocol is available at maps.org/mapp1.

2.2. Participants

Participants who provisionally met criteria for PTSD as assessed by the PTSD Checklist per DSM-5 (PCL-5) were recruited and screened for eligibility after providing written informed consent. Participants were required to have PTSD symptoms for at least 6 months and a Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) Total Severity Score of 35 or greater at baseline. Participants were assessed for psychiatric disorders and ASUDs in the last 12 months via the Mini-International Neuropsychiatric Interview (MINI). Exclusion criteria included, but were not limited to, current primary psychotic disorder, bipolar disorder 1, or dissociative identity disorder, and any clinically significant condition for which an acute increase in heart rate or blood pressure might pose a significant clinical concern. Participants were permitted to have current mild alcohol or cannabis use disorder, or moderate (meets 4 or 5 of the 11 diagnostic criteria per DSM-5) alcohol or cannabis use disorder, in early remission in the 3 months prior to enrollment. Participants were excluded for any other active substance use disorder at any severity within the 12 months prior to enrollment. A history of any ASUD was permitted more than 12 months prior to enrollment. Full inclusion and exclusion criteria are described in the study protocol (maps.org/mapp1).

2.3. Intervention

Following safety and eligibility screening and taper from psychiatric medications, participants underwent three 90-minute preparatory therapy sessions. Participants who met eligibility criteria (CAPS-5 score ≥ 35 as assessed by blinded independent raters), were randomized to MDMA-AT or Placebo+Therapy for the experimental sessions. In each of the 3 8-hour experimental sessions, participants received a divided-dose of MDMA or placebo, with an initial dose followed by a supplemental dose 1.5–2 h later (80 + 40 mg in the first session and escalated to 120 + 60 mg for the second and third sessions). The supplemental doses and the dose escalation could be withheld if tolerability issues emerged with the initial dose or if declined by the participant. Each experimental session was followed by 3 90-minute therapy sessions spaced 1 week apart over 3–4 weeks to allow the participants to understand and integrate their experiences into their lives. Participants, site staff, and the sponsor were blinded to the treatment arm until they were informed after database lock.

2.4. Outcome measures

The present analysis examined outcome measures related to alcohol and substance use. The Alcohol Use Identification Test (AUDIT) is a 10-question self-report measure designed as a screening instrument for hazardous alcohol consumption that may be indicative of alcohol use disorder or at-risk alcohol use (Saunders et al., 1993). This measure assesses domains of alcohol consumption, drinking behavior, and alcohol-related problems over the last 12 months. The Drug Use Identification Test (DUDIT) was developed as a parallel instrument to the AUDIT and is a 11-item self-report measure designed to identify the patterns of substance use and drug-related problems (Berman et al., 2005). The DUDIT assesses domains relating to frequent and heavy use, craving, relationship to drug use, and harmful use. Though the AUDIT and DUDIT are not diagnostic assessments, they have demonstrated validity as screening measures across various populations (Higgins-Biddle and Babor, 2018, Hildebrand, 2015, Nadkarni et al., 2019). AUDIT and DUDIT were assessed

at baseline with standard instructions for a 12-month lookback and at study termination with altered instructions to base responses on the time period since the end of treatment. Other measures assessed throughout the study included: PTSD symptom severity (CAPS-5), clinician rated functional impairment (an adapted Sheehan Disability Scale (SDS) for PTSD; Sheehan et al., 1996), self-reported depressive symptoms (Beck Depression Inventory II (BDI-II); Beck et al., 1996), and clinician rated suicidality (a modified Columbia Suicide Severity Rating Scale (C-SSRS); Posner et al., 2011).

2.5. Statistical methods

Descriptive analyses were performed on all demographic, baseline, and outcome variables and reported as mean (SD). MDMA-AT vs. Placebo+Therapy group means were compared using t-tests and proportions were compared using chi-square tests. Student's t-tests compared between-group change scores from baseline to study termination among MDMA-AT and Placebo+Therapy groups for AUDIT and DUDIT scores. Models examined treatment group differences in AUDIT and DUDIT change scores and results from both unadjusted and adjusted models for baseline values were reported. Pearson's correlations tested linear relationships between AUDIT change scores with baseline and change in CAPS-5, SDS, and BDI-II scores. Hedge's g effect sizes were calculated for statistically significant treatment effects. All analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, North Carolina).

3. RESULTS

3.1. Sample characteristics

Participants were recruited from 7 November 2018–26 May 2020 and a total of 90 participants were randomized and received either MDMA or Placebo. Three participants in the MDMA and 4 in the Placebo group withdrew from the study, leaving a total of 82 participants that completed both baseline and study termination assessments for the AUDIT or DUDIT. Participants with complete data were used in the present analysis. More details on the study demographics and baseline characteristics were previously published (Mitchell et al., 2021).

Table 1 provides a summary of baseline variables relevant to the present study. The overall study sample consisted of participants that were mostly female (64.6%), White (80.3%), non-Hispanic or Latino (92.7%), and had a mean age of 41.4 (12.22) years. Mean baseline CAPS-5 total severity score was 43.8 (6.00) indicating severe PTSD, mean BDI-II score was 32.3 (13.01) indicating severe depression, and mean modified SDS score was 7.06 (1.89) which based on the modified average, a score greater than 5 indicates significant functional impairment in work, social and family life. A total of 21 (25.61%) participants reported past alcohol use disorders and no current alcohol use disorder; 14 (17.07%) reported past substance use disorders, and 2 (2.50%) Placebo participants reported current mild cannabis use disorder. At baseline, 69 (84.2%) participants had an AUDIT score ≥ 1 and 48 (58.5%) had a DUDIT score ≥ 1 to indicate any use of alcohol/substances. There were no group differences between MDMA-AT vs. Placebo+Therapy treatment groups on demographic and baseline characteristics, AUDIT scores, or DUDIT scores.

3.2. AUDIT and DUDIT scores

The MDMA-AT group compared to Placebo+Therapy had a greater statistically significant reduction (improvement) in AUDIT scores from baseline to study termination [F (80, 1) = 4.20, p = 0.0436; Hedge's g = .45] (Fig. 1a). There was no statistically significant difference in AUDIT scores at baseline between treatment groups (p = .10) and AUDIT change scores between treatments were no longer statistically significant after adjusting for baseline AUDIT (p = 0.52). Mean AUDIT scores for MDMA group were 4.09 (4.16) at baseline and 3.24 (3.36) at study termination (p = .30, Hedge's g = .22), with a change score of – 1.02 (3.52); and for Placebo+Therapy were 2.80 (3.18) at baseline and 3.23 (3.65) at study termination (p = .57 Hedge's g=.13), with a change score of 0.40 (2.70). Mean DUDIT scores for MDMA group were 2.70 (4.31) at baseline and 1.33 (3.14) at study termination (p = .10), Hedge's g = .36); and for Placebo+Therapy were 3.45 (4.46) at baseline and 2.70 (6.33) at study termination (p = .53), Hedge's g = .14). Change in mean DUDIT scores between MDMA-AT vs. Placebo+Therapy were not statistically different at study termination [− 1.36 (3.00) vs. − 0.78, (5.39); F (80, 1) = 0.37; p = 0.5452; Hedge's g = .13, 95% CI = 0.013, 0.89] (Fig. 1b). There were no statistically significant linear correlations between AUDIT change scores with baseline and change in CAPS-5, BDI-II, and SDS scores in the overall sample. A significant correlation between AUDIT change scores and baseline CAPS-5 scores in the MDMA group (r = .32, p = .04) was observed (data not shown).

4. DISCUSSION

The current analyses found that MDMA-AT, compared to Placebo + Therapy, was associated with a statistically significant decrease in alcohol use from baseline to termination among Phase 3 study participants with severe PTSD and no incidence of current AUD (as per MINI). Although the treatment effect in AUDIT change scores was no longer significant after adjusting for baseline, there was no significant treatment group differences at baseline. Change in AUDIT score was independent of depression and functional impairment but was positively associated with baseline PTSD severity within the MDMA-AT group. While preliminary, these findings suggest that the reduction in alcohol use and alcohol-related consequences may be uniquely associated with MDMA-AT.

The primary limitation of this analysis was the absence of more severe levels of current ASUD in which no participant with even mild AUD was recruited into the study, despite being permitted. In effect, the narrow sample distribution of AUDIT scores limited the potential to detect a statistically significant measurable change from baseline and the opportunity to examine cut-off and factor scores (i.e., consumption, consequences, and dependence) that could have served as a more sensitive measure of risk (Doyle et al., 2007, Nadkarni et al., 2019). The non-AUD sample characteristics and exploratory nature of this study also limits clinical interpretation of our findings.

The absence of group differences in DUDIT change scores may also be related to the absence of current SUD diagnosis at baseline and potential heterogeneity in the type of substance use reported. Mean baseline DUDIT scores (2.51 (3.39), range 1–15) were slightly above some validated cut-off thresholds for females in the total sample (Hildebrand

et al., 2015) suggesting the possible prevalence of increased risk of problematic drug use in this sample.

Importantly, it is encouraging that the current MDMA-AT treatment protocol did not demonstrate increased risk of substance use, abuse, or dependence, or increased MDMA use during and 2 months following treatment. Long-term follow-up data are being collected from these Phase 3 participants which will include changes in AUDIT and DUDIT as well as self-reported MDMA craving and use post study at least 12 months after the parent study and will be published separately. Long-term follow-up after previous Phase 2 MDMA-AT trials (Jerome et al., 2020) showed limited abuse potential from the use of MDMA in clinical settings involving comprehensive eligibility assessment, use in a controlled environment, and consistent therapeutic support.

A growing body of research on integrated psychotherapeutic treatments for both PTSD and ASUD, have shown to be safe, well-tolerated, and lead to reductions in severity of PTSD symptoms and substance use (Flanagan et al., 2016, Najavits and Hien, 2013). Thus, in light of the current findings and promising outcomes from an open-label of MDMA-assisted therapy for primary AUD (Sessa et al., 2021), future studies investigating the application of MDMA-AT as an integrated treatment for co-occurring AUD and PTSD, or AUD alone, may be warranted.

Acknowledgments

The authors would like to express appreciation to all the participants and research staff who made this work possible. The clinical trial was sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), a 501(c)(3) nonprofit organization. MAPS provided the MDMA and fully funded this study from private and foundation donations. MAPS Public Benefit Corporation (MAPS PBC), a wholly owned subsidiary of MAPS, was the trial organizer.

Role of funding sources

The clinical trial was sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), a 501(c)(3) non-profit organization. MAPS provided the MDMA and fully funded this study from private donations. MAPS Public Benefit Corporation (MAPS PBC), wholly owned by MAPS, was the trial organizer.

Declaration of Competing Interest

JBW, AC, and AE received salary support for full-time employment with MAPS PBC. BY-K and RD received salary support for full-time employment with MAPS. CRN, JM, and SK received funding from MAPS PBC during the conduct of the current study and other studies. CRN also receives funding for contract work as an MDMA-assisted therapy trainer.

REFERENCES

Beck AT, Steer RA, Brown GK, 1996. BDI-II: Beck Depression Inventory Manual, second ed. Psychological Corporation, San Antonio, TX.

Berman AH, Bergman H, Palmstierna T, Schlyter F, 2005. Evaluation of the drug use disorders identification test (DUDIT) in criminal justice and detoxification settings and in a Swedish population sample. Eur. Addict. Res 11 (1), 22–31. 10.1159/000081413. [PubMed: 15608468]

Bowe A, Rosenheck R, 2015. PTSD and substance use disorder among veterans: characteristics, service utilization and pharmacotherapy. J. Dual Diagn 11 (1), 22–32. 10.1080/15504263.2014.989653. [PubMed: 25513763]

Boudreaux MH, Murdoch M, 2019. Association of Comorbid Substance Use Disorders and PTSD on Later Symptom Severity, Functioning, and Economic Outcomes Among Veterans Applying for Department of Veterans Affairs PTSD Disability Benefits: A Retrospective Cohort Study. PsyArXiv. 10.31234/osf.io/eavj6.

Doyle SR, Donovan DM, Kivlahan DR, 2007. The factor structure of the alcohol use disorders identification test (AUDIT). J. Stud. Alcohol Drugs 68 (3), 474–479. 10.15288/jsad.2007.68.474. [PubMed: 17446988]

Flanagan JC, Korte KJ, Killeen TK, Back SE, 2016. Concurrent treatment of substance use and PTSD. Curr. Psychiatry Rep 18 (8), 1–9. 10.1007/s11920-016-0709-y. [PubMed: 26685903]

Hawn SE, Cusack SE, Amstadter AB, 2020. A systematic review of the self-medication hypothesis in the context of posttraumatic stress disorder and comorbid problematic alcohol use. J. Trauma Stress. 33 (5), 699–708. 10.1002/jts.22521. [PubMed: 32516487]

Hien DA, L'opez-Castro T, Fitzpatrick S, Ruglass LM, Fertuck EA, Melara R,2021. A unifying translational framework to advance treatment research for comorbid PTSD and substance use disorders. Neurosci. Biobehav. Rev 127, 779–794 doi: 10.1016. [PubMed: 34062208]

Higgins-Biddle JC, Babor TF, 2018. A review of the alcohol use disorders identification test (AUDIT), AUDIT-C, and USAUDIT for screening in the United States: past issues and future directions. Am. J. Drug Alcohol Abus 44 (6), 578–586. 10.1080/00952990.2018.1456545.

Hildebrand M, 2015. The psychometric properties of the drug use disorders identification test (DUDIT): a review of recent research. J. Subst. Abus. Treat 53, 52–59. 10.1016/j.jsat.2015.01.008.

Jerome L, Feduccia AA, Wang JB, Hamilton S, Yazar-Klosinski B, Emerson A, Mithoefer MC, Doblin R, 2020. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. Psychopharmacology 237 (8), 2485–2497. 10.1007/s00213-020-05548-2. [PubMed: 32500209]

Khantzian EJ, 1997. The self-medication hypothesis of substance use disorders: A reconsideration and recent applications. Harvard review of psychiatry 4 (5), 231–244. [PubMed: 9385000]

Logrip ML, Zorrilla EP, Koob GF, 2012. Stress modulation of drug selfadministration: implications for addiction comorbidity with post-traumatic stress disorder. Neuropharmacology 62 (2), 552–564. 10.1016/j.neuropharm.2011.07.007. [PubMed: 21782834]

McCauley JL, Killeen T, Gros DF, Brady KT, Back SE, 2012. Posttraumatic stress disorder and co-occurring substance use disorders: Advances in assessment and treatment. Clin. Psychol.: Sci. Pract 19 (3), 283.

Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, Ot'alora GM, Garas W, Paleos C, Gorman I, Nicholas C,Mithoefer M, Carlin S, Poulter B, Mithoefer A, Quevedo S, Wells G, Klaire SS, van der Kolk B, Tzarfaty K, Amiaz R, Worthy R, Shannon S, Woolley JD, Marta C, Gelfand Y, Hapke E, Amar S, Wallach Y, Brown R, Hamilton S, Wang JB, Coker A, Matthews R, de Boer A, Yazar-Klosinski B, Emerson A, Doblin R, 2021. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. Nat. Med 27 (6), 1025–1033. 10.1038/s41591-021-01336-3. [PubMed: 33972795]

Nadkarni A, Garber A, Costa S, Wood S, Kumar S, MacKinnon N, Ibrahim M, Velleman R, Bhatia U, Fernandes G, Weobong B, Rane A, 2019. Auditing the AUDIT: a systematic review of cut-off scores for the alcohol use disorders identification test (AUDIT) in low-and middle-income countries. Drug Alcohol Depend. (202), 123–133. 10.1016/j.drugalcdep.2019.04.031. [PubMed: 31349205]

Najavits LM, Hien D, 2013. Helping vulnerable populations: a comprehensive review of the treatment outcome literature on substance use disorder and PTSD. J. Clin. Psychol 69 (5), 433–479. [PubMed: 23592045]

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ, 2011. The Columbia-suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am. J. Psychiatry 168 (12), 1266–1277. 10.1176/appi.ajp.2011.10111704. [PubMed: 22193671]

Saladin ME, Brady KT, Dansky BS, Kilpatrick DG, 1995. Understanding comorbidity between PTSD and substance use disorder: two preliminary investigations. Addict. Behav 20, 643–655. 10.1016/0306-4603(95)00024-7. [PubMed: 8712061]

Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M, 1993. Development of the alcohol use disorders identification test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption–II. Addiction 88 (6), 791–804. 10.1111/j.1360-0443.1993.tb02093.x. [PubMed: 8329970]

Sessa B, Higbed L, O'Brien S, Durant C, Sakal C, Titheradge D, Williams TM, Rose-Morris A, Brew-Girard E, Burrows S, Wiseman C, Wilson S, Rickard J, Nutt DJ, 2021. First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. J. Psychopharmacol 35 (4), 375–383. 10.1177/0269881121991792. Epub 2021 Feb 18. [PubMed: 33601929]

Sheehan DV, Harnett-Sheehan K, Raj BA, 1996. The measurement of disability. Int Clin. Psychopharmacol 11 (Suppl 3), 89–95.

Tate SR, Norman SB, McQuaid JR, Brown SA, 2007. Health problems of substance-dependent veterans with and those without trauma history. J. Subst. Abus. Treat 33 (1), 25–32.

HIGHLIGHTS

- A phase 3 trial demonstrated the safety and efficacy of MDMA-assisted therapy (MDMA-AT) for the treatment of severe PTSD.
- Participants met DSM-5 criteria for severe PTSD and were permitted to have current mild alcohol or cannabis use disorder.
- Outcomes on standardized measures of hazardous alcohol and substance use at baseline and at study termination were examined.
- Compared to Placebo+Therapy, MDMA-AT was associated with greater decreases in alcohol consumption and risk for hazardous use.
- MDMA-AT was not associated with an increased risk for illicit substance use.

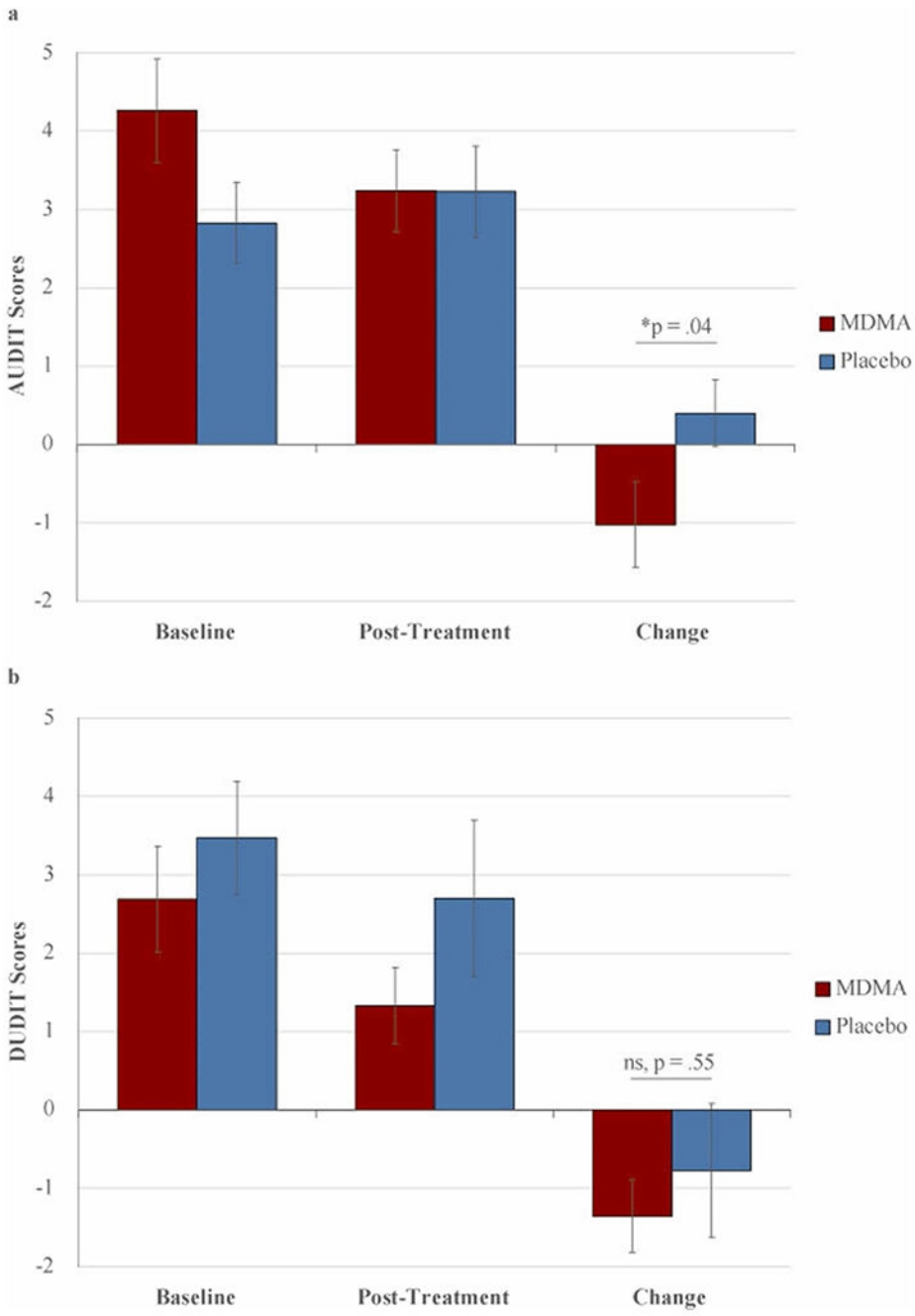

Figure 1.

a. Alcohol use disorder identification test (AUDIT) scores by treatment group, depicted as mean (SEM). Total scores range from 0 to 40. P-value tested treatment group differences for LSMEANS change scores that adjusted for unequal sample sizes,

b. Drug Use Disorder Identification Test (DUDIT) Scores by treatment group depicted as mean (SEM). Total scores range from 0 to 44. P-value tested treatment group differences for LSMEANS change scores that adjusted for unequal sample sizes.

Table 1.

Demographics and baseline characteristics.

	MDMA-AT	Placebo+Therapy	Total sample
	(N = 42)	(N = 40)	(N = 82)
Age (years), mean (SD)	44.18 (13.10)	38.53 (10.64)	41.42 (12.22)
Sex, n (%)			
Male	18 (42.86%)	11 (27.50%)	29 (35.37%)
Female	24 (57.14%)	29 (72.50%)	53 (64.63%)
Ethnicity, n (%)			
Hispanic or Latino	3 (7.14%)	2 (5.00%)	5 (6.10%)
Not Hispanic or Latino	39 (92.86%)	37 (92.50%)	76 (92.68%)
Not reported	0	1 (2.50%)	1 (1.22%)
Race, n (%)			
American Indian or Alaska Native	3 (7.14%)	0	3 (3.70%)
Asian	0	5 (12.83%)	5 (6.17%)
Black or African American	0	2 (5.13%)	2 (2.47%)
White	37 (88.10%)	28 (71.79%)	66 (80.25%)
More than one	2 (4.76%)	4 (10.26%)	6 (7.41%)
Trauma History, n (%)			
Veteran status	10 (23.81%)	5 (12.50%)	15 (19.29%)
Served in combat area	6 (14.29%)	4 (10.00%)	10 (12.20%)
Multiple trauma (yes)	38 (90.48%)	36 (90.00%)	74 (90.24%)
Developmental trauma	37 (88.10%)	32 (80.00%)	69 (84.15%)
Alcohol Use Disorder[2], n (%)			
Past (yes)	13 (30.95%)	8 (20.00%)	21 (25.61%)
Current (yes)	0	0	0
Substance Use Disorder[2], n (%)			
Past (yes)	8 (19.05%)	6 (12.50%)	14 (17.07%)
Current (yes)	0	2 (5.00%)	2 (2.44%)
Baseline Measures[3]			
CAPS-5, mean (SD)	43.98 (6.15)	43.7 (5.85)	43.84 (5.97)
BDI-II, mean (SD)	30.60 (13.29)	34.03 (12.65)	32.27 (13.01)
SDS, mean (SD)	6.81 (2.11)	7.25 (1.58)	7.06 (1.89)
C-SSRS, Lifetime			
Suicidal Ideation, mean (SD)	3.10 (1.72)	2.98 (1.56)	3.04 (1.64)
Serious Suicidal Ideation, mean (SD)	12.74 (5.31)	12.35 (6.03)	12.55 (5.64)
Suicidal Behavior (yes), n (%)	15 (35.71%)	11 (27.50%)	26 (31.71%)
AUDIT, mean (SD)	4.26 (4.28)	2.83 (3.27)	3.56 (3.87)
0 Never, n (%)	5 (11.90%)	8 (20.00%)	13 (15.85%)
≥ 1 Any use, n (%)	37 (88.10%)	32 (80.00%)	69 (84.15%)
DUDIT, mean (SD)	2.69 (4.37)	3.48 (4.56)	3.07 (4.45)

	MDMA-AT	Placebo+Therapy	Total sample
0 Never, n (%)	17 (40.48%)	17 (42.50%)	34 (41.46%)
≥ 1 Any use, n (%)	25 (59.52%)	23 (57.50%)	48 (58.54%)

1. Means (SD) compared using t-tests or ANOVAs and proportions using overall chi-square tests

2. Measures derived from baseline medical history and the Mini-International Neuropsychiatric Interview

3. Abbreviations: CAPS-5 = Clinician Administered PTSD Scale for DSM-5; BDI-II = Beck Depression Inventory II (moderate depression = 21–30, severe depression = 31 or greater); SDS = Sheehan Disability Scale (5 or greater indicates significant functional impairment); C-SSRS = Columbia-Suicide Severity Rating Scale; AUDIT = Alcohol Use Disorders Identification Test; DUDIT = Drug Use Disorders Identification Test