MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder: Examining Ethnoracial Differences in Efficacy and Safety, and a Mixed-Methods Case Study of a Participant of Color

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MDMA-assisted psychotherapy was shown in previous clinical trials to be efficacious and safe for alleviating treatment-resistant posttraumatic stress disorder (PTSD). However, due to low ethnoracial diversity, the question remains as to whether ethnoracial minority participants would benefit similarly. Thus, in Study 1, ethnoracial differences in PTSD symptoms, secondary outcomes, and suicidality were examined for a multisite, open-label trial of MDMA-assisted psychotherapy. A total of 11 ethnoracial minority and 26 non-Hispanic White participants formed the modified intent-to-treat (ITT) set. General and generalized linear model analyses were used to test group differences. Correlational analyses were conducted to test relationships between changes in certain secondary outcomes/putative mechanisms of action and PTSD symptoms for the entire sample. Results indicated overall ethnoracial equivalence in efficacy and safety/suicidality, with majority large effect sizes in symptom improvement across groups. Ethnoracial minority participants seemed to self-report lower PTSD symptom reduction after the first dose, although this difference was erased after the second and third doses. Additionally, improved alexithymic tendencies, emotion regulation ability, and self-compassion were significantly correlated with reduced PTSD symptoms. These findings provided preliminary support for the efficacy and safety of MDMA-assisted psychotherapy for treating PTSD across ethnoracial groups, although more research needs to be conducted with larger, more diverse samples. In Study 2, a mixed-methods case study was conducted on an ethnoracial minority participant from the same open-label trial, to provide a culturally informed lens on recovery from PTSD in a participant of color with MDMA-assisted psychotherapy. A case profile was provided, documenting quantitative symptom improvement on all measures from Study 1. This was followed by an interpretative phenomenological analysis (IPA) of effects and mechanisms of action for this participant, based on integration session transcripts. Lastly, linguistic variables inherent within the participant’s transcripts were entered into exploratory correlational analysis with his PTSD symptom
scores. Results of IPA indicated recurrent themes related to: mechanisms of change; reduced PTSD symptoms; additional effects beyond PTSD symptom reduction; and navigating interpersonal relationships. Correlational findings indicated meaningful relationships between several linguistic variables (e.g., increased authenticity) and PTSD symptom reduction. Lastly, recommendations for diversifying ongoing MDMA-assisted psychotherapy trials were provided.
MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder: Examining Ethnoracial Differences in Efficacy and Safety, and a Mixed-Methods Case Study of a Participant of Color

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APPROVAL PAGE

Doctor of Philosophy Dissertation

MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder: Examining Ethnoracial Differences in Efficacy and Safety, and a Mixed-Methods Case Study of a Participant of Color

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1. Introduction

1.1. What is PTSD?

Posttraumatic stress disorder (PTSD) is characterized in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) by five main criteria (APA, 2013): (A) direct, indirect, or repeated exposure to a perceived life-threatening event or physical or sexual violence; (B) re-experiencing the trauma; (C) avoidance of internal and external trauma reminders; (D) persistently negative mood and distorted cognitions; and (E) increased arousal and exaggerated reactivity. PTSD tends to be chronic and debilitating, and is typically associated with severe impairment in occupational and social functioning (Smith, Schnurr, Rosenheck, & Salzer, 2005) and decreased overall quality of life (Pagotto et al., 2015). PTSD is also associated with significant mental health comorbidity (e.g., mood disorders, substance use disorders; Kessler, Chiu, Demler, Merikangas, & Walters, 2005), increased suicidality (LeBouthillier, McMillan, Thibodeau, & Asmundson, 2015; Rojas et al., 2017), and poor physical health (e.g., cardiovascular diseases, chronic pain; Sareen et al., 2007).

1.2. Stress, Trauma, and PTSD in Ethnoracial Minority Communities

It has been proposed that experiences of ethnoracial discrimination that individuals of color are at high risk for can be sufficiently traumatic to warrant inclusion as “Criterion A” for PTSD. For example, in a cross-sectional study, Pieterse, Carter, Evans, and Walter (2010) found that Asian and Black students reported experiencing more frequent ethnoracial discrimination than their non-Hispanic White counterparts. Additionally, after controlling for non-ethnoracial-specific life stress, perceived ethnoracial discrimination uniquely predicted trauma-related symptoms among Black students. In a longitudinal study with a sample of Mexican American adolescents, Flores, Tschann, Dimas, Pasch, and de Groat (2010) found that perceived ethnoracial discrimination uniquely predicted traumatic stress symptoms assessed six months later, after controlling for gender, age, and socioeconomic status. Further, in another longitudinal study of risk factors for PTSD symptoms in a
sample of Hispanic college students, Cheng and Mallinckrodt (2015) found that experiences of ethnoracial discrimination predicted PTSD symptoms one year later.

The prevalence and expression of PTSD symptoms may also vary by race or ethnicity in the United States. Specifically, there are racial/ethnic differences in traumatic exposure, development of PTSD, and treatment-seeking for PTSD in the United States. Indigenous peoples, as well as Black and Latinx individuals, tend to be at increased risk for PTSD, compared with non-Hispanic Whites (Alegría et al., 2013; Hall-Clark, Sawyer, Golik, & Asnaani, 2016; Kisely et al., 2017; Roberts, Gilman, Breslau, Breslau, & Koenen, 2011). In fact, in their umbrella review of risk factors for PTSD based on strength of evidence ranging from weak to convincing, Tortella-Feliu et al. (2019) found that being indigenous people of the Americas showed convincing evidence as a sociodemographic risk factor for PTSD. Additionally, compared with non-Hispanic Whites, African-Americans with PTSD may view the world as more threatening but demonstrate less heightened arousal (Williams, Jayawickreme, Sposato, & Foa, 2012). Hispanic Americans also tend to report more intense hypervigilance or flashbacks than non-Hispanic Whites (Marshall, Schell, & Miles, 2009).

Retention rates in clinical trials for psychological treatments for PTSD may also vary by participants’ race/ethnicity. While the literature is limited in this aspect, there is suggestive evidence that ethnoracial minority participants may drop out at higher rates than non-Hispanic White individuals in psychotherapy trials for PTSD (Lester, Artz, Resick, & Young-Xu, 2010; cf., Zoellner, Feeny, Fitzgibbons, & Foa, 1999). Interestingly, Lester et al. (2010) found no ethnoracial differences in efficacy for participants who completed these trials, similar to Zoellner et al.’s (1999) study. Other evidence suggests that African Americans may also mistrust research staff and/or be subject to racial discrimination in a therapeutic setting, thus negatively impacting retention in treatment studies (Alim, Charney, & Mellman, 2006). Lastly, in a naturalistic two-year follow-up study of African Americans in treatment for anxiety-related disorders, Benítez et al. (2014) found comparatively lower rates of recovery from PTSD (probability of 0.10) than previous longitudinal research with predominantly non-Hispanic White samples (e.g., probability of 0.18; Zlotnick et al., 2004). The researchers
attributed this difference to the co-occurrence of ongoing social stressors which impeded symptom alleviation among their African American sample.

1.3. What is MDMA?

In the search for innovative ways to treat PTSD, researchers have begun examining the viability of 3,4-methylenedioxymethamphetamine (MDMA). MDMA is the active ingredient of the street drug ecstasy, which the United States Drug Enforcement Administration has classified as a Schedule 1 illicit substance (i.e., highest penalty for recreational/illegal use, and strictly prohibited outside of research settings) (United States Drug Enforcement Agency, 2018). However, contrary to what may be suggested by its Schedule 1 status, there is strong evidence that MDMA can be used in a non-addictive manner and does not cause brain damage (Vizeli & Liechti, 2017), and is not significantly correlated with mental health problems in epidemiologic studies (Johansen & Krebs, 2015).

Neurochemically, MDMA is an entactogen/empathogen, promoting increases in the release and inhibited reuptake of serotonin (5-HT) and norepinephrine, alongside the possible release of the neuropeptide oxytocin (Meyer, 2013; Parrott, 2016), with users typically reporting significant increases in subjective feelings of trust, empathy, sociability, and connectedness to both their own internal emotional experiences, as well as with other individuals in the immediate setting (Greer & Tolbert, 1986). These prosocial effects, including other effects such as perceptual alterations, aesthetic effects, sexual arousal, happiness/euphoria, improved depressed mood, and positive appraisals of the drug, have been consistently observed across studies examining mostly healthy participants and recreational users (Dolder, Müller, Schmid, Borgwardt, & Liechti, 2018; Kirkpatrick et al., 2014; Sumnall, Cole, & Jerome, 2006), but also female polydrug users in a pharmacotherapeutic context (Kuypers et al., 2018).

1.4. MDMA-Assisted Psychotherapy for PTSD

Because of these established psychedelic properties, MDMA was studied, albeit mostly via non-scientifically rigorous methods, as a psychotherapeutic tool prior to its nationwide prohibition
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(for a historical review, see Grob, 2000). Fortunately, in the past two decades, there has been an immense resurgence of research interest in the promise of MDMA as an adjunct medication to psychotherapy for chronic mental health conditions, primarily spearheaded by the Multidisciplinary Association of Psychedelic Studies (MAPS). In 2017, MDMA-assisted psychotherapy was designated a ‘breakthrough therapy’ for treatment-resistant posttraumatic stress disorder (PTSD; i.e., that which has not responded to pharmacological and/or psychotherapeutic treatment) by the FDA (Burge, 2017). Currently, MDMA-assisted psychotherapy for treatment-resistant PTSD is in MAPS-sponsored Phase 3 trials (i.e., multiple sites within and outside of the United States).

In this particular treatment approach, MDMA is viewed as a catalyst that facilitates re-processing of past traumatic events and memories in a therapeutic way (similar to the goal of trauma reprocessing in prolonged exposure [PE]; Foa, Hembree, Rothbaum, & Rauch, 2019), without being overwhelmed by fear and anxiety related to these memories (Mithoefer, 2016). Notably, this treatment approach emphasizes having appropriate set and setting (e.g., intent and motivations for use; environment in which the dosing session will take place; instrumental music playlists with an ‘ascent-peak-descent/return’ structure) to maximize psychedelic-induced self-exploration (as pertaining to past traumas) and therapeutic gain (Barrett, Preller, & Kaelen, 2018; Barrett, Robbins, Smooke, Brown, & Griffiths, 2017; Carhart-Harris, Roseman et al., 2018; Haijen et al., 2018; Kaelen et al., 2018).

Essentially, the MAPS-sponsored protocol for MDMA-assisted psychotherapy involves two different-gender (i.e., one male, one female) therapists in the room, in a safe and comfortable location (i.e., setting; Mithoefer, 2016). The basic structure of the treatment program involves three initial preparatory psychotherapy sessions before the first eight-hour MDMA overnight dosing session, in order to create a conducive mindset for exploring traumatic memories during the dosing session (i.e., creating an appropriate set; see section 3.4. for details). After each overnight MDMA dosing session, there are three integration psychotherapy sessions to facilitate meaning-making out of trauma-related therapeutic insights achieved during the dosing session (Mithoefer, 2016).

1.5. Efficacy and Safety of MDMA-Assisted Psychotherapy for PTSD
Recently published studies based on pooled Phase 2 study data for MDMA-assisted psychotherapy supported the efficacy and safety of the approach for alleviating treatment-resistant PTSD. For instance, Mithoefer et al. (2019) evaluated differences in efficacy and safety between active dose (75-125 mg) and placebo/control dose (0-40 mg) conditions pooled across six Phase 2 randomized, double-blind, controlled clinical trials, and found that the active dose group showed significantly greater PTSD symptom reduction and marginally greater depressive symptom reduction after two dosing sessions, with a large effect size in the former. Approximately 54% of participants in the active group did not meet criteria for PTSD after two dosing sessions, compared to 23% in the control group. In terms of safety, Mithoefer et al. (2019) found that the active group experienced more expected reactions (mild to moderate anxiety, jaw clenching, headaches, etc.), most of which decreased in frequency in the week following each dosing session. Additionally, Feduccia et al. (2019) compared the efficacy and safety of MDMA-assisted psychotherapy against paroxetine and sertraline, which are FDA-approved medications for the treatment of PTSD. They found that MDMA-assisted psychotherapy consistently evinced larger treatment effects sizes for PTSD symptom reduction. MDMA-assisted psychotherapy trials also showed lower dropout rates than the medication trials, and required significantly lower frequency and duration of use, with little to no evidence of withdrawal symptoms upon discontinuation. Notably, Amoroso and Workman (2016) also found a considerably lower average dropout rate in two randomized controlled pilot studies of MDMA-assisted psychotherapy for PTSD (12.7%), when compared against that of 13 randomized controlled trials of PE for PTSD (27%) meta-analyzed by Powers, Halpern, Ferenschak, Gillihan, and Foa (2010).

1.6. Psychological Effects and Theorized Mechanisms of Action

There is a growing parallel interest in psychological effects of MDMA-assisted psychotherapy that could function as mechanisms of action for PTSD symptom reduction. One study analyzed changes in openness to experiences (a personality trait) as a putative mechanism of action in Phase 1 trials (Wagner et al., 2017). The researchers found that at long-term follow-up, increased openness accompanied PTSD symptom reduction following MDMA administration. The researchers speculated
that an increased openness to experience may have increased engagement with the treatment, which in turn, aided its effectiveness in reducing PTSD symptoms.

Other extant research can be categorized into three broad clusters. First, MDMA has been discussed as increasing relaxation (i.e., reducing hypervigilance) and reducing the fear response (hence, improving ability to reflect on traumatic memories), indicative of enhanced emotion regulation (Johansen & Krebs, 2009; Sessa, 2017). This increased emotion regulation occurs on a neurobiological level as well, since MDMA enhances release of serotonin, norepinephrine, dopamine, and oxytocin (among other downstream neurochemical circuitries) to modulate activation of fear-related brain regions (i.e., amygdala and insula; Feduccia & Mithoefer, 2018). In this state of lowered defensiveness, MDMA is thus hypothesized to increase introspectiveness and catalyze discovery of new insights about past traumatic experiences (Grinspoon & Doblin, 2001; Hendricks, 2018). This is similarly represented by MDMA’s hypothesized ability to increase connectivity between the amygdala and hippocampus to facilitate reprocessing and reconsolidation of traumatic memories (Feduccia & Mithoefer, 2018; Johansen & Krebs, 2009).

Second, the majority of studies on the socioemotional effects of MDMA provide converging evidence that MDMA specifically increases social reward processing (e.g., increased emotional disclosure, increased recognition of positive facial cues; Baggott et al., 2016; Bedi, Hyman, & de Wit, 2010; Bedi, Phan, Angstadt, & de Wit, 2009; Carlyle et al., 2019; Gabay et al., 2018; Hysek, Domes, & Liechti, 2012; Hysek et al., 2014). As a result, MDMA has been discussed as increasing feelings of positive emotional empathy, as well as associated feelings of trust, both within the self and with others, all of which have been posited to improve the therapeutic alliance and treatment outcomes (Bershad, Miller, Baggott, & de Wit, 2016; Carhart-Harris, Erritzoe, Haijen, Kaelen, & Watts, 2018; Jungaberle et al., 2018). Importantly, the experience of emotional empathy implicates awareness and recognition of a variety of emotions both in the self and others, the opposite of which is, arguably, alexithymia, or difficulties in identifying and labeling emotional feelings (Taylor, Bagby, & Parker, 1997). In fact, alexithymia is strongly associated with PTSD symptomatology (Frewen, Dozois, Neufeld, & Lanius, 2008). Therefore, a possible route through which MDMA-assisted psychotherapy
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may alleviate PTSD symptoms is by reducing alexithymic tendencies that impede emotional engagement with trauma-related memories during dosing (Feduccia & Mithoefer, 2018). It is also possible that reducing alexithmic tendencies can encourage approach towards socially rewarding interpersonal interactions (including verbal processing of the trauma with others) that can help correct dysfunctional trauma-related cognitions about the self, others, and/or the world.

Third, MDMA has been discussed as encouraging the growth of self-compassion, which aids individuals with PTSD to better understand and find meaning in the traumatic experiences that they have undergone (McDaniel, 2017). In this sense, and in accordance to the humanistic tradition, MDMA capitalizes on one’s capacity to authentically relate to, connect with, and integrate one’s sense of self with lessened defensiveness, which has been hypothesized as foundational to establishing trustful and authentic connection with others and the world (Bershad et al., 2016; Carhart-Harris, Erritzoe et al., 2018). Indeed, in a smaller pooled set data from three Phase 2 trials, Gorman et al. (2020) found that the active dose group who received MDMA-assisted psychotherapy also demonstrated significant increases in the related outcome of posttraumatic growth, or, positive and meaningful alterations in self-perception or philosophy in life, as well as interpersonal functioning.

2. Study 1

2.1. Limitations of Previous Research

Despite the ‘psychedelic renaissance’ in research on MDMA-assisted psychotherapy for treatment-resistant PTSD, the enrollment of ethnoracially diverse participants in previous Phases 1 and 2 trials was poor. In fact, out of the 105 participants who were enrolled in the six Phase 2 trials, only 13 (12.4%) were ethnoracial minorities (Mithoefer et al., 2019). There are multiple interwoven explanations for this disparity.

First, there is a persistent lack of emphasis on increasing diversity in clinical research, in spite of federal mandates to increase minority inclusion (National Institutes of Health, 1994). For example, Michaels, Purdon, Collins, and Williams (2018) conducted a systematic review of 18 psychedelic
studies from 1993 to 2017 that reported demographic data, and found that only 17.4% of the aggregated sample did not identify as non-Hispanic White. They discussed their findings as indicative of an overarching culture in the research community that does little to prioritize inclusivity, often resulting in ethnoracially homogenous, often non-Hispanic White research staff and participant pools. Michaels et al. (2018) additionally criticized the use of convenience sampling in clinical mental health research, which tends to be culturally unresponsive to the needs of diverse minority communities (e.g., individuals of color being more likely to seek medical instead of psychological help, utilizing clergy instead of clinical trials, etc.).

Second, low ethnoracial minority inclusion in previous MDMA-assisted psychotherapy trials may also signal cultural aversion toward the use of a psychedelic substance to aid psychological healing. When ethnoracial minorities are faced with the prospect of using a psychedelic drug, they may confront the historical stigma attached to drug use, activate inherited cultural perceptions of psychedelic drug use as risky and dangerous (Rigg, 2017; Rigg & Lawental, 2018), and experience stereotype threat as a ‘deviant drug user’ (McLeod, 2015; Neitzke-Spruill, 2020; Provine, 2011). This makes sense especially given the racialized sociopolitical history of drug use in the United States (i.e., the War on Drugs; George, Michaels, Sevelius, & Williams, 2020; Harvey, 2016). For example, African Americans continue to be arrested and charged with drug-related offenses at higher rates, and suffer harsher penalties and/or longer incarceration, despite equivalent rates of use and possession as non-Hispanic White Americans (Alexander, 2010; Forman, 2012; Nellis, 2016). While emerging research indicates more openness to use of psychedelics among younger ethnoracial minority individuals (e.g., Rigg, 2017), individuals of color generally perceive less protection in their ability to explore potential uses of psychedelic substances than their White counterparts (Beckett, Nyrop, & Pfingst, 2006; Davis & Munoz, 1968). Even in private ayahuasca ceremonies, sexual assault of individuals of color in a vulnerable state is unfortunately prevalent (Fernández, 2018).

Third, several atrocities have been committed in clinical trials against marginalized populations. These include the Tuskegee Syphilis Study (Cooper, 2015; Katz et al., 2006), as well as abusive psychedelic research carried out on people of color at the Addiction Research Center at the
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Public Health Service Hospital in Lexington, Kentucky (Williams & Labate, 2020). These incidents have cultivated persistent mistrust of medical research and staff among ethnoracial minority communities (Harris, Gorelick, Samuels, & Bempong, 1996; Poussaint & Alexander, 2000; Suite, La Bril, Primm, & Harrison-Ross, 2007). Essentially, all of these factors have contributed to little to no knowledge in the literature about whether MDMA-assisted psychotherapy can be equally efficacious and safe for treating PTSD in ethnорacial minorities.

2.2. Purpose of the Present Study

In summary, MDMA-assisted psychotherapy was, on average, efficacious and psychologically safe for participants with PTSD enrolled in Phase 2 trials. However, most of these participants identified as non-Hispanic White. To date, there is no published evidence on whether this treatment is similarly efficacious and psychologically safe for individuals of color, due to under-recruitment. As such, the purpose of the present study was to first examine ethnорacial differences in efficacy (for PTSD symptoms and various secondary outcomes) and psychological safety (i.e., suicidality) among participants recruited in a MAPS-sponsored, open-label, multisite trial for MDMA-assisted psychotherapy for treatment-resistant PTSD (i.e., MP-16/17; ClinicalTrials.gov identifier: NCT03282123). The MP-16/17 trial acts as a lead-in to Phase 3 randomized controlled trials, allowing Phase 3 clinicians to gain experience and supervision from MAPS-approved trainers for the larger-scale Phase 3 trials. More importantly, in this trial, there was a more deliberate effort to improve minority inclusion, which has resulted in the recruitment of a higher proportion of ethnорacial minority participants, compared with previous trials (Williams, Reed, & Aggarwal, 2020).

A secondary purpose of this study was to examine relationships between changes in PTSD symptoms and changes in certain secondary outcomes that have been theorized to act as mechanisms of change in MDMA-assisted psychotherapy. Based on the literature reviewed in section 1.6., MDMA-assisted psychotherapy might improve emotion regulation ability, reduce alexithymic tendencies, and increase self-compassion, all of which might be associated with PTSD symptom reduction. Although causality cannot be inferred in any statistically significant relationships from above, the present study nonetheless sought to elucidate possible ways in which PTSD symptom
reduction might be achieved during MDMA-assisted psychotherapy to serve as hypotheses for future study.

2.3. Aims and Hypotheses

2.3.1. Aim 1 (efficacy – primary outcome): First, the present study aimed to examine potential ethnoracial differences in treatment efficacy for the primary outcome of PTSD symptoms among participants in the MP-16/17 trial. While Lester et al. (2010) found no ethnoracial differences in reported gains among individuals who completed a clinical trial for PTSD, Benítez et al. (2014) found lower probability of recovery among individuals of color in treatment for PTSD. Because of the mixed evidence, the present study sought to explore whether there would be differences in improvements in PTSD symptoms (in terms of statistical change and reliable improvement/recovery; Jacobson & Truax, 1991) between ethnoracial minority and non-Hispanic White participants.

2.3.2. Aim 2 (efficacy – secondary outcomes): Next, the present study sought to additionally explore whether there would be differences in treatment efficacy (i.e., statistical change and reliable improvement; Jacobson & Truax, 1991) for the secondary outcomes of depressive symptoms, alcohol and substance use, trauma-related psychosocial functioning, emotion regulation ability, alexithymic tendencies, and self-compassion between ethnoracial minority and non-Hispanic White participants in the MP-16/17 trial.

2.3.3. Aim 3 (psychological safety): Additionally, although there was no concrete hypothesis regarding psychological safety (i.e., suicidality), the present study would similarly explore the data to determine if there were ethnoracial differences in indices of treatment-emergent suicidality among participants in the MP-16/17 trial.

2.3.4. Aim 4 (correlations): Lastly, the present study sought to examine relationships between changes in certain secondary outcomes (i.e., emotion regulation ability, alexithymic tendencies, and self-compassion) and changes in the primary outcome of PTSD symptoms among all participants in the MP-16/17 trial. Results from testing these relationships may provide preliminary
support for the potential mechanistic roles of emotion regulation ability, alexithymic tendencies, and self-compassion in PTSD symptom reduction in MDMA-assisted psychotherapy.

2.3.4.1. Hypothesis 4A-C: It was hypothesized that pre-post changes in emotion regulation ability (4A), alexithymic tendencies (4B), and self-compassion (4C) would be significantly correlated with pre-post changes in the primary outcome of PTSD symptoms.

3. Method

3.1. Sources of Recruitment

The MP-16/17 trial was a MAPS-sponsored, multisite study which recruited participants across university-affiliated academic medical centers and private practices in the United States (MP-16: California, Colorado, Connecticut, Louisiana, Massachusetts, New York, South Carolina, and Wisconsin) and Canada (MP-17: British Columbia, Quebec). As mentioned, this trial deliberately sought to increase ethnoracial minority representation within the participant pool through culturally responsive recruitment strategies described in Williams et al. (2020). Each site was headed by its own principal investigator, co-investigator(s), and study physician, all of whom may also function as study therapists. All study site members received intensive training (approximately 100 hours) in MDMA-assisted psychotherapy by MAPS-approved trainers. These researchers also received supervision throughout the trial in treatment administration and protocol adherence by MAPS-approved supervisors. Information about the MP-16/17 trial was disseminated through online platforms (e.g., on the study information page of the official MAPS webpage) and physical media (e.g., site-specific flyers). Data collection lasted from November 2017 to February 2019. The MP-16/17 trial was reviewed and approved by the Western Copernicus Institutional Review Board (IRB).

3.2. Participant Inclusion and Exclusion Criteria

One hundred and six participants were screened via phone call for their eligibility to participate. Sixty-four participants were excluded at this stage because they did not meet eligibility criteria, while 42 participants (29 non-Hispanic White, 13 ethnoracial minority) were preliminarily enrolled in the MP-16/17 trial. Figure 1 displays subsequent participant flow throughout the MP-
16/17 trial. Because of its nature as a lead-in trial to Phase 3 trials, the sample size for the MP-16/17 trial was determined by the fact that each of the two to four teams of study therapists at each of the 14 sites had to complete the study protocol for just one study participant.

Participants were eligible if they met the following criteria at the informed consent interval: had a current diagnosis of PTSD as per DSM-5 criteria, with symptoms having lasted 6 months or longer; had at least severe PTSD symptoms in the past month, based on a total score of 50 or greater on the PTSD Checklist for DSM-5 (PCL-5; Blevins, Weathers, Davis, Witte, & Domino, 2015); had currently well-controlled hypertension, if at all, and no underlying cardiovascular disease; and had currently asymptomatic Hepatitis C virus (HCV), if at all, and no symptomatic liver disease. To confirm enrollment, participants also needed to have at least severe PTSD symptoms at Visit 3 baseline assessment by an independent rater, based on a Total Severity Score of 35 or greater in the past month on the Clinician-Administered PTSD Scale for DMS-5 (CAPS-5; Weathers et al., 2013a).

Additionally, participants needed to be: at least 18 years old; proficient in English; able to swallow pills; agreeable to have all sessions recorded; have an emergency contact; not be pregnant (if of childbearing potential) and agreeable to use adequate birth control at study entry and throughout participation; and willing to notify investigators promptly of any medical conditions and procedures during participation. Participants also needed to comply with other study procedures, such as: fasting immediately prior to dosing; tapering off prescribed medications according to personal or study physician’s instructions and abstaining from non-prescription substances if necessary; submitting to drug tests prior to dosing; completing all necessary ongoing assessment and telephone contact; not participating in any other interventional clinical trials during the duration of the study; and remaining overnight at the study site after each dosing session and be transported home safely by a support person the morning after.

Among other criteria, participants were excluded if they: were likely to be re-exposed to their index trauma or other significant trauma; used Ecstasy more than 10 times within the past 10 years or at least once within 6 months of the scheduled first dosing session; had a lifetime primary psychotic disorder, bipolar I disorder, or dissociative identity disorder; had a current eating disorder with active
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purging, major depressive disorder with psychotic features, or an active substance use disorder for substances other than caffeine or nicotine in the past 60 days; had a current personality disorder; or had serious current suicidal and/or homicidal risk.

3.3. Measures

3.3.1. Screening measures. Table 1 shows the screening measures that were administered at the informed consent interval. At the informed consent interval, medical screening, bloodwork, electrocardiographic procedures, drug testing, and pregnancy testing (if applicable) were conducted as well.

3.3.1.1. Life Events Checklist for DSM-5 (LEC-5; Weathers et al., 2013b). The LEC-5 is currently the most widely used self-report checklist of lifetime exposure to 16 different types of potential ‘Criterion A’ traumatic events (in addition to an ‘other’ inordinately stressful event option), all of which can be associated with a PTSD diagnosis or clinically significant distress. These events include experiencing a ‘natural disaster,’ ‘motor vehicle accident,’ ‘physical assault,’ ‘sexual assault,’ ‘combat,’ etc. Participants endorsed each event based on the following response options: ‘happened to me;’ ‘witnessed it;’ ‘learned about it;’ and/or ‘part of my job;’ or ‘not sure;’ or ‘doesn’t apply.’ The LEC-5 is slightly modified from the LEC, which was based on DSM-IV criteria, and which demonstrated good test-retest reliability and convergent validity among college students and combat veterans (Gray, Litz, Hsu, & Lombardo, 2004). However, the LEC-5 has not been extensively studied in ethnoracially diverse samples. The LEC-5 was used to identify the index/worst traumatic event prior to administration of the PCL-5 (see next).

3.3.1.2. PTSD Checklist for DSM-5 (PCL-5; Blevins et al., 2015). The PCL-5 is a 20-item self-report measure assessing the 20 symptoms of PTSD in the past month, according to DSM-5 criteria. The PCL-5 was used to rate current PTSD symptom severity associated with the index/worst traumatic event identified on the LEC-5. Items 1 to 5 assess ‘Criterion B’ symptoms (i.e., trauma-related intrusions), items 6 and 7 assess ‘Criterion C’ symptoms (i.e., trauma-related avoidance), items 8 to 14 assess ‘Criterion D’ symptoms (i.e., negative, trauma-related alterations in cognitions
and mood), and items 15 to 20 assess ‘Criterion E’ symptoms (i.e., marked, trauma-related alterations in arousal and reactivity). Participants rated each symptom on a five-point Likert scale from ‘0’ (not at all) to ‘4’ (extremely), and scores were summed for total PTSD symptom severity (range = 0 to 80). Higher scores indicated more severe PTSD symptoms. The minimum total score for inclusion in the present study was 50. The PCL-5 was also used to provide a provisional diagnosis of PTSD according to the dichotomous diagnostic scoring system, in which a score of at least ‘2’ indicated symptom presence/endorsement, after which DMS-5 symptom criteria was followed to determine the presence or absence of a PTSD diagnosis. The PCL-5 demonstrated strong internal consistency, test-retest reliability, and convergent and discriminant validity, and good fit with the DSM-5 four-factor model in two large samples of trauma-exposed college students (Blevins et al., 2015), and has been used with diverse samples (e.g., ethnoracial minority college students who have experienced intracultural interpersonal trauma; Gómez, 2019). Internal consistency of the PCL-5 was acceptable in the present study, with baseline Cronbach’s $\alpha$ of .76 (non-Hispanic White: .73; ethnoracial minority: .80).

### 3.3.1.3. Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993)

The AUDIT is a 10-item self-report measure of alcohol use severity over the past year (e.g., frequency and level of alcohol consumption, extent of dependence and associated functional impairment). Participants rated the first eight items in increasing severity from ‘0’ to ‘4’, and rated the last two items ‘0,’ ‘2,’ or ‘4,’ giving a maximum possible total score of 40. Higher scores indicated higher alcohol use severity. Total scores of 8 or more indicate possible problematic alcohol use. In the present study, participants who endorsed total AUDIT scores of 8 or more were further inquired whether their problematic alcohol use occurred in the past 60 days; none endorsed problematic alcohol use in the past 60 days prior to screening. The AUDIT demonstrated high sensitivity and specificity in a large international sample of patients in primary healthcare settings, with 92% of individuals diagnosed with alcohol use disorder (AUD) scoring 8 or more, and 94% of individuals without a diagnosis of AUD scoring less than 8 (Saunders et al., 1993). The AUDIT also demonstrated good reliability and validity in ethnoracially and nationally diverse samples (e.g., Osaki
et al., 2014). Internal consistency of the AUDIT was acceptable in the present study, with baseline Cronbach’s α of .72 (non-Hispanic White: .75; ethnoracial minority: .70).

3.3.1.4. Drug Use Disorders Identification Test (DUDIT; Berman, Bergman, Palmstierna, & Schlyter, 2005). The development of the DUDIT was modeled after the AUDIT (Saunders et al., 1993). The DUDIT is an 11-item self-report measure of drug use severity over the past year (e.g., frequency and level of drug use, extent of dependence and associated functional impairment). Participants rated the first nine items in increasing severity from ‘0’ to ‘4’, and rated the last two items ‘0,’ ‘2,’ or ‘4,’ giving a maximum possible total score of 44. Higher scores indicated higher drug use severity. Total scores of 6 or more indicate possible problematic drug use. In the present study, participants who endorsed total DUDIT scores of 6 or more were further inquired whether their problematic drug use occurred in the past 60 days; none endorsed problematic drug use in the past 60 days prior to screening. The DUDIT demonstrated good to excellent internal consistency, test-retest reliability, validity and sensitivity and specificity across several studies with diverse samples in various settings (for a review, see Hildebrand, 2015). Internal consistency of the DUDIT was good in the present study, with baseline Cronbach’s α of .86 (non-Hispanic White: .80; ethnoracial minority: .93).

3.3.1.5. Columbia-Suicide Severity Rating Scale (C-SSRS; Posner et al., 2008). The Lifetime version of the C-SSRS was administered during screening to assess for lifetime suicidal ideation and behavior. Items assess severity of suicidal intent, intensity of suicidal ideation (frequency, duration, controllability, deterrents, and reasons for suicide), as well as attempts (actual, aborted, and interrupted attempts, preparatory behaviors, and non-suicidal, self-injurious behaviors) and lethality of attempts (Posner et al., 2008). In the present study, C-SSRS scores were recoded into the categories of positive ideation (PI), serious ideation (SI), and positive behavior (PB), as per previous studies of MDMA-assisted psychotherapy (see Mithoefer et al., 2019). PI was defined as a score of 1 or greater on the suicidal ideation subscale. SI was defined as a score of 4 or 5 on the suicidal ideation subscale. PB was defined as a score of 1 or greater on the suicidal behavior subscale. The C-SSRS evinced acceptable to excellent internal consistency, convergent, discriminant, and
predictive validity, as well as sensitivity and specificity across diverse samples, nationalities, and settings (e.g., Posner et al., 2011). In the present study, internal consistency of the Lifetime version of the C-SSRS was acceptable, with baseline Cronbach’s $\alpha$ of .73 (non-Hispanic White: .71; ethnoracial minority: .82).

3.3.1.6. Other screening measures. Other measures were also administered during the online independent rater visit in order to verify a PTSD diagnosis and screen for additional exclusion criteria. These included the CAPS-5 (see section 3.3.2.1.), the Mini-International Neuropsychiatric Interview for DSM-5 (MINI; Sheehan et al., 1998), the Dissociative Disorders Interview Schedule for DSM-5 (DDIS; Ross & Ellason, 2005), the Structured Clinical Interview for DSM-5 Personality Disorders (SCID-5-PD; First, Williams, Benjamin, & Spitzer, 2016), and the Since Last Visit version of the C-SSRS (Posner et al., 2008), which is identical to the Lifetime version, except for the time reference.

3.3.2. Primary outcome measures. Table 1 displays when the following primary outcome measures of PTSD symptoms were administered.

3.3.2.1. Clinician-Administered PTSD Scale for DMS-5 (CAPS-5; Weathers et al., 2013a). The CAPS-5 is a 30-item structured interview used to assess PTSD symptom severity over the past month, and is currently viewed as the gold-standard instrument for PTSD symptom evaluation. The 20 items of interest in the present study corresponded to the 20 DSM-5 PTSD symptoms, all of which were inquired in relation to the ‘Criterion A’ index/worst traumatic event identified on the LEC-5 (Weathers et al., 2013b). Each symptom was rated from ‘0’ (absent) to ‘4’ (extreme/incapacitating), for a maximum total PTSD symptom severity score of 80. Higher scores indicated more severe PTSD symptoms. Similar to the PCL-5, the dichotomous diagnostic scoring system was used to determine whether there is a diagnosis of PTSD or not. Specifically, a symptom was considered as present/endorsed if it was rated as ‘2’ (moderate/threshold) or more, and the DMS-5 symptom criteria (e.g., at least one symptom for Criterion B) was followed to determine the presence or absence of a PTSD diagnosis. The CAPS-5 has demonstrated strong internal consistency and interrater test-retest reliability, as well as good convergent validity with the PCL-5 (Blevins et al., 2015) and other measures of commonly comorbid symptoms (e.g., depression, anxiety) across diverse samples (e.g.,
Weathers et al., 2018). Internal consistency of the CAPS-5 was acceptable at baseline, with Cronbach’s α of .72 (non-Hispanic White: .70; ethnoracial minority: .79).

The PCL-5 (Blevins et al., 2015) was also included as a corroborative primary outcome measure. Section 3.3.1.2. contains details for the PCL-5. Besides the informed consent interval, the PCL-5 was also administered during the preparatory session prior to the first dosing session (i.e., Visit 4), the third integration session after the first dosing session (i.e., Visit 9), the third integration session after the second dosing session (i.e., Visit 14), and at study termination (i.e., Visit 20).

**3.3.3. Secondary outcome measures.** Table 1 displays when the following secondary outcome measures were administered, including the AUDIT (Saunders et al., 1993) and DUDIT (Berman et al., 2005) (see sections 3.3.1.3. and 3.3.1.4. respectively for details).

**3.3.3.1. Beck Depression Inventory – Second Edition (BDI-II; Beck, Steer, & Brown, 1996).** The BDI-II is a 21-item self-report measure of the dysfunctional cognitive, emotional, and neurovegetative aspects of depressive symptoms over the past two weeks. Participants rated items on a four-point Likert scale from ‘0’ to ‘3,’ giving a maximum total score of 63. Higher scores indicated more severe depressive symptoms, ranging from minimal (0 to 13), to mild (14 to 19), to moderate (20 to 28), to severe (29 to 63) (Beck et al., 1996). The BDI-II has demonstrated good to excellent reliability, validity, sensitivity, and specificity in diverse clinical and non-clinical samples (Carmody, 2005; Segal, Coolidge, Cahill, & O’Riley, 2008). In the present study, internal consistency of the BDI-II was excellent, with baseline Cronbach’s α of .96 (non-Hispanic White: .95; ethnoracial minority: .97).

**3.3.3.2. Inventory of Psychosocial Functioning (IPF; Bovin et al., 2018).** The IPF is an 80-item self-report measure of PTSD-related psychosocial impairment in multiple domains over the past month (i.e., romantic and familial relationships, parenting ability, friendships, occupational and academic functioning, and self-care). Participants respond only to personally relevant domains on the IPF (e.g., items assessing parenting ability would be skipped if the person does not have a child). Participants rated each item on a seven-point Likert scale from ‘0’ (never) to ‘6’ (always), and
participants’ overall scores are derived as the mean of summed subscale scores, with higher overall scores indicating more severe overall PTSD-related functional impairment. The IPF was validated in two phases with relatively ethnoracially diverse veterans, and demonstrated overall good reliability and convergent and discriminant validity (Bovin et al., 2018). In the present study, the listwise deletion command for data inclusion in SPSS resulted in too few cases (precisely, \( N = 1 \)) for computation of the internal consistency for the whole scale. Therefore, items for each subscale were separately entered instead. Internal consistencies of the various subscales of the IPF ranged from good to excellent in the present study, with baseline Cronbach’s \( \alpha \)s varying from .83 to .94 (non-Hispanic White: .83 to .95; ethnoracial minority: .77 to .91).

3.3.3.3. Inventory for Altered Self-Capacities – Affect Dysregulation scale (IASC-AD; Briere & Runtz, 2002). The IASC is a 63-item self-report measure of respondents’ difficulties over the past six months in the three broad domains of: (1) forming and maintaining meaningful relationships; (2) creating a stable sense of personal identity and self-awareness; and (3) modulating and tolerating negative affect. In the present study, the nine-item Affect Dysregulation scale was of interest, given that it assesses extent of dysphoria (e.g., “Having many ups and downs in your feelings”) and deficits in one’s ability to regulate negative emotions (e.g., “Having a hard time calming down once you get upset”), constructs that are highly related to the enhanced emotion regulation typically observed with MDMA (see section 1.6.). Participants rated these items on a five-point Likert scale from ‘1’ (never) to ‘5’ (very often), for a maximum total of 45. Higher IASC-AD scores indicate more severe emotion dysregulation. The IASC was found to have good reliability and validity in community, clinical, and college samples (Briere & Runtz, 2002), and have been utilized in studies with diverse individuals who have experienced trauma (Allen, 2011; Freh, Chung, & Dallos, 2013). In the present study, internal consistency of the IASC-AD was excellent, with baseline Cronbach’s \( \alpha \) of .93 (non-Hispanic White: .93; ethnoracial minority: .92).

3.3.3.4. Toronto Alexithymia Scale, 20-item version (TAS-20; Bagby, Parker, & Taylor, 1994; Bagby, Taylor, & Parker, 1994). The TAS-20 is a 20-item self-report measure of alexithymia, or difficulties in identifying and describing emotions (e.g., “I am often confused about what emotion I
am feeling;” “It is difficult for me to find the right words for my feelings”), as well as the tendency to minimize emotional experience and to focus one’s attention externally. Participants rated each item on a five-point Likert scale from ‘1’ (strongly disagree) to ‘5’ (strongly agree). Five items needed to be reversed-scored, and item scores were summed for a maximum total of 100. Higher scores indicated more severe alexithymia. Additionally, recommended severity ranges included non-alexithymia (51 or less), possible alexithymia (52 to 60), and alexithymia (61 or more). The TAS-20 has demonstrated good internal consistency and test-retest reliability, and adequate convergent and concurrent validity in clinical and non-clinical samples (Bagby, Parker et al., 1994; Bagby, Taylor et al., 1994), and has also showed sound psychometric properties across diverse languages and cultures (Taylor, Bagby, & Parker, 2003). In the present study, internal consistency of the TAS-20 was good, with baseline Cronbach’s α of .89 (non-Hispanic White: .88; ethnoracial minority: .93).

3.3.3.5. Self-Compassion Scale (SCS; Neff, 2003). The SCS is a 26-item self-report measure of self-compassion, or one’s tendency to be kind and understanding toward oneself during moments of failure or pain, and to be able to hold such moments in mindful awareness as part of the larger human experience, instead of being overly self-critical, negatively identifying with such challenges, or feeling isolated in one’s experiences. Example items include: “I try to be loving towards myself when I’m feeling emotional pain;” “When I’m feeling down I try to approach my feelings with curiosity and openness;” and “When things are going badly for me, I see the difficulties as part of life that everyone goes through” (Neff, 2003). Participants rated each item on a five-point Likert scale from ‘1’ (almost never) to ‘5’ (almost always). The 12 negatively worded items needed to be reverse-scored before computing the average score of all items, giving a possible range from 1 to 5. Higher scores indicated more self-compassion. The SCS demonstrated good reliability and validity in the original validation study (Neff, 2003), as well as sound psychometric properties across diverse international samples (Neff et al., 2018). Internal consistency of the SCS was excellent in the present study, with baseline Cronbach’s α of .94 (non-Hispanic White: .94; ethnoracial minority: .94).

3.3.4. Psychological safety measure. Table 1 displays when the Lifetime, Since Last Visit, and Pre- and Post-Drug versions of the C-SSRS were administered. Drug safety was additionally
assessed in the MP-16/17 trial by measuring blood pressure, heart rate and body temperature during dosing sessions, and collecting any adverse events whenever applicable. However, for brevity, the present study will only report findings with the C-SSRS as a measure of treatment-emergent psychological safety. Section 3.3.1.5. contains details for the C-SSRS.

3.4. Design and Procedure

The multisite, open-label MP-16/17 trial was designed and conducted in accordance with good clinical practices and Consolidated Standards of Reporting Trials (CONSORT) guidelines (Moher et al., 2010). Because of its open-label nature, the present study also adhered to the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND; Des Jarlais, Lyles, Crepaz, & TREND Group, 2004) checklist, which was compatible with CONSORT guidelines.

The first two rows of Table 1 (i.e., Duration and Visits) displays the overall study schedule in terms of number and types of study visits, and estimated duration of each phase of the study. Each study site had two to four male-and-female co-therapist pairs, and was projected to complete with two to four participants.

After passing a phone screen and obtaining written informed consent, each participant was screened extensively over a few visits by the assigned co-therapy team, the study physician and other non-study-affiliated healthcare professionals, and an independent rater, with regards to PTSD symptoms, other psychiatric history, and other potential exclusionary criteria. After enrollment (Visit 0), to establish proper set and setting and therapeutic alliance before the first MDMA dosing session (Visit 5), participants underwent three 90-minute preparatory sessions (Visits 1, 2, and 4) with the co-therapy team, while also being tapered off exclusionary psychiatric medications by the study physician. During these preparatory sessions, the emphasis was on establishing appropriate set and setting for the first dosing session (e.g., by answering remaining concerns about the medicine and therapy approach, co-establishing intention and motivation for healing, collaboratively customizing elements of the therapy setting to the participant’s preferences, etc.).
In the first dosing session, an initial dose of 80 mg (for the 12 sites in the United States) or 100 mg (for the two sites in Canada) of MDMA compounded with lactose was prescribed and administered, followed 1.5 to 2 hours later by a supplemental half-dose (40 mg or 50 mg, respectively) that was offered as an option for each participant. In the second and third dosing sessions, the initial dose increased to 120 mg and 150 mg for the sites in United States and Canada, respectively. The optional supplemental half-dose in these sessions also increased to 60 mg and 67.5 mg, respectively. Drug safety was assessed by measuring suicidality throughout with the C-SSRS. Notably, for participants who participated in dosing sessions, all prescribed initial and supplemental dosage amounts were ingested voluntarily, except for one participant whose supplemental dose for the third dosing session was withheld by the study physician, who decided not to prescribe and administer the supplemental dose for personal and religious reasons.

During dosing sessions, co-therapists remained non-directive, curious, open, communicative, and attentive to the participant’s developing experience, creating a sense of safety and communicating trust in the participant’s innate capacity for healing. Eyeshades and headphones (though which a playlist of instrumental music intended to support the participant’s process played) were available to help participants focus attention on their developing experience. After the effects of the MDMA subsided, participants could eat dinner of their choice if desired, and remained overnight at the site with a night attendant in the adjacent room.

On the morning following each dosing session, the first of three integration psychotherapy sessions was conducted, in order to assess the participant’s mental state and stability, and to facilitate assimilation of experiences and insights (as pertaining to the index trauma) gained during the dosing session. Fifteen-minute phone contact occurred twice over the seven days following the first integration session, before the second integration session. The second dosing session (Visit 10) occurred a week after the third integration session (Visit 9) following the first dosing session. After the third integration session (Visit 19) following the third dosing session has been conducted, participants met with the independent rater for the final CAPS-5 assessment (Visit 19), followed by study termination (Visit 20).
3.5. Data Analytical Plan

3.5.1. Descriptive analyses. Descriptives for demographic characteristics and index/worst traumas on the LEC-5 were first obtained for the recruited sample, split by participation status and ethnoracial group. Descriptives for post-baseline LEC-5 stressors (split by participation status and ethnoracial group) were then obtained for the modified intent-to-treat (ITT) set (see next). Thereafter, non-Hispanic White and ethnoracial minority participants in the modified ITT set were compared on age, gender, marital status, and employment status using t-tests and chi-square tests of independence with exact tests of significance (due to small sample size).

3.5.2. Modified ITT set. All of the following analyses (except for C-SSRS indices) were performed using a modified ITT set (N = 37) (Gupta, 2011) that excluded the five pre-dosing termination participants. These participants were ineligible to participate at enrollment confirmation, and did not complete any dosing sessions. The modified ITT set included, however, one non-Hispanic White participant who terminated after two dosing sessions. The last observation carried forward (LOCF) method was used to impute missing data for this participant. This method assumes stability in the last observed value for relevant variables, and is viewed as a conservative method for handling missing data in clinical trials (Streiner, 2002; Unnebrink & Windeler, 2001). Missing data not due to premature termination in this study were minimal; indeed, data was missing at baseline for certain secondary outcome (and mechanisms of change) measures only for one non-Hispanic White participant who completed the study, due to researchers’ loss of paper scores. Missing baseline data for that participant were imputed using the respective group means.

For the following primary outcome analyses, initial analysis indicated no ethnoracial differences in baseline CAPS-5 and PCL-5 scores, both ts < 1.23, all ps > .05. Hence, baseline scores for these measures were not entered as covariates. There were also no ethnoracial differences in baseline scores for all secondary outcome measures, all ts < 1.78, all ps > .05.

3.5.3. Primary outcome analyses. To address Aim 1, separate mixed analyses of variance (ANOVAs) with time (CAPS-5: Visits 3, 8, 13, and 19; PCL: informed consent, Visits 4, 9, 14, and
20) as the within-subjects variable and ethnoracial group (non-Hispanic White vs. ethnoracial minority) as the between-subjects variable were conducted. The Greenhouse-Geisser correction for degrees of freedom for the repeated-measures component (Greenhouse & Geisser, 1959) was applied wherever necessary (i.e., violation of sphericity assumption). Additionally, reliable change indices (RCIs) (absolute difference required for a change score to be regarded as being reliably more than measurement error – i.e., standard deviation of the errors of measurement of the difference score multiplied by 1.96) were calculated for the CAPS-5 and PCL-5 (see Jacobson & Truax, 1991). Thereafter, the following RCI categories were derived: (1) deterioration beyond RCI; (2) unreliable change; (3) reliable improvement but no recovery (PTSD diagnosis present); and (4) reliable improvement and recovery (PTSD diagnosis absent). Finally, separate Pearson’s chi-square tests of independence with exact tests of significance were conducted for each measure, in which ethnoracial group was entered as one factor, and the corresponding RCI categories were entered as the other factor.

3.5.4. Secondary outcome analyses. To address Aim 2, separate mixed analyses of variance (ANOVAs) with time (AUDIT and DUDIT: informed consent vs. Visit 20; BDI-II, IPF, IASC-AD, TAS-20, and SCS: Visits 4 vs. 20) as the within-subjects variable and ethnoracial group (non-Hispanic White vs. ethnoracial minority) as the between-subjects variable were conducted. Additionally, the following RCI categories for all secondary outcome measures were derived: (1) deterioration beyond RCI; (2) unreliable change; and (3) reliable improvement. Separate Pearson’s chi-square tests of independence with exact tests of significance were then conducted for each measure, with ethnoracial group and the corresponding RCI categories being entered as separate factors.

3.5.5. Psychological safety analysis. To address Aim 3, ethnoracial differences (‘non-Hispanic White’ = ’1; ‘ethnoracial minority’ = ‘2’) in binary outcomes (‘yes’ = ‘1; ‘no’ = ‘0’) in positive ideation, serious ideation, and positive behavior on the C-SSRS across all assessment intervals were investigated via separate repeated-measures binary logistic regressions using generalized estimating equations (GEE; Liang & Zeger, 1986). This approach effectively takes into
account missing values in the entire sample. Maximum likelihood estimation was specified. Additionally, participants’ identification number was entered as the subject variable, time (25 C-SSRS assessment intervals) was entered as the within-subjects variable, robust estimator was set as the covariance matrix, and the working correlation matrix was specified as exchangeable. The lowest value (i.e., ‘no’ = ‘0’) was specified as the reference category for all dependent variables. The main effects of ethnoracial group and time, as well as the group × time interaction effect, were tested in the model. The data will also be visually inspected to describe possible group differences and trends in treatment-emergent suicidality from the independent rater visit to study termination.

3.5.6. Correlational analyses. To test Hypotheses 4A-C, zero-order correlations were conducted with the entire sample to assess relationships between pre-post difference scores for secondary outcome measures that could act as putative mechanisms of change (i.e., IASC-AD, TAS-20, SCS) and pre-post difference scores for primary outcome measures (i.e., CAPS-5 and PCL-5). All aforementioned analyses were conducted using IBM SPSS Statistics 26, with $\alpha = .05$.

4. Results

4.1. Descriptive Statistics

Table 2 displays the demographic characteristics of the recruited sample split by participation status and ethnoracial group. Notably, in the modified ITT set, non-Hispanic White participants ($M = 37.35, SD = 11.45$) were significantly older than ethnoracial minority participants ($M = 30.27, SD = 5.88$); Levene’s test: $F(1, 35) = 5.58, p < .05$; $t(33.42) = 2.47, p < .05$, 95% CI = $[1.25, 12.89]$. However, the psychological intervention literature consistently indicates that age does not moderate PTSD treatment response (e.g., Ehlers et al., 2013; Zandberg et al., 2016). Indeed, in supplementary analyses, age did not correlate significantly with CAPS-5 and PCL-5 pre-post difference scores, or even with difference scores for all of the other measures, in the modified ITT set, all $ps > .05$. Thus, age was not included as a covariate in the following analyses. No significant associations emerged between ethnoracial status and other demographic variables (i.e., gender, marital status, and employment status) in the modified ITT set in separate chi-square tests of independence, all $ps > .05$. 
Table 3 displays the index/worst traumatic events on the LEC-5 for the recruited sample, while Table 4 displays the post-baseline LEC-5 stressors in the modified ITT set, both split by participation status and ethnoracial group.

4.2. Primary Outcome

Results of a mixed ANOVA with CAPS-5 scores indicated a non-significant time × group interaction effect, $F(2.42, 84.66) < 1$, and a non-significant main effect of group, $F(1, 35) = 1.67, MSe = 208.01, p > .05$, partial $\eta^2 = .05$. There was a significant main effect of time, $F(2.42, 84.66) = 64.18, MSe = 103.16, p < .001$, partial $\eta^2 = .65$. Post-hoc tests with Bonferroni correction indicated significant reductions in CAPS-5 scores across groups from Visit 3 ($M = 45.30, SD = 7.76$) to Visit 8 ($M = 28.68, SD = 11.25$) (i.e., after the first dosing), and from Visit 8 to Visit 13 ($M = 20.22, SD = 12.33$) (i.e., after the second dosing), both $ps < .001$, 95% CIs = [8.50, 23.29] and [3.51, 14.72], Cohen’s $d$ = 1.14 and 0.76, respectively. CAPS-5 scores were maintained from Visit 13 to Visit 19 ($M = 16.11, SD = 11.27$) (i.e., after the third dosing), $p > .017$. Figure 2 displays changes in CAPS-5 scores between groups across time.

Results of a mixed ANOVA with PCL-5 scores similarly indicated a non-significant time × group interaction effect, $F(2.88, 100.68) = 1.74, MSe = 129.86, p > .05$, partial $\eta^2 = .05$. The main effect of group was not significant either, $F(1, 35) = 2.48, MSe = 283.22, p > .05$, partial $\eta^2 = .07$. However, visual inspection of the data suggested a possible ethnoracial group difference in PCL-5 scores at the Visit 9 assessment interval (i.e., after the first dosing). Indeed, tests of simple effects with Bonferroni correction indicated that ethnoracial minority participants ($M = 40.64, SD = 14.38$) self-reported significantly higher PCL-5 scores than non-Hispanic White participants ($M = 28.38, SD = 15.23$) only at the Visit 9 assessment interval, $p < .01$, 95% CI = [1.30, 23.20], Cohen’s $d$ = 0.82, all other $ps > .01$. Additionally, there was a significant main effect of time, $F(3.09, 99.01) = 178.27, MSe = 104.41, p < .001$, partial $\eta^2 = .85$. Bonferroni-corrected post-hoc tests indicated stability in PCL-5 scores across groups from informed consent ($M = 60.30, SD = 7.72$) to Visit 4 ($M = 58.35, SD = 10.08$) (i.e., prior to the first dosing), $p > .013$, significant reductions in scores after each of the first two dosings at Visits 9 ($M = 32.03, SD = 15.84$) and 14 ($M = 20.89, SD = 12.61$), both $ps < .001$, 95%
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CIs = [15.12, 33.20] and [6.51, 19.20], Cohen’s $d$s = 1.52 and 0.91, respectively, as well as maintenance in scores at study termination ($M = 13.46$, $SD = 10.25$) (i.e., after the third dosing), $p > .013$. Figure 3 displays changes in PCL-5 scores between groups across time.

RCIs for CAPS-5 and PCL-5 scores were 10.79 and 10.4, respectively. Results of separate chi-square tests of independence indicated no significant associations between ethnoracial group and RCI category for CAPS-5 and PCL-5 scores, $\chi^2s(2, N = 37) = 2.54$ and 1.38, respectively, both $ps > .05$. Table 5 displays RCI categories between groups for the CAPS-5 and PCL-5, as well as all other measures. From Table 5, based on CAPS-5 scores, approximately 73% of participants in the modified ITT set achieved full remission (i.e., PTSD absent) at study termination. When considering PCL-5 scores for a provisional PTSD diagnosis, approximately 92% of participants in the modified ITT set achieved full remission (i.e., PTSD absent) at study termination.

4.3. Secondary Outcomes

Results of a mixed ANOVA with BDI-II scores showed no significant time × group interaction effect, $F(1, 35) < 1$, or main effect of group, $F(1, 35) = 1.45$, $MSe = 227.46$, $p > .05$, partial $\eta^2 = .04$. There was, however, a significant main effect of time, $F(1, 35) = 61.74$, $MSe = 127.57$, $p < .001$, 95% CI = [16.74, 28.40], partial $\eta^2 = .64$, indicating pre-post reductions in depressive symptoms across groups ($Ms = 30.51$ vs. 7.89, $SDs = 15.81$ vs. 10.23), Cohen’s $d = 1.44$. Figure 4 displays changes in BDI-II scores between groups across time.

Analysis of AUDIT scores via a mixed ANOVA demonstrated no significant time × group interaction effect, $F(1, 35) = 1.45$, $MSe = 1.75$, $p > .05$, partial $\eta^2 = .04$, or main effect of group, $F(1, 35) < 1$. There was a significant main effect of time, $F(1, 35) = 6.64$, $MSe = 1.75$, $p < .05$, 95% CI = [0.18, 1.55], partial $\eta^2 = .16$, with pre-post reductions in AUDIT scores across groups ($Ms = 3.73$ vs. 3.03, $SDs = 3.41$ vs. 3.67), Cohen’s $d = 0.37$. Figure 5 displays changes in AUDIT scores between groups across time.

An initial inspection of the data revealed that the assumption of normality of difference scores was held for all measures, except on the DUDIT. A log transformation of baseline and study
termination DUDIT scores (plus the positive constant of 1, to prevent value of zero) was thus conducted, and log-transformed difference scores indicated that the normality assumption was held. Analysis of log-transformed DUDIT scores via a mixed ANOVA similarly indicated no significant time × group interaction effect or main effect of group, both $F$s(1, 35) < 1. There was, however, a significant main effect of time, $F(1, 35) = 12.58, MSe = 0.08, p < .001, 95\% CI = [0.11, 0.41]$, partial $\eta^2 = .26$, with pre-post reductions in log-transformed DUDIT scores across groups ($Ms = 0.47$ vs. $0.24, SDs = 0.43$ vs. $0.35$), Cohen’s $d = 0.48$. Figure 6 displays changes in log-transformed DUDIT scores between groups across time.

A mixed ANOVA with overall IPF scores indicated non-significance for the time × group interaction effect and main effect of group, both $F$s(1, 35) < 1. On the other hand, trauma-related impairment in psychosocial functioning significantly decreased across groups from baseline ($M = 42.59, SD = 15.41$) to study termination ($M = 24.55, SD = 9.74$), $F(1, 35) = 49.69, MSe = 102.84, p < .001, 95\% CI = [12.95, 23.42]$, partial $\eta^2 = .59$, Cohen’s $d = 1.28$. Figure 7 displays changes in overall IPF scores between groups across time.

Results of a mixed ANOVA with IASC-AD scores indicated non-significance for the time × group interaction effect and main effect of group, both $F$s < 1. On the other hand, IASC-AD scores significantly decreased across groups between baseline ($M = 24.93, SD = 9.24$) and study termination ($M = 14.22, SD = 5.32$), $F(1, 35) = 48.76, MSe = 37.11, p < .001, 95\% CI = [7.67, 13.97]$, partial $\eta^2 = .58$, Cohen’s $d = 1.26$. Figure 8 displays changes in IASC-AD scores between groups across time.

A mixed ANOVA with TAS-20 scores indicated no significant time × group interaction effect or main effect of group, both $F$s(1, 35) < 1. On the other hand, alexithymic tendencies significantly decreased across groups between baseline ($M = 50.66, SD = 12.75$) and study termination ($M = 38.89, SD = 10.79$), $F(1, 35) = 24.64, MSe = 78.80, p < .001, 95\% CI = [6.62, 15.79]$, partial $\eta^2 = .41$, Cohen’s $d = 0.95$. Figure 9 displays changes in TAS-20 scores between groups across time.

Lastly, results of a mixed ANOVA with SCS scores showed no significant time × group interaction effect, $F(1, 35) < 1$, or main effect of group, $F(1, 35) = 1.65, MSe = 0.74, p > .05$, partial
On the other hand, self-compassion significantly increased across groups between baseline ($M = 2.29, SD = 0.70$) and study termination ($M = 3.65, SD = 0.85$), $F(1, 35) = 55.63, MSe = 0.46, p < .001$, $95\%$ CI $= [0.94, 1.65]$, partial $\eta^2 = .61$, Cohen’s $d = 1.42$. Figure 10 displays changes in SCS scores between groups across time.

RCIs for BDI-II, AUDIT, DUDIT, and IPF scores were 8.89, 4.99, 5.64, and 14.37, respectively (see Table 6). Separate chi-square tests of ethnoracial differences in reliable change indicated no significant associations between group and RCI category on the BDI-II ($\chi^2[1, N = 37] = 0.07, p > .05$), AUDIT ($\chi^2[1, N = 37] = 5.00, p > .05$), DUDIT ($\chi^2[2, N = 37] = 2.01, p > .05$), or IPF ($\chi^2[1, N = 37] = 0.16, p > .05$). Approximately 11% to 76% of participants in the modified ITT set achieved reliable improvement on these measures. Notably, two participants (one from each ethnoracial group) reported DUDIT scores that fell in the ‘deterioration’ category.

RCIs for IASC-AD, TAS-20, and SCS scores were 6.77, 11.88, and 0.48, respectively (see Table 6). Analyses of ethnic differences in reliable change of these measures via separate chi-square tests of independence indicated no significant associations between group and RCI category on the IASC-AD ($\chi^2[1, N = 37] = 0.01, p > .05$), TAS-20 ($\chi^2[2, N = 37] = 0.82, p > .05$), or SCS ($\chi^2[2, N = 37] = 2.54, p > .05$). Approximately 46% to 81% of participants in the modified ITT set achieved reliable improvement on these measures. However, two participants (one from each ethnoracial group) reported TAS-20 scores that fell in the ‘deterioration’ category, and one ethnoracial minority participant reported deterioration in their SCS score.

4.4. Psychological Safety

Results of GEE analyses with C-SSRS indices consistently indicated no significant interaction effects for positive ideation, serious ideation, and positive behavior, Wald $\chi^2$s(1) = 0.000001, 0.10, and 0.02, all $ps > .05$, respectively. There were also no significant main effects of group for positive ideation, serious ideation, and positive behavior, Wald $\chi^2$s(1) = 0.0003, 0.26, and 0.02, respectively, all $ps > .05$. On the other hand, there were significant main effects of time, albeit only for positive ideation and positive behavior, odds ratios (ORs) = 0.91 and $5.70 \times 10^{-11}$, Wald $\chi^2$s(1) = 12.67 and
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12142.85, both \( p < .001 \), 95% CIs for ORs = [0.86, 0.96] and [3.75\(\times\)10\(^{-11}\), 8.67\(\times\)10\(^{-11}\)], respectively. The main effect of time for serious ideation was marginally significant, OR = 0.78, Wald \( \chi^2(1) = 2.74 \), \( p = .10 \), 95% CI = [0.57, 1.05]. In summary, there were no ethnoracial differences in change in likelihoods of all indices of suicidal risk on the C-SSRS across time. There were also no differences between ethnoracial groups on likelihoods of all indices of suicidality, when averaged across time. There was, however, significantly reduced likelihood of positive ideation and behavior (and marginally so, serious ideation) across time, when considering the entire sample.

Figures 11A-C display changes in percentage endorsement of all C-SSRS variables across time by ethnoracial group. Visual inspection revealed overall decline in treatment-emergent positive ideation for both groups across time, as well as minimal to no endorsement of treatment-emergent serious ideation or positive behavior beyond the informed consent interval for both groups.

Descriptively, a greater proportion of non-Hispanic White participants endorsed positive ideation than ethnoracial minority participants immediately before the first dosing (Visit 5-pre-drug; 32% vs. 9%) and at Visit 17 (second integration session after the third dosing session; 16% vs. 0%), while the reverse was true at Visit 9 (third integration session after first dosing; 45% vs 15%). Additionally, a greater (but still small) proportion of ethnoracial minority participants endorsed serious ideation than non-Hispanic White participants at Visit 9 (9% vs. 0%), the second phone call after the second dosing session (11% vs. 0%), and Visit 18 (the third integration session after the third dosing session; 9% vs. 0%). Similarly, a greater (but still small) proportion ethnoracial minority participants endorsed positive behavior than non-Hispanic White participants at Visit 18 (9% vs. 0%).

4.5. Correlations

Zero-order correlations were conducted between pre-post difference scores (i.e., scores at study termination minus scores at baseline) on primary outcome measures and pre-post difference scores on the IASC-AD, TAS-20, and SCS with the entire modified ITT sample. Table 7 displays these correlations. Results indicated significant moderate zero-order correlations between change in CAPS-5 scores and changes in IASC-AD, TAS-20, and SCS scores, \( r_s = .55, .41, \) and -.52, \( p_s < .001, .05, \) and .001, respectively. There were also significant moderate zero-order correlations observed
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between change in PCL-5 scores and changes in IASC-AD, TAS-20, and SCS scores, \( r_s = .39, .59, \) and \( .49, ps < .05, .001, \) and \( .01, \) respectively. Therefore, Hypotheses 4A-C were supported; greater reductions in emotion dysregulation and alexithymic tendencies and greater increases in self-compassion were associated with greater reductions in PTSD symptoms on the CAPS-5 and PCL-5.

5. Discussion

The MP-16/17 open-label trial was the most intentional effort to date to increase recruitment of ethnoracial minority participants in the investigation of the efficacy and psychological safety of MDMA-assisted psychotherapy for PTSD. MDMA-assisted psychotherapy, on average, was efficacious in terms of primary and secondary outcomes for both non-Hispanic Whites and ethnoracial minority participants. There were large effect sizes in terms of improvements in PTSD symptoms, depressive symptoms, trauma-related psychosocial functional impairment, emotion regulation ability, alexithymic tendencies, and self-compassion, as well as moderate-to-large effect sizes in terms of improvements in alcohol and drug use severity.

In fact, in terms of reliable change in CAPS-5 and PCL-5 scores, approximately 73% and 92%, respectively, of participants in the modified ITT set achieved full remission (i.e., PTSD absent) at study termination. Additionally, there were no iatrogenic effects in terms of PTSD symptom deterioration for the entire modified ITT sample. Similarly, the majority of participants achieved reliable improvement on most secondary outcome measures. Drug use severity fell into the ‘deterioration’ range for only two participants (one from each ethnoracial group), only two participants (one from each ethnoracial group) reported alexithymic tendencies that deteriorated, and only one ethnoracial minority participant reported deterioration in their self-compassion scores. In other words, MDMA-assisted psychotherapy was beneficial (or at least, non-iatrogenic) on all outcome measures for the vast majority of the sample in this trial. Our findings cohere with those of previous randomized controlled trials of MDMA-assisted psychotherapy, in which participants who received active doses experienced clinically significant reductions in PTSD symptoms, compared to inactive dose groups (e.g., Mithoefer et al., 2019). The present study also expanded upon previous
findings by examining a wider variety of secondary outcomes, with consistently positive findings on these measures.

Interestingly, when examining mid-treatment changes, ethnoracial minority participants self-reported significantly less PTSD symptom reduction on the PCL-5 after the first dosing session than non-Hispanic White participants, although this difference was erased post-second and -third dosing. This difference might be due to a variety of reasons, including possible discordance between self-reported and clinician-administered measures of PTSD symptoms (Cody, Jones, Woodward, Simmons, & Beck, 2017). Participants of color might also have had less trust in the therapeutic process initially, due to cultural histories of medical atrocities committed against communities of color in clinical trials (Harris et al., 1996; Suite et al., 2007). However, these explanations remain speculative. The rate of symptom change should continue be examined in future studies as an additional indicator of treatment response, especially in light of the related risk of higher dropout rates among ethnoracial minority participants in clinical trials for PTSD (Lester et al., 2010).

On a related note, the first two dosing sessions were accompanied by significant reductions in both self-reported and clinician-scored PTSD symptom severity, with the third dose serving to maintain gains until study termination. In Ot'alora G et al.’s (2018) recently published Phase 2 randomized controlled trial of MDMA-assisted psychotherapy, the 100 mg and 125 mg active dose groups exhibited further significant reductions in PTSD symptoms after the third dose, while the crossover 40 mg inactive dose group did not exhibit similar reductions after the third open-label dose. Therefore, our finding overlapped partly with what was observed for Ot'alora G et al.’s (2018) crossover inactive dose group, perhaps indicative of an emerging trend of a ‘floor’ effect in PTSD symptom reduction after two dosing sessions when participants know that they are receiving the medicine.

In terms of psychological safety, on average, likelihood of endorsement of most indices of suicidality on the C-SSRS lessened over time for both non-Hispanic White and ethnoracial minority participants. Specifically, there was overall decline in treatment-emergent positive ideation for both groups across time, as well as minimal to no endorsement of treatment-emergent serious ideation or
positive behavior beyond the informed consent interval for both groups. In terms of visually inspected group differences, for example, a greater proportion of non-Hispanic White participants endorsed positive ideation than ethnoracial minority participants immediately before the first dosing and after the third dosing, while the reverse was true during after the second dosing session. It might be interesting to speculate reasons for these differences. For instance, a few of the ethnoracial minority participants might have had challenging experiences come up during the second dosing session that might have been related to unique and chronic identity-related stressors. They might also have been subjected to culturally insensitive interactions during dosing with a predominantly non-Hispanic White pool of study therapists (Williams & Leins, 2016). However, these reasons remain speculative, since these observations have not been subjected to further inferential tests. Nonetheless, our psychological safety findings generally spoke to the low risks accompanying the MAPS protocol (e.g., see safety findings in Mithoefer et al., 2019), as well as infrequent reports of pernicious psychological reactions to psychedelic medicines in clinical trials when protocols were strictly adhered to (Johnson, Richards, & Griffiths, 2008; Vizeli & Liechti, 2017).

Our findings of overall lack of ethnoracial group differences in efficacy and safety were consistent with previous studies indicating similar findings for ethnoracial minority participants who completed clinical trials for PTSD. Indeed, Zoellner et al. (1999) and Lester et al. (2010) found no differences in efficacy between non-Hispanic White and African American females who participated in randomized controlled trials of cognitive-behavior therapy (CBT) for PTSD. This might mean that although ethnoracial minority individuals and communities likely encounter unique sources of prejudice and stressors on the basis of their race/ethnicity (Holmes, Facemire, & DaFonseca, 2016), they might still respond favorably to MDMA-assisted psychotherapy for PTSD. The present study adds meaningfully to the emerging literature on MDMA-assisted psychotherapy for chronic, treatment-resistant PTSD by attempting to answer the important question of whether this ‘breakthrough therapy’ is equally efficacious for individuals who have been severely underrepresented in previous trials. This is significant; while MDMA-assisted psychotherapy is currently in Phase 3 trials with potential FDA approval for administration to the general public in the
foreseeable future, no previous studies have specifically examined ethnoracial differences in efficacy and safety, a mandated area of research, at least in federally funded clinical trials (National Institutes of Health, 1994).

Another aim of the present study was to examine mechanisms of action potentially operating in MDMA-assisted psychotherapy among the present sample. As hypothesized, mean improvements in emotion regulation ability, alexithymic tendencies, and self-compassion were correlated with PTSD symptom reduction. First, it was possible that MDMA promoted participants’ ability to regulate their emotions effectively (e.g., increased relaxation, reduced hypervigilance/fear response). This in turn might have facilitated approach toward and adaptive reprocessing and reconsolidation of traumatic memories, when empathically supported throughout the dosing and integrations sessions by study therapists (Feduccia & Mithoefer, 2018; Johansen & Krebs, 2009). Second, MDMA might have reduced participants’ difficulties in effectively recognizing rewarding internal and external emotional cues in the therapeutic space (e.g., understanding feelings of joy or even euphoria during dosing, and/or recognizing empathic validation by study therapists while revisiting traumatic memories; Bershad et al., 2016; Jungaberle et al., 2018). In removing these alexithymic barriers to adequate emotional engagement with trauma-related memories, MDMA might have also facilitated corrective interpersonal interactions and concurrent PTSD symptom reduction during dosing and integration sessions (Feduccia & Mithoefer, 2018). Third, by encouraging the growth of self-compassion, MDMA might also have facilitated cognitive defusion from painful traumatic memories and increased feelings of common humanity. This might have in turn promoted authentic reconnection with loved ones and others in participants’ social spheres, thus contributing to PTSD symptom reduction (Carhart-Harris, Erritzoe et al., 2018). Importantly, however, the intervals at which these secondary outcome measures were administered precluded further prospective tests in support of these relationships. Future studies should aim to assess these variables in a manner that makes more temporal sense, and/or utilize innovative means of assessing change in putative mechanisms and outcomes of interest via, for example ecological momentary assessment (Shiffman, Stone, & Hufford,
2008). Specifically, moment-to-moment assessments of these variables can serve to predict changes in outcome variables at the next closest interval down the timestream.

5.1. Limitations and Other Suggestions for Future Research

The present study reported MP-16/17 data from baseline to study termination, and no information was available from the sponsoring organization (i.e., MAPS) about whether gains were maintained at long-term follow-up (or indeed, whether measures were even re-administered). Therefore, Phase 3 trials should continue to implement long-term follow-up measurements of gains.

The MP-16/17 trial was also open-label in nature, and participants were not randomly assigned to active or inactive dose conditions. As a result, although previous trials indicated significantly greater reductions in PTSD symptoms for active dose groups, it is still unknown whether, for example, ethnoracial minority participants receiving active doses of MDMA would exhibit greater gains than their inactive dose condition counterparts. The ethnoracial minority subsample in the modified ITT set was also small ($n = 11$), and so some analyses (especially with the suicidality data) might have been underpowered. Further, within our ethnoracial minority subsample, individuals of Asian descent were overrepresented, while other groups, such as African Americans, were underrepresented. Thus, the participants of color in the present study might not be representative of the general population’s racial demographics. Phase 3 trials should aim to recruit more ethnoracial minority participants in both the active and inactive dose conditions, with perhaps at least 50% of the enrolled sample comprising demographically representative ethnoracial minority participants, so as to allow for more statistically sound group comparisons of efficacy and safety.

On a related note, Phase 3 trials should consider expanding participant recruitment along additional parameters of diversity. An important methodological limitation in the MP-16/17 trial was that information on other demographic characteristics was not collected. Particularly, participants’ sexual orientation was not explicitly assessed in the MP-16/17 trial, which precluded additional analyses of whether treatment response might be influenced by sexual identity. This is important since there is some evidence of poorer trauma recovery rates among certain groups of sexual minorities,
compared to their heterosexual counterparts (e.g., bisexual women who experienced sexual assault; Sigurvsdottir & Ullman, 2016). There is also emerging recognition of the negative, compounding effects of stress related to intersecting ethnoracial, sexual, and gender minority identities on psychological well-being in the literature. For instance, Ching et al. (2018) reviewed how Asian American sexual and gender minorities were at elevated risk for increased stress exposure (e.g., ranging from interpersonal prejudice to aggression and violence) due to their multiple minority statuses. This exposure likely induces emotional and cognitive dysregulation processes that in turn contribute to internalization of stigma (i.e., internalized racism, homophobia, and/or transphobia), which then lead to psychopathology (Ching et al., 2018). At the same time, there is some discussion in the literature about the potential benefits of MDMA-assisted psychotherapy for ameliorating intersectional minority stress. For example, Ching (2020) described personal insights from an MDMA-assisted psychotherapy therapist training trial (i.e., MT-1; ClinicalTrials.gov identifier: NCT01404754), detailing insights regarding the need for radical self-acceptance of the intersectional aspects of his racial and sexual minority identities. As such, Phase 3 trials should seek to understand how participants’ different identities (e.g., race, ethnicity, gender, age, sexual orientation, etc.) may interact to influence treatment response. Related considerations include exploring how well differences in participants’ and therapists’ identities are recognized and broached in an inclusive and culturally sensitive manner during preparatory, dosing, and integration sessions. For example, it may be pertinent to have therapist pairings that are responsive to certain participant’s preferences (e.g., having sexual and/or gender minority [SGM] therapists for SGM participants). Regardless, examples of inclusive questions about demographic characteristics include those discussed in the guide by Hughes, Camden, and Yangchen (2016), and should be referenced by Phase 3 researchers to improve assessment of diversity in those trials.

In the modified ITT set, ethnoracial minority participants were significantly younger than non-Hispanic White participants. This was somewhat consistent with research indicating more openness toward MDMA/psychedelic drug use among younger compared to older individuals of color (Rigg, 2017). In fact, in the 2018 National Survey on Drug Use and Health (Substance Abuse and
Mental Health Services Administration, 2018), respondents of color aged 21 to 29 who endorsed lifetime use of MDMA comprised 37.7% of the ethnoracial minority sub-population surveyed, while respondents of color aged 50 years and older comprised only 5.5% of the same sub-population. This represented a wider disparity compared to the respective rates for non-Hispanic White respondents (ages 21 to 29: 27.4%; ages 50 and older: 17%). Additionally, in Barnett, Siu, and Pope, Jr.’s (2018) survey with a large sample of psychiatry resident-fellows and attending psychiatrists across the United States, a large minority (predominantly younger trainees) expressed optimism regarding the therapeutic potential of psychedelic medicines. In support, Wildberger, John, and Hallock (2017) found that while college students were reluctant to agree that psychedelic substances could be beneficial for a variety of mental disorders when used in a therapeutic setting, a majority endorsed the conduct of more research to explore the medicinal benefits of these substances. These findings are perhaps reflective of an emerging cultural zeitgeist about the beneficial effects of these substances, particularly among younger individuals. At the same time, the age difference was perhaps indicative of greater generational stigma toward participating in a drug-related clinical among older ethnoracial minority participants, compared with older non-Hispanic White participants (Neitzke-Spruill, 2020). This again supported the discussed difficulties inherent in recruiting marginalized populations in psychedelic research, such as differences in privilege that would influence volition and feelings of empowerment to participate (George et al., 2020).

Further, participants who enroll in MDMA-assisted psychotherapy for PTSD might arguably hold less skepticism about the viability of this approach for ameliorating their suffering. In fact, dropout was low in this trial (only one, after the second dosing session), and no ethnoracial minority participants prematurely terminated at all. This is in sharp contrast to previous psychotherapy and pharmacotherapy trials that have found significantly lower retention rates among ethnoracial minorities in clinical research (e.g., completion rate of 45%, vs. 73% for non-Hispanic Whites; Lester et al., 2010), owing to mistrust and fear of medical misconduct (Alim et al., 2006; Benítez et al., 2014). This perhaps speaks to the intentional emphasis on set and setting in MDMA-assisted psychotherapy, ranging from thoroughly addressing concerns and dispelling myths about the effects
of MDMA, to establishing and cultivating deep trust amongst the participants and co-therapists. It is possible that the ethnoracial minority participants in the present study felt comfortable, assured, and supported enough to have an overall positive experience with MDMA-assisted psychotherapy. However, at the same time, attitudes toward MDMA-assisted (or broadly psychedelic-assisted) psychotherapy were not measured here, and would be a worthwhile focus of research in Phase 3 trials. Specifically, attitudes, intentions, and motivations regarding the use of MDMA or any other classic psychedelic or consciousness-altering medicine can be conceptualized as part of participants’ set as they enter the therapeutic space (Hartogsohn, 2016). Research has shown that ethnoracial minority individuals tend to prefer pharmacotherapy to empirically supported psychotherapies (e.g., PE) for PTSD (Feeny, Zoellner, & Kahana, 2009). Skeptical attitudes toward pharmacotherapy can also negatively impact adherence (De las Cuevas, Motuca, Baptista, & de Leon, 2018). It would be interesting to see how stigma and skepticism toward the healing properties of psychedelics (especially among ethnoracial participants; Rigg, 2017; Rigg & Lawental, 2018), can be addressed during preparatory sessions. These extra-pharmacological factors should be assessed concretely to investigate whether they influence treatment response, and if so, how best to optimize them, based on participants’ needs.

Lastly, our findings showed that MDMA-assisted psychotherapy facilitated therapeutic processes beyond PTSD symptom reduction, in terms of improvements in emotion regulation ability, alexithymic tendencies, and self-compassion. Future studies can investigate the effects on other related constructs that may also function as additional mechanistic routes of change, such as posttraumatic growth (see Gorman et al., 2020). At the same time, it should be acknowledged that there is vast diversity in psychedelic experiences, the psychological mechanistic pathways of which can be mystical, spiritual, noetic, or even ineffable in quality (Leneghan, 2013). As such, inherent mechanisms of action may not be adequately or accurately captured by existing, standardized self-report measures, including even newer measures oriented toward psychedelic experiences (e.g., Mystical Experiences Questionnaire; Barrett, Johnson, & Griffiths, 2015). Mixed-method analyses of transcripts from MDMA-assisted psychotherapy sessions therefore allow for researchers to work in a
data-driven manner to pull together novel themes of therapeutic change and collate additional linguistic variables that may offer varied explanations as to why participants experience PTSD symptom reduction. Therefore, in Study 2, a mixed-methods case study incorporating qualitative and quantitative analyses of transcripts from an ethnoracial minority participant in the MP-16 trial was conducted. This case study also served the purpose of attempting to destigmatize the use of MDMA in PTSD treatment in a person of color, while simultaneously recognizing the limits of generalizability to the experiences of other ethnoracial minorities.

6. Study 2

6.1. Qualitative Psychedelic Research

Existing qualitative studies on the effects of classic psychedelics were pioneering in that they uncovered novel mechanisms of change for the psychotherapeutic process under investigation. Much of this work was done with psilocybin, the psychoactive component of ‘magic mushrooms.’ In qualitative interviews with participants who received psilocybin-assisted psychotherapy for clinical anxiety related to a cancer diagnosis, themes that commonly emerged included feelings of bliss and connectedness with the self, body, and others, ineffable experiences filled with spirituality and religious themes, as well as meaningful visions that lead to renewed vigor to face their cancer diagnosis, as well as revised priorities in life post-treatment (Belser et al., 2017; Swift et al., 2017). Similar qualitative studies have been conducted with psilocybin-assisted psychotherapy for treatment-resistant depression (Watts, Day, Krzanowski, Nutt, & Carhart-Harris, 2017), alcohol dependence (Nielson, May, Forcehimes, & Bogenschutz, 2018), and smoking cessation (Noorani, Garcia-Romeu, Swift, Griffiths, & Johnson, 2018).

There have been fewer qualitative attempts to uncover novel psychological mechanisms of action in MDMA-assisted psychotherapy for PTSD. To date, only one qualitative study has been conducted at the one-year follow-up interval to examine perceived beneficial effects of MDMA-assisted psychotherapy beyond PTSD symptom reduction (Barone, Beck, Mitsunaga-Whitten, & Perl, 2019). In that study, a substantial number of participants reported improved self-awareness, in that
they gained deeper self-understanding (e.g., reflecting, questioning, and altering their pre-treatment beliefs and actions) and self-compassion (e.g., that they were not to blame for their traumas), which led to better management of their PTSD symptoms. Additional themes included improved familial and social relationships owing to enhanced empathy and social skills, increased engagement in new activities owing to newfound motivation and sense of urgency to “live life to the fullest,” (p. 204), as well as reduced reliance on pre-treatment medications or problematic substance use to manage residual PTSD symptoms.

Therefore, while Barone et al.’s (2019) study was innovative in detailing the long-term effects of MDMA-assisted psychotherapy that served to maintain treatment gains over time, it was nonetheless retrospective in nature, and therefore subjected to memory decay and inaccurate recall, and/or extraneous/confounding factors and life events post-treatment. As such, this case study focused on transcripts from MDMA-assisted psychotherapy. This is because such data would detail, arguably, the most immediate and ecologically valid change processes and mechanisms of action for MDMA-assisted psychotherapy.

6.2. Quantitative Linguistic Research on PTSD

Tausczik and Pennebaker (2010) emphasized how word choice in language reflects variability in the way people think, feel, and potentially behave about different things. In other words, word use in language offers information about our internal experiences and potentially external reactions to different topics (Pennebaker, 2011). Thus, it is possible that changes in linguistic variables during PTSD treatment may serve as an indicator of mechanistic change free from the inherent biases of self-report measures.

A limited review of the literature on quantitative analysis speech and writing among participants who have undergone stressors or traumatic events revealed a range of relationships between certain linguistic variables and PTSD symptoms, or psychological distress broadly. Dunnack and Park (2009) found that at baseline, when participants engaged in repeated expressive writing about a traumatic experience, use of the pronoun ‘I’ was correlated with increased intrusiveness and
avoidance of thoughts about the traumatic event, and use of third-person pronouns being correlated with less adaptive emotion- and problem-focused coping. They explained the former as indicative of perceived personal responsibility for the traumatic event, and the latter as indicative of psychological distancing or avoidance of stimuli related to the traumatic experience.

Additionally, Fernández-Lansac and Crespo (2015) found that traumatized participants had significantly longer verbalized traumatic narratives (based on word count) and greater anxiety during disclosure than controls, and that narrative length was inversely correlated with time since the event. These findings were taken to support experiences of traumatic disclosure as high-arousal events, which might have led to more detailed and vivid (albeit not necessarily accurate) recollections, as well as demonstrative of the autobiographical memory decay effect over time, even for emotionally significant events.

Other researchers found evidence of relationships between PTSD symptom severity (or psychological distress) and words indicative of emotional, cognitive, sensory, and temporal processes. Greenhoot, Sun, Bunnell, and Lindboe (2013) found that greater use of negative emotion and sensory terms in young adults’ recount of past physical and/or sexual abuse predicted more severe PTSD symptoms (indicative of maladaptive reliving of their traumatic experiences), while greater use of cognitive terms predicted less severe PTSD symptoms (indicative of greater cognitive processing of their traumas).

Further, Jelinek et al. (2010) found that in trauma survivors’ recount of the worst moments of their traumatic memories (i.e., ‘hot spots’), those with PTSD used significantly more present-tense words and less cognitive processing terms (e.g., terms that involve causation, insight, discrepancy, tentativeness, certainty) in their narratives than those without PTSD, although no differences were observed for affect terms. These findings were taken to indicate that trauma survivors with PTSD suffered from poorly organized index trauma memories that contributed to maintenance of symptoms.

Lastly, Wardecker, Edelstein, Quas, Cordón, and Goodman (2017) investigated relationships between use of emotional language in trauma narratives of adults who experienced childhood sexual
abuse and self- and caregiver-reported indices of mental health. Results indicated that the use of negative emotion words was negatively correlated with self-reported PTSD symptoms and positively correlated with caregiver-reported emotional and behavioral problems. The authors explained the relationship between higher negative emotion word use and lower PTSD symptoms as indicative of approaching, instead of avoiding, and emotionally processing difficult trauma memories, which might have resulted in certain negative externalizing behaviors around caregivers.

It is worth noting that all of these studies have focused on expressive disclosure (written or verbalized) of stressful or traumatic experiences. This is methodologically dissimilar from the present case study’s focus on linguistic variables inherent in textual transcripts of the participant’s exchanges with the therapists in naturalistic integration psychotherapy sessions.

6.3. Purpose and Aims of the Present Case Study

In summary, qualitative methods allow researchers to investigate a wide variety of effects of MDMA-assisted psychotherapy that may serve as mechanisms for alleviating PTSD symptoms. At the same time, quantitative linguistic analysis may also help uncover novel variables that can additionally explain how symptom reduction may occur during MDMA-assisted psychotherapy. Thus, this case study utilized a mixed-methods approach to analyze transcripts from MDMA-assisted psychotherapy with an ethnoracial minority participant from the MP-16 trial.

Furthermore, as mentioned in Study 1, ethnoracial minority communities face multiple cultural barriers when attempting to access MDMA-assisted psychotherapy for PTSD. As such, the present case study focused on a South Asian American male participant who successfully completed treatment in the MP-16 trial, in hopes of providing an idiosyncratic cultural lens on recovery from PTSD for this participant. It is also hoped that this case study would serve as a destigmatizing report of what it would be like to receive this therapy for PTSD for people of color, while acknowledging limits in generalizability to participants from other marginalized groups.

This case study was primarily explanatory in nature (Baxter & Jack, 2008). First, a case profile was provided, which included descriptions of quantitative changes in the participant’s primary
and secondary outcomes, as well as suicidality, based on the same measures as Study 1. Next, qualitative analysis of the participant’s integration session transcripts was conducted to detail recurrent themes that represented effects and potential mechanisms of change. Only integration session transcripts were qualitatively analysed, because of their importance in prolonging effects and insights that might have arose during MDMA dosing sessions (Richards, 2017). Finally, linguistic variables derived from the participant’s preparatory and integration session transcripts were entered into exploratory zero-order correlation analyses with the participant’s PTSD symptom scores. Because the naturalistic transcripts in this case study differed methodologically from previous related research (see section 6.2.), there were no hypotheses about relationships between PTSD symptom severity and specific linguistic variables.

7. Method

7.1. Case Study Data

The case study participant was enrolled in an MP-16 site at the University of Connecticut Health Center in Farmington, CT. The participant was recruited by a flyer disseminated at the University of Connecticut’s main campus in Storrs, CT. The author was on the study team as a study therapist, and thus was granted access to the participant’s transcripts by the sponsoring organization (MAPS) for this case study, for pragmatic reasons. The participant, however, was assigned to a different therapist team consisting of a non-Hispanic White male psychiatrist and an African American female license-eligible marriage and family therapist. Transcripts used in this case study were provided in their raw form by MAPS on the online Descript software (2019), which transcribed audio recordings from preparatory and integration sessions with the participant into text documents. Two research assistants then collaboratively edited these raw transcripts for typos and organized them into dialogue format based on session recordings available on Descript. Only the participant’s transcribed speech was utilized for the analyses described in sections 7.3. and 7.4. From Study 1, section 3.2., sections 3.3.1. to 3.3.4., and section 3.4 contain information about eligibility criteria that the participant met, screening, primary and secondary outcome and safety measures that the participant completed, as well as the flow of procedures that the participant engaged in during the
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trial, respectively. This mixed-methods case study adhered to the Case Report (CARE; Riley et al., 2017) and the Consolidated Criteria for Reporting Qualitative Research (COREQ; Tong, Sainsbury, & Craig, 2007) guidelines.

7.2. Case Profile

A case profile of the participant was provided, including background information about his demographics, his reported index/worst trauma, a list of additional psychiatric diagnoses that he met criteria for during screening, as well as his psychological and pharmacological treatment history. Information was also provided on his vitals, drug testing results, and experience(s) of potentially adverse events throughout the study. The role of music in his dosing sessions was also described. Finally, descriptives of his scores on each measure from Study 1 were also briefly discussed and presented as graphs to provide a quantitative picture of his therapeutic progress throughout the study.

7.3. Interpretative Phenomenological Analysis

Transcripts from the participant’s nine integration psychotherapy sessions were entered into NVivo 12 (QSR International [Americas] Inc., 2018), a qualitative data analysis software used to code and analyze textual data for trends, themes, and patterns. All of the participant’s speech portions were coded for recurrent themes that detailed effects and potential mechanisms of change of MDMA-assisted psychotherapy using interpretative phenomenological analysis (IPA; Smith, Flowers, & Larkin, 2009), an idiographic approach highlighting the links between the participant’s speech, cognitions, emotions, and reported behaviors. A benefit of an IPA approach is the ability to garner a rich variety of results from a small sample size, or even a single case study. IPA was the analytical approach of choice in qualitative research on effects of psilocybin-assisted psychotherapy for clinical anxiety in patients with cancer (Belser et al., 2017; Swift et al., 2017). IPA and was also used as the primary qualitative analytical approach for long-term follow-up interviews of MDMA-assisted psychotherapy participants by Barone et al. (2019).

Transcripts were read and recursively coded in a data-driven manner, with codes eventually reaching saturation (i.e., at least 5 consensual codes for each node) and being abstracted into higher-
order themes. The coding team comprised of the author and the female co-therapist of the participant, who met regularly to achieve consensual agreement on reportable themes, with a final interrater reliability of .93. The coding team was restricted to these individuals due to the strong need for familiarity with the therapeutic process in order to maximize interrater reliability. Indeed, both coders had undergone the MAPS MDMA-assisted psychotherapy therapist training program, which included an experiential component with MDMA administration (see ClinicalTrials.gov identifier: NCT01404754; Ching 2020). Relatedly, Nielsen and Guss (2018) discussed the potential merits of experiential training with MDMA for enhancing attunement to participants’ challenges, needs, and experiences during dosing sessions, given the unique elements in MDMA-assisted psychotherapy that have no substantial parallels in modern training programs in psychopharmacology and/or psychotherapy.

7.4. Quantitative Linguistic Analysis

Finally, linguistic variables within the participant’s speech in his preparatory and integration session transcripts were derived using the Linguistic Inquiry and Word Count 2015 software (LIWC; Pennebaker, Booth, Boyd, & Francis, 2015). LIWC is a program designed to generate frequencies of different types of words in any given transcript, in order to infer cognitions, emotions, personality patterns, and motivations inherent in the transcribed material. Linguistic variables within each transcript were calculated as percentages of the total number of words analyzed for that transcript. The 2015 version of the LIWC dictionary contained linguistic categories that ranged from personal pronouns to affective, cognitive, and biological processes (Pennebaker, Boyd, Jordan, & Blackburn, 2015). Thereafter, exploratory zero-order correlational analyses were conducted between all generated linguistic variables and the primary outcome (i.e., CAPS-5 & PCL-5 scores) at intervals that made temporal sense. In other words, for example, the participant’s percentage use of linguistic variables averaged across the first two integrative sessions after the first dosing session (Visits 6 and 7) was paired in correlational analysis with his Visit 8 CAPS-5 score, while his percentage use of linguistic variables averaged across all three integrative sessions after the first dosing session (Visits 6, 7, and 9) would be paired with his Visit 9 PCL-5 score.
8. Results

8.1. Case Profile

8.1.1. Demographics and trauma history. Kenneth (pseudonym) was an 18-year-old, first-generation South Asian American, heterosexual, cisgender male college freshman student in a large public university in the Northeast region of United States, who participated in the MP-16 trial from April 2018 to November 2018. Kenneth identified his index/worst trauma as sexual assault by a family friend at age 13 on four separate occasions over the course of two months. He kept these experiences to himself for several years, and eventually disclosed them only to close friends. During the study, Kenneth reported that he still had not disclosed the abuse to his parents, owing to cultural stigma about the topic. He also endorsed multiple traumatic events in his late childhood to adolescence, including being the victim of racially motivated bullying at school (e.g., being called racial slurs while being hit and punched by non-Hispanic White male classmates). Furthermore, during his adolescence, on a camping trip, he witnessed a tree falling on his friends’ tent, suddenly killing two of his friends.

8.1.2. Psychiatric diagnoses. At baseline assessment, Kenneth met diagnostic criteria for PTSD; severe, recurrent major depressive disorder (MDD); and attention-deficit/hyperactivity disorder (ADHD), combined type. At the time of study enrollment, Kenneth reported no disability status, and denied lifetime use of MDMA/ecstasy.

8.1.3. Treatment history. Kenneth had sought out mental health treatment on several occasions during his adolescence, but was unable to engage meaningfully due to lack of perceived gains. Specifically, Kenneth reported receiving four sessions of supportive counseling from June 2016 to August 2016 for PTSD. Kenneth added that his parents’ disapproval of him being in treatment was an additional barrier. He elaborated that his parents held stigmatizing beliefs about mental illness and mental health treatment, attitudes that persisted throughout his participation in the study. As a result, Kenneth also had to keep his participation in the study “a secret” from his parents. Approximately
three months prior to study enrollment, Kenneth was receiving twice-weekly individual CBT for PTSD, and similarly reported lack of significant improvement in his PTSD symptoms.

In terms of pharmacotherapy, Kenneth was prescribed Wellbutrin XL (150 mg), which he took once-daily orally for a month from mid-March 2018 to mid-April 2018 to help with his depressive symptoms. He was also prescribed Vyvanse (40 mg), which he took once-daily orally for two weeks before study participation, before being switched over to Adderall (40 mg), to help with his ADHD symptoms during the academic semester. Due to study requirements, and under the supervision and assistance of the study physician and his prescriber, Kenneth was tapered off his antidepressant medication prior to study enrollment confirmation, to prevent contamination of efficacy findings. Throughout the study, Kenneth was advised to take his ADHD medication only during the periods when MDMA dosing did not occur (i.e., only during integration session weeks).

8.1.4. Vitals, other biometrics, and potentially adverse event(s). Throughout the study, Kenneth exhibited no clinically significant elevations in his vitals (i.e., systolic and diastolic blood pressure, pulse, body temperature). At pre-enrollment, Kenneth also exhibited normal electrocardiogram (ECG) and rhythm strip results, as well as normal clinical labs results. Furthermore, Kenneth did not experience significant changes in his appetite, weight, and BMI. The only minor potentially adverse event was a single episode of mild headache at the end of the second MDMA dosing session (i.e., Visit 10), which was quickly resolved with the ingestion of a single prescribed pill of ibuprofen. Table 8 displays all biometric measurements taken from informed consent to study termination.

8.1.5. Drug test results. During initial drug testing at the informed consent interval, Kenneth screened positive for cannabis and amphetamine use. He agreed to discontinue cannabis use throughout treatment, as well as temporarily stop stimulant medication for his ADHD symptoms prior to each MDMA session, all tapered off according to the study physician's instructions. Kenneth reported smoking marijuana mostly recreationally, but attributed a portion of his smoking as a means of managing his PTSD symptoms (e.g., to reduce arousal and hypervigilance). Kenneth screened negative for both substances immediately prior to first dosing session. However, he screened positive
for amphetamine use immediately prior to originally scheduled second dosing session, which was then postponed. Kenneth reported that he failed to abstain from his ADHD medication. Thereafter, he demonstrated full cooperation with study protocol and screened negative for all substances immediately prior to the rescheduled second dosing session, as well as the third dosing session.

**8.1.6. Music.** Time and care put into customizing the music playlist for each dosing session for Kenneth. For example, Kenneth requested for “galactic-sounding” instrumental music to be played at the start of the second dosing session, as a means to continue/build on “cosmic” experiences during the first dosing session. As such, the playlist was modified accordingly. Overall, Kenneth expressed satisfaction with the music selection for all of his dosing sessions, and reported that the music facilitated his therapeutic experiences during the dosing sessions.

**8.1.7. Treatment outcomes.** As a result of the treatment, Kenneth experienced clinically significant improvements in his PTSD symptoms. His baseline CAPS-5 and PCL-5 scores were 51 and 62; at study termination, they were 10 and 5, respectively. Figures 12 and 13 display his CAPS-5 and PCL-5 scores for all intervals, respectively. Based on the CAPS-5 dichotomous diagnostic scoring system, Kenneth did not meet DSM-5 criteria for PTSD at Visit 13 (i.e., after the second dosing session), and maintained recovery at Visit 19 (i.e., after the third dosing session). Based on the PCL-5 dichotomous diagnostic scoring system, Kenneth did not meet DSM-5 criteria for a provisional diagnosis of PTSD at Visit 9 (i.e., after the first dosing session), and maintained recovery at Visits 14 and 20 (i.e., after the second and third dosing sessions, respectively).

Kenneth also experienced clinically significant improvements in his depressive symptoms. At baseline, Kenneth scored 48 (severe range) on the BDI-II, while at termination, he scored at 6 (non-clinical range). In terms of his alcohol and drug use, he scored 5 and 4 on the AUDIT and DUDIT at baseline, respectively; his scores were 4 and 0 at study termination, respectively. These scores indicated that Kenneth did not report problematic alcohol or drug use throughout the study. Additionally, Kenneth experienced improvement in his trauma-related psychosocial impairment, with an overall pre-post score of 59.43 vs. 36.29 on the IPF. Furthermore, Kenneth experienced pre-post
improvements on the remaining secondary outcomes of emotion dysregulation (IASC-AD: 35 vs. 13), alexithymic tendencies (TAS-20: 67 vs. 40), and self-compassion (SCS: 1.65 vs. 3.27).

In terms of psychological safety, Kenneth endorsed positive ideation on the C-SSRS in the preparatory sessions leading up to the first dosing, and infrequently so in the sessions leading up to the second dosing, and did not endorse any positive ideation thereafter. Importantly, beyond endorsement of lifetime serious ideation and positive behavior on the C-SSRS at the informed consent interval, Kenneth did not report any treatment-emergent serious ideation or positive behavior.

8.1.8. Post-treatment outcomes. After study termination, based on correspondence with his female study therapist, Kenneth reported continuing freedom from his PTSD. He continued with individual talk therapy to continue “moving forward.” He was engaged in mental health activism, with a revitalized passion for helping others “find a way through their traumas.” Particularly, due to being helped by a female therapist of color, and being enrolled in the study at a site that prioritized minority mental health, he reported being inspired and motivated to create and promote mental health initiatives on campus. He was specifically interested in helping other students of color who might be struggling with mental health problems, but who lacked an encouraging presence (i.e., another person of color) on campus to discuss these issues with.

8.2. Master Themes

When all nine integration session transcripts were subjected to qualitative analysis via IPA, four master themes meaningfully emerged: (A) mechanisms of change; (B) reduced PTSD symptoms; (C) additional effects; and (D) navigating interpersonal relationships. Notably, certain nodes within almost all subthemes had meaningful connections with other nodes in other subthemes, illustrating the complex and interwoven nature of effects and mechanisms of action of MDMA-assisted psychotherapy for Kenneth.

8.2.1. Mechanisms of change. Kenneth narrated several pathways of therapeutic change that meaningfully emerged as three subthemes: (1) trauma reprocessing; (2) cognitive change; and (3) emotional awareness and regulation. These descriptions provide a comprehensive response to the
question, “How did MDMA-assisted psychotherapy bring about therapeutic change for this participant?” Details of each of these subthemes are described below in terms of their constituent nodes and exemplar quotes (see also Figure 14).

8.2.1.1. Trauma reprocessing.

8.2.1.1.1. Revisiting index trauma without being overwhelmed. Kenneth shared his experiences revisiting his index trauma without being overwhelmed. In the first integration session after the first dosing session, he recounted, with the aid of the MDMA, being able to dive into his memories of sexual trauma without “freaking out,” describing it as “tough, but manageable.”

The challenging part was just diving into those memories. But I wasn’t crying. In fact, I was able to sometimes laugh at some things. I was able to get through it, and was able to really dive into my own mind. It’s like, “I’m gonna go for it.” And I just went in and did it, you know?

In that integration session, he also voluntarily shared the experience of organizing memories of his sexual trauma using the metaphor of a filing cabinet, describing his trauma memories as now being whole, complete, and neatly organized as folders in the filing cabinet that is his mind, and accessible whenever he wants (see also section 8.2.2.3.1.).

Now it's like, I can remember if I want to, and I don't have to remember if I don’t want to. Now, they're all there, so that's really nice. It almost felt like I was going through files yesterday. Like, “Hmm, where is the hidden file?” Now, I can fully remember the whole kind of experience. It’s all there.

Kenneth also described other metaphorical experiences that fleshed out his journey of revisiting his past sexual trauma. In the first integration session after the first dosing session, he described being able to revisit moments of his sexual abuse rapidly as different “planets of experiences,” as a way to process them quickly and efficiently. He also described assuming a persona – manifesting as a cosmic comic character – which allowed him to survey his “planets of experiences.”

Each of my thoughts was its own planet, and I landed on each one. I lived at those planets, got embedded in them, and it was like I lived multiple lifetimes every couple of hours. That’s what it was like. That’s what it felt like to me, and that was awesome. It was nice to really dive into them, and live on those planets of experiences. While all that was happening, I also remember being Galactus, a giant cosmic character in the
Marvel Universe. He's essentially a god. So, I was just looking around, being him, and watching myself. I was watching my own experiences and it was just so cool.

8.2.1.1.2. Revisiting other traumas without being overwhelmed. In the integration sessions following the first dosing session, Kenneth also recounted other opportunities to process other traumatic experiences besides his past sexual trauma without being overwhelmed. Notably, he described his memories of shadowing a doctor in the terminal cancer unit of a hospital in the United Kingdom, and coming face-to-face with patients who were dying, and hearing the doctor break the news about their imminent mortality to these patients. He described these memories as having bothered him “only a little bit” during the dosing session, and how he was able to “talk them out” or “breathe through them.” He also discussed not being bothered by his other childhood traumas, such as his father beating him with a belt or his parents stuffing his face with spices as punishment. He elaborated that he accepted that those events happened and were in the past, and that he was no longer worried about any intrusive symptoms (which were now minimal) related to these events.

We would have to go into these cancer wards, and it was horrible. I don't regret the experience, but I also don't know if I was really old or ready enough to go and do that, you know what I mean? The doctor I was shadowing, he's very charismatic and stuff, especially when he gave what I came to understand as the “you're going to die” talk. In terms of being beaten with a belt, I feel more relaxed almost, just kind of more accepting that he [his father] is too old to do anything like that now. In the past two weeks, these memories have come back only once. I was like, “Oh, I guess this is coming back.” It was really surprising because I was expecting it to be more jarring, and it just wasn’t.

Kenneth also shared a segment of particularly vivid visual experiences during the second dosing session, which culminated in him carrying his younger self out of his home while his parents were fighting. He viewed this moment as potentially related to the process of integrating different parts of his self (see section 8.2.1.1.3. for more details).

Something triggered me to go back to when I was younger, and I remember witnessing my parents fighting and stuff. I also remember entering the house as my current self, and finding the younger me, and just carrying the younger me safely out of there.

8.2.1.1.3. Merging parts of self. Through several symbolic metaphors and visions in the first dosing session, Kenneth was able to experience the merging of his pre-trauma (i.e., “innocent child”), post-trauma (i.e., “angsty teenager”), and ideal selves (i.e., “final God-like form”). Through this process, he also experienced the merging of the various emotions that these parts represent (e.g.,
happiness, joy, calmness) as a way to honor and validate the “angsty teenager's anger,” whom he described as a soldier who had to struggle through the trauma. Ultimately, in merging his various selves, he was able to “remove the mask” that he had to put up in order to navigate the world after his sexual trauma, and emerge as an integrated person. In his exposition during the third integration session after his first dosing session, Kenneth expressed references to pop culture (e.g., Star Wars) and Hinduism and its associated gods, all of which serve as cultural inspiration for this integration of selves after his sexual trauma.

There was the innocent child, angsty teenager, and the adult God form. The innocent child is the one that existed before any of the abuse, who’s happy and relaxed, before any of the bad stuff happened. The angsty teenager’s right after that, and the God is the final form. I feel like now the angsty teenager’s personality is dying a little. There’s not enough reason to be angsty anymore. Now the innocent child’s happiness and pureness is mixing with that God-like form. However, I don’t think the angsty teenager dies off per se, I think he merges with the God. The angsty teenager feels like a fallen soldier almost. You have done your service, go and rest. You need it. Let go of the pain. It’s almost like he’s dying, but he’s also reaching a higher state. It’s kind of like the pain and sacrifices the angsty teenager endured and made are still taken as guidance, he’s just not in the main picture anymore. It’s like when a Jedi dies. They don’t actually die, they just become a part of the Force. It’s also kind of like a Hinduism thing. In the Baghavad Gita, Krishna can be at times a baby. It can also be the chariot driver for Arjuna, and it can also have an all-powerful universal form too, you know? It’s kind of like all these things mixed together. Now, all of the parts of myself can work well together. It's also like Harvey Dent and Two-Face coming together and being able to coexist. And it's really nice, because it's easier to show up fully in all of my interactions and not have to hide or mask myself in different relationships.

8.2.1.2. Cognitive restructuring.

8.2.1.2.1. Identifying cognitive distortions. In the second integration session after the first dosing, Kenneth expressed the insight that in the past, his need for achievement and perfectionism, which he saw as a way to cope with the sexual trauma, have typically led him to feel disappointed with himself whenever he did not meet his own standards. In doing so, he gained a retrospective realization of how these dysfunctional patterns of thinking were maintaining his difficulties in functioning.

It would be this vicious cycle where like I wouldn't necessarily achieve what I wanted to achieve, feel guilty about it, feel bad, and then those feelings would impede me from doing well, which would then stop me from achieving something. Eventually, it becomes real. If things spin in a negative way, I’ll feel down, and that's not good. I
realize now that if I continue to have very, very high goals for myself and no room for error or failure at all, then things are almost always going to take a downward spiral.

8.2.1.2.2. Challenging cognitive distortions. As a result of his newfound awareness of his cognitive distortions, Kenneth reported being better able to challenge them in ways that he was not able to. For example, in the second integration session after the first dosing, he described, without much prompting, being able to positively reframe past failures as situations in which he had tried his best, which led him to feel more satisfied with himself. Doing so also led him to view things as less “high-stakes.”

With every achievement, there are bound to be some flaws along the way. For example, Michael Phelps didn’t win a perfect 28 gold medals, he got a few silver and bronze medals on the way. That’s still an amazing achievement. In the past, I was striving to achieve, but I was never satisfied. Now, I’m satisfied. The striving to achieve is still there. However, instead of being negative or critical with myself, I’m more constructive with myself in a lot of ways.

He was also able to accurately recognize that he was older and less physically vulnerable, which made him less fearful about trauma-related cues and reminders (see also effects of these cognitive reappraisals in section 8.2.2.3.2.).

Before all this, when my parents called my name, I’m a little fearful, but it’s less now. Now, I fully realize that they can’t really do much to me anymore. They can’t do any of those physical punishments that they did when I was younger. I’m too grown for that. There’s no need to protect myself or be as fearful anymore. There’s no danger anymore.

8.2.1.2.3. Self-efficacy against future stressors. During the final integration session after the third dosing, Kenneth described a sense of self-efficacy in taking on any potential negative events in his future, and felt sufficiently resourced to be buffered against future stressors. He endorsed a lack of worry about stressors in his future, because: (1) he believed that he was prepared to handle them; (2) he trusted that others (e.g., any therapist he might see in the future) would help him out; and (3) his PTSD symptoms were very much improved.

I think there’s just a lot fewer things bothering me right now. If I hadn’t received the treatment, in terms of relationships and stuff with my family, plus the PTSD, I would just be a mess. Now I’m just ready to take things on. Everything just feels stable, I’m not worried about anything. Anything bad can happen, and I’ll be able to take care of myself. And if not, I’ll just ask others for help.

8.2.1.3. Emotional awareness and regulation.
8.2.1.3.1. Experiencing emotions in their fullness. Kenneth reported experiencing emotions in their fullness during the first dosing session, which he discussed as different than his usual mode of “bottling things up” and not being aware exactly of what emotion(s) he felt internally. Specifically, he was able to experience the release of anger – emotionally, verbally, and somatically – which he had attempted to suppress or numb throughout his teenage years, ever since his sexual trauma. He was also able to recognize and experience other emotions, such as sadness, in the form of crying and self-talk. Kenneth also reported utilizing motivational lyrics in rap music to bring forth positive emotions during the night of the first dosing session. These changes were consistent with his improvements in alexithymic tendencies on the TAS-20.

Typically, I wouldn’t be that angry. I would just kind of bottle it up, and this time I just didn’t want to bottle it up. It's not going back in my muscles. That’s not happening. I’ve also become more kind of expressive, I’m more able to cry and stuff which is a lot nicer. It was nice to feel things, and know exactly what they mean and represent. Right now, it feels better because I’m also talking it out. Also, after the session, when I was alone, I put some Lil Uzi Vert on and I realized, Lil Uzi is so happy. There’s a song where he is like, “I can do what I want, I’m better now.” I was like, “Damn, that’s relatable.”

8.2.1.3.2. De-escalating negative situations. After the first dosing session, Kenneth reported successfully de-escalating arguments with his parents by not shouting back, or responding with affectionate behaviors (e.g., hugging them). He would also resort to humor to highlight the absurdity of situations that used to make him angry. At other times, he would offer solutions to his parents to minimize arguments. Prior to the treatment, Kenneth would display negative emotional responses during conflicts with others, which would cause the conflicts to escalate. Now, he would instead turn to these healthier ways of responding, which he attributed to an increased awareness of how negative emotions could often influence people’s responses in conflicts. These changes were consistent with his improved emotion regulation ability on the IASC-AD.

The other day, my parents were really mad at me for spending a bunch of money because I was buying a lot of food. Instead of getting mad, I told them to take my credit card back, and give me an allowance instead. Every time they would yell at me, I was just able to bring the situation back down. To be honest, I just treated my mom the way I would treat Paula [pseudonym; his romantic interest during the study] when she gets mad at me. If I just calm myself down and give her a hug, she'll relax and won’t freak out on me. I was like, “If it works with her, why not try it on my mom?” And I did just that, and it worked pretty well.
8.2.1.3.3. Meditation and stretching. In terms of additional strategies to regulate his emotions, Kenneth reported starting a regular practice of brief meditations after the first dosing session to calm down or increase his concentration. He expressed the desire to maintain his meditation practice so that his feelings of calmness could be sustained in the long term. He also described how these meditations have allowed him to further develop his ability to mentally let go of anger, likening it to “dropping a hot object.” He also reported using meditation to manage other negative internal experiences (e.g., paranoia), to the extent that he would feel calmer and much less affected by these internal experiences whenever they surface, even in the presence of trauma triggers. Additionally, due to the use of therapeutic touch in the second dosing session (see Mithoefer, 2016), Kenneth expressed an interest in regular practice of full-body stretches, which he endorsed as helping to release muscle tension in his neck and shoulders, as well as any residual anger that was associated with his adolescence and past sexual trauma.

I now like to meditate for brief periods because it helps me calm down. The effects tend to last a good amount of time. You know how some people describe being angry as holding on to something hot? That’s what it feels like to me when I’m meditating, kind of letting the anger go. If I’m angry, I’ll just meditate. It helps me to cope with it and accept it. Because I’m meditating, I’m just a lot less angry, and also less tense, and I feel a lot less paranoid. Also, when you pressed on the spots of tension on my body during the second session, it felt really good. I just felt so much relief. I feel like I can breathe more, because I’m constantly like, stretching out. So much tension has been relieved from my body because of that.

8.2.1.3.4. Compassion toward self and others. Through a variety of metaphors during the integration sessions after the first dosing session, Kenneth also developed a softer, more relaxed, less angry, and more compassionate inner voice whenever he introspects about his current problems. He described his inner voice as calmer and more solution-focused, as opposed to being frustrated and annoyed. Metaphorically, he described his inner voice as akin to a mature God voice which was not so hard on himself, as opposed to his earlier, angsty teenager voice. These changes paralleled his increased self-compassion on the SCS.

If someone else comes to me for advice, I’m calm and collected. I’m like, "Why don’t you try this?" However, if I’m talking to myself, I’m like, "Why are you such an idiot?" Now it’s changed. That voice for others is also now for myself, which is nice. If I have a problem it’s like, "Alright, what are we gonna do here?"
Furthermore, after the first dosing session, Kenneth was also able to experience compassion toward his perpetrator, as well as others who have engaged in potentially trauma-inducing behaviors (e.g., people who engaged in sexual misconduct on campus, his father who beat him when he was a child). He described being able to see their pain and the reasons why they might have acted the way they did, and was able to acknowledge and be compassionate to their motivations.

I don't think anyone does anything bad because they’re inherently evil. I think they do it because they’re in some sort of pain, and this is what comes from that pain, or how they cope with it.

8.2.2. Reduced PTSD symptoms. Kenneth further described various domains of PTSD symptom reduction that meaningfully emerged as four subthemes: (1) reduced intrusions; (2) reduced avoidance; (3) improved cognitions and mood; and (4) reduced vigilance and arousal. These descriptions provide a comprehensive response to the question, “What are the effects of MDMA-assisted psychotherapy on PTSD symptoms for this participant?” These themes correspond to Kenneth’s overall PTSD symptom reduction on the CAPS-5 and PCL-5 (see Figures 12 and 13). Details of each subtheme are described below in terms of their constituent nodes and exemplar quotes (see also Figure 15).

8.2.2.1. Reduced intrusions.

8.2.2.1.1. Reduced flashbacks. Kenneth denied experiencing any flashbacks after the first two dosing sessions, and found it easier to focus since these symptoms were not there to distract him from tasks at hand. He was also able to relate a sense of surprise at how his flashbacks were absent even just after the first dosing session, even in the presence of trauma reminders. Furthermore, he described the function of flashbacks as his brain’s way of helping him fill in gaps in his index trauma memory, which he believed was now unnecessary (and hence, non-existent), since he reported now having complete memory about his sexual abuse (see section 8.2.2.3.1.).

A lot of times whenever I was doing anything, especially when I was working on things, sometimes I’d have flashbacks, and that would bother me a lot. I’d almost dissociate. I wouldn’t remember where I am, and then I’d have to recalibrate, because I’m distracted. Now I don’t have any flashbacks at all.
8.2.2.1. Reduced nightmares. After the first two dosing sessions, Kenneth denied having nightmares related to his sexual abuse or other traumas. Instead, his dreams have been “neutral or normal.” Now, whenever he woke from dreams in the morning, he would be able to get on with his day, since these dreams neither were trauma-related nor induced terror.

Now, when I have dreams at night, they’re normal. They’re not like the nightmares I had about the trauma. These days, I haven’t woken up in a cold sweat at all.

8.2.2.2. Reduced avoidance.

8.2.2.2.1. Reduced avoidance of trauma memories. Even after the first dosing session, Kenneth was able to approach his trauma-related memories, which have decreased in frequency and intensity. He viewed them now as non-intrusive, and was not distressed or overwhelmed by them.

Now I just let those memories play through. I can easily deal with those experiences now. I don’t have to avoid them or distract myself.

8.2.2.2.2. Reduced avoidance of trauma reminders. Similarly, after the first dosing session, he was able to approach trauma-related reminders. For example, he was able to actively listen to news on the radio about sexual assault and misconduct perpetrated by influential figures, whereas in the past, he would immediately switch the station to prevent distressing flashbacks.

There was something on NPR where they're talking about how the New York prosecutor in the Harvey Weinstein case actually has his own sexual assault claims. I just let it play through. I can now kind of deal with those experiences that remind me of the trauma, and not avoid them.

8.2.2.3. Improved cognitions and mood.

8.2.2.3.1. Complete index trauma memory. Kenneth described flashbacks prior to the study as his brain's way of remembering bits and pieces of the sexual trauma. However, after the first dosing session, he was able to remember everything about the sexual trauma, which he believed was the reason why he no longer experienced flashbacks or other intrusive symptoms.

Whenever I got the flashbacks, it felt like they were missing pieces that pop up, and were just another thing that I have to make sense of. Now, it feels like I don’t need to have those moments. Even though the flashbacks were really annoying and frustrating, they also definitely helped with trying to remember things. It was one of those things that really bothered me. Like, how can I not remember something? I think it was just always stuck in my brain, my brain was constantly trying to remember it.
Whenever I would remember something, it was like, “Oh, we got something. Here! Here!” It’s like my brain is that “Over here!” kid who found something cool in the dirt and had to share it, but it’s actually disgusting. I would be like, “Put that down! Put it back!” Now I just feel good. I don’t need to keep searching, it’s just all there. I remember everything, and I don’t see it being a problem now.

8.2.2.3.2. Resolution. Kenneth also described accepting the sexual trauma as an event in his personal history. This was a stark contrast from his previous perseverative self-blame for not having been able to defend himself against the perpetrator. After the first dosing session, he also expressed feeling, for the first time in his life, like he was able to “deal with” and resolve his thoughts and feelings about his sexual trauma on a deep level, which elicited a lasting sense of contentment.

I was going through the trauma in my head during the session. Just accepting it once again, affirming it, like, “Yes. It happened. But I’m alright now.” You know how when you have a problem you and you deal with it and feel content afterwards because you handled the problem? It feels a lot like that, but on a deeper level.

He also described greater clarity after the first dosing session, due to improved PTSD symptoms. He reported feeling more focused, and was able to process things in his life more clearly, even with persisting inattention symptoms.

After the session, things are a lot clearer, and I feel like I’ve just gotten so good at figuring out problems, that I don’t need to go to others for advice. I just figure them out by myself. I can just ponder and come up with a solution, just like that. It’s like archery, and I’m aiming for the bullseye, and I’m rapid firing, and I keep splitting the bows in half every time because it just keeps working.

Because of this clarity, during the second dosing session, he was able to move beyond acceptance of his sexual trauma, and attempted to internally resolve his residual trauma-related feelings of paranoia, anger, and irritability, as an active form of problem-solving.

Now, things are clearer, and if I just focus on something, I can handle it. So during the second session, I was like, “Alright, I have this trauma, and I want to do this. Let me go dive into that. I still have a few symptoms, let me go dive into those.” And I just went for it. There was a time when I sat up and I was repeating the symptoms that were bothering me. The paranoia, the irritability, the anger, I just kept naming them out loud over and over again until I started having that dialogue with these feelings, and then I was able to handle them. They don’t bother me now.

Finally, after the third dosing session, Kenneth articulated that his traumas have been resolved, and was now looking forward to seeing what life had in store for him next. He described a deep feeling of freedom and liberation from his traumas, and wanted to metaphorically “charge
forward into the unknown” that was his future and embrace it, instead of being afraid of it.

Essentially, he felt like he was ready for a “fresh start in life.” This might also account for his motivation to accomplish several things near study termination (see section 8.2.3.3.1.).

*It feels like I’m finally moving forward. It feels like the traumas had been taken care of. I’m figuring out what to do going forward. It’s really relaxing, really freeing. It’s like, “Yes, we got it.” Now it’s time to charge forward into the unknown and see how things come out, and embrace what comes next.*

8.2.2.3.3. Feeling happy. In the integration sessions after the first two dosing sessions, Kenneth described experiencing sustainable feelings of happiness and optimism, and reported being able to smile more. He also reported being more motivated to do things, and believed that negative events in his life or the world could be confronted and solved. Notably, after the third dosing session, a few interpersonal conflicts managed to upset him, but he was able quickly seek emotional support from his brother. These changes were consistent with Kenneth’s improved BDI-II scores.

*I just feel like my motors are running a lot quicker because there’s less gunk. Less sadness gunking up everything. These days, I wake up and I’m not so pessimistic about everything. It won’t even be a sunny and cheery day, and I would be like, “Let’s go do some work. Let’s get to it.” I’m smiling a lot more, and I feel a lot happier, in a sustainable way.*

8.2.2.4. Reduced vigilance and arousal.

8.2.2.4.1. Reduced vigilance. After the first two dosing sessions, Kenneth described significantly reduced vigilance for signs of physical danger in his surroundings, such as when going to bed at night, or crossing his backyard in the dark to get to the shed, where he would spend most of his time at home.

*Last night when I was like, “The door’s closed, the curtains set, I’m gonna go to bed.” In the past, I would have checked way more for safety. It was interesting because I could sleep normally. I wasn’t worried, you know? I didn’t have to distract myself from thoughts about danger or anything. Also, now when I’m walking to the shed at night, I’m much less fearful. Before the treatment, I would carry a stick with me, but now I don’t.*

8.2.2.4.2. Somatic relaxation. Kenneth also described experiences of progressive somatic relaxation. He described not being as “tensed up” as before, and felt less physiologically aroused, and less jumpy or “on edge,” and less irritable. For example, after the first dosing session, he said:
I just feel like more relaxed and stuff, you know?

After the second dosing session, he elaborated:

I feel pretty relaxed. I’m also definitely less easily aroused. I am less jumpy. It’s kind of one of those things I had to work on taming a little in the past, but now I’m naturally less on edge.

After the third dosing session, he added:

It felt more physical than mental this time in terms of the experience. And it was almost like, I was so relaxed, like too relaxed. Like, how am I this relaxed? Like, what is going on? I just felt like I was sinking into the couch.

8.2.2.4.3. Restful sleep. Kenneth also reported improved sleep quality, with significantly reduced waking after the first two dosing sessions. However, he reported significant sleep deprivation during the last integration session after the third dosing, because he was investing a lot of time in academic and extracurricular priorities and passions (see section 8.2.3.3.2.).

It’s been really nice to get some solid sleep, to sleep soundly through without waking from nightmares. I realize with the MDMA, like in my head, I’d just be like, “Take me.” And when I’m in bed, I just do the same thing. I just think to myself, “Take me,” and I just think about that until I just pass out, you know? And so that’s been really nice.

8.2.3. Additional effects. Kenneth narrated additional effects of the treatment that meaningfully emerged as four subthemes: (1) reduced suicidality; (2) reduced illicit substance use; (3) pursuing priorities; and (4) negative effects. These descriptions provide a comprehensive response to the question, “What are the additional effects of MDMA-assisted psychotherapy for this participant?” Details of each subtheme are described below in terms of their constituent nodes and exemplar quotes (see also Figure 16).

8.2.3.1. Reduced suicidality.

8.2.3.1.1. Vision of future self. During the first dosing session, Kenneth saw himself living life as 60-year-old, which signaled to him that he needed to abandon his distorted, suicidal belief that he would not be able to live past age 40. He described the effects of MDMA as propelling him forward in time, so that he could envision what life would be like for him as a healthy 60-year-old, with several healthy reasons for living.
The MDMA definitely helps you zoom forward, you know, like seeing past the age 40. That was always the arbitrary number. It's so much easier to believe you'll live past that age if you can see past that age. It's really hard to say you're gonna die at 40 when you see yourself at 60. I just couldn't hold onto that belief anymore.

8.2.3.1.2. Reduced suicidal ideation. As a result of the aforementioned insight, as well as his significant reduction in PTSD symptoms after the first two dosing sessions, Kenneth experienced rapid reductions in the frequency and intensity of his suicidal thoughts. He described these thoughts as being much less egosyntonic, and was able to easily and quickly control, dismiss, or ignore these thoughts with minimal distress. Additionally, when his suicidal thoughts would occur, he reported nonetheless able to attend to activities that he would be engaging in, instead of being distracted by those thoughts. These changes were consistent with his reductions in suicidality on the C-SSRS.

I had a suicidal thought just once. That was on Saturday. But I’d also like to point out that one was a lot different than before. It felt much more surface-level than actually, genuinely wanting to do it. And it was also much less intense. Before all this, it would feel like an 8 or a 9 out of 10, but now it’s at most 2 at the worst. I would say after a minute or two I was able to control and dismiss it pretty solidly.

After the third dosing session, he would still get upset by negative events, but not to the extent that he would have suicidal thoughts.

Nope, no wishes that I was dead since the last time you asked. Like I’ll get somewhat sad but it never gets to that point which is like, “I don’t want to live anymore.” I’m all done with thinking that way.

8.2.3.2. Reduced illicit substance use.

8.2.3.2.1. Appreciating potential of psychedelics. Kenneth also expressed deep appreciation of the potential of MDMA and other psychedelics for catalyzing foresight in people he admired, such as Steve Jobs. At the same time, he was also cognizant that these substances should not be used recklessly, and after three dosing sessions, expressed no desire to engage in psychedelic use.

I can now see why Steve Jobs did so much after taking psychedelics. In his biography or in the movie they talk about how he wouldn’t have been who he was if he didn’t have those experiences that allowed him to kind of, see forward.

8.2.3.2.2. Reduced desire for marijuana. After first two dosing sessions, Kenneth also expressed less desire or need for marijuana as a way to cope with his PTSD symptoms. In fact, during the study, he turned down multiple opportunities to “smoke weed” when offered by his roommates.
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This was consistent with his reduced drug use on the DUDIT. However, while Kenneth reported decreased marijuana use, he would engage in occasional overuse of stimulant medication for his ADHD, which he endorsed as primarily to assist him in completing schoolwork on time so that he could devote more time to extracurricular initiatives (see sections 8.2.3.3.1. and 8.2.3.4.2.).

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I \text{ have much less need or want for weed now, since that was mostly to help with the PTSD. My friends brought me more weed for my birthday, and I was like, “I don’t want that, you know?” I cannot smoke while I’m in this study. I also just don’t want to smoke, you know? I don’t need to.}
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8.2.3.3. Pursuing priorities.

8.2.3.3.1. Hypermotivated. In the integration sessions after the third dosing, Kenneth reported feeling “hypermotivated” to accomplish multiple goals. He described this motivation as being dormant before the start of the study, and which he had managed to “reignite” due to the effects of the MDMA. He further described in detail his approach (i.e., “going for overkill”) for achieving these goals, which ranged from academic aspirations to extracurricular initiatives, as well as medical internships and lab assistantships. On one hand, these changes were consistent with his improved functioning on the IPF. On the other hand, however, he conveyed a strong belief that he would need to shoulder most of the responsibility to create and maintain his restorative justice and minority mental health initiatives (see also section 8.2.3.3.2.), which added significant stress. Additionally, while he was cognizant that he would need adequate sleep so that he could have energy to pursue his goals, he reported being unsure how to achieve this “balance” between accomplishing his goals and maintaining a healthy sleep schedule (see also section 8.2.3.4.1.).

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\text{Preferably I want to get into an M.D./Ph.D. program. That’s my goal. That’s also really hard to do. But I’m gonna go for overkill. I think the only sure-fire way you can achieve something is if you just go for overkill. If you get used to doing that, you can make it sustainable, and then that becomes your natural state. But I also know that for problem-solving and learning, sleep is very necessary. The problem is that there’s so much schoolwork. Add to that the important causes that I want to support that I sometimes forget about the fact that sleep is very necessary. I just have to figure out a way to find a balance. I have to be able to make this last so that my dreams and initiatives will last, you know? And as for my initiatives, if I don’t pursue them, no one else is going to pursue them. No one else has the passion, or knows exactly what to do. They’re my initiatives, so I have to focus on them, I have to be the one doing them, you know?}
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8.2.3.3.2. Posttraumatic advocacy. After the third dosing session, Kenneth was actively attempting to create initiatives pursuing restorative justice for sexual misconduct on campus. In doing so, he had to peruse complaints that he had requested access to through the relevant institutional department. Notably, this was another indication of non-avoidance of trauma reminders. He described feeling motivated to get implicated organizations on campus shut down, so that others would not be subjected to the sexual violations that these organizations seemed to perpetrate.

“If I pursue these cases and get these organizations shut down, or get an investigation into the system going and call people out and fix policy and get people removed, that’s a change that matters. Because that means that there would not be any future or people suffering. And as long as I can do something about it, I’m going to do something about it.”

8.2.3.4. Negative effects.

8.2.3.4.1. Sleep deprivation. While Kenneth reported occasional fatigue throughout treatment, he experienced significant sleep deprivation after the third dosing. This was because the new academic semester had begun, and Kenneth was also feeling hypermotivated to accomplish several goals (see section 8.2.3.3.1. above). Around this time, Kenneth would stay up most nights to complete schoolwork and work on his initiatives, and not get sufficient sleep. He reported that his sleep debt, as well as his occasional overuse of his ADHD medication (see section 8.2.3.4.2.), had led to transient side effects such as mild visual blurring.

“I sleep very sporadically. During the week, there will be around two days where I just won’t sleep and then the weekend is when I catch up a lot on it, which is not healthy. And if I don’t sleep for a couple days, some things, like lines and colors, tend to blur, but it’s not very bad or noticeable. But like, how else does one get all of this work done?”

8.2.3.4.2. Chest discomfort. Post-third dosing, Kenneth would occasionally use more Adderall than prescribed, which he believed contributed to mild chest pain/discomfort, when coupled with his sleep debt. He expressed the primary reason for this overuse of Adderall as wanting to be able to complete all of his schoolwork so that he could pursue his various initiatives. He also expressed concern about having chest pains at his age, and described a commitment to comply with his prescribed dosage after study termination.
I was on 30 mg of Adderall a while back, and it increased to 40 mg over the summer, but now I occasionally take 60 mg per day to help me get more work done. But whenever I do that, I would get light chest pain. It's not something I'm used to. When I texted my brother, who’s in medical school, he said it’s probably the Adderall, and lack of sleep. I think so too.

8.2.4. Navigating interpersonal relationships. Kenneth also shared in much detail his thoughts, feelings, and behaviors related to past, current, and future envisioned interpersonal relationships. These descriptions meaningfully emerged as three subthemes: (1) navigating relationship with parents; (2) navigating romantic relationships; and (3) navigating friendships. These descriptions provided more information on additional effects of MDMA-assisted psychotherapy for Kenneth. Details of each subtheme are described below in terms of their constituent nodes and exemplar quotes (see also Figure 17).

8.2.4.1. Navigating relationship with parents.

8.2.4.1.1. Non-disclosure. Even after two dosing sessions, Kenneth was still adamant about not telling his parents about his sexual trauma, his involvement in the study, his past and current stressors, his restorative justice and mental health initiatives, or his dating life. Instead, he chose to come up with cover stories whenever he needed to attend study sessions. He elaborated that he “[did] not see the point in being truthful” because he anticipated that his parents would not fully understand the extent of his experiences. He added that such conversations were also not necessary at that juncture, since his PTSD symptoms had improved significantly.

I’m still ambivalent about sharing things about my life with my parents. I don’t see the point necessarily of sharing all of this with them if they don’t need to know. Even though I sometimes think about sharing my trauma and this treatment with my family, I think it would work better in an ideal world.

8.2.4.1.2. Reconnecting while setting boundaries. In spite of wanting to maintain privacy about his experiences with trauma and the study, Kenneth described, after the second dosing session, a sense of forgiveness toward his parents for their maltreatment of him in his childhood. This forgiveness was perhaps linked to his increased compassion toward perpetrators during the first dosing session (see section 8.2.1.3.4.). As a result of this forgiveness, Kenneth expressed wanting to reconnect with his parents through shared activities, such as having dinner with them. This change
might have also contributed to his improved psychosocial functioning on the IPF. Kenneth viewed this reconnection with his parents as a means to also learn how to trust others. At the same time, he established a dialectic in navigating his relationship with his parents, by expressing an active desire to set and maintain an appropriate boundary or distance from his parents, so he could also learn to be independent (see also section 8.2.4.1.3.).

I forgive my parents, and I also want to reconnect with them so that our relationship can be a little bit better. I think this will also help me trust other people more. I might have more dinners with them because I know that they like that. I’d just do things with them so they feel more connected, you know? Not as much as they want, but a little more. I don’t want to feel suffocated. Because at the same time, I also want to be able to feel more independent. That way they’ll be content, I’ll be content, I’ll have my space, but they’ll still feel like they’re connected, you know?

8.2.4.1.3. Freedom and autonomy. Throughout the study, Kenneth progressively expressed a desire to have his personal space away from the influence of his parents, wanting a job or career with a lot of freedom and autonomy, and not wanting to be “controlled” by other authority figures. For example, he had the following to say in the second integration session after the first dosing session:

My mom was like “Oh, it doesn’t look like you enjoy coming home.” I’m not gonna say, “Yes, I don’t enjoy coming home,” to my own mother, but it is what it is. In a couple of years, I’ll be moving out anyway. I just feel like a bird that was never meant to be in a caged. You just can’t keep me in a confined space. I don’t want to be in a cage, I want to go fly.

Notably, after the third dosing session, Kenneth also described having gained some measure of freedom from his PTSD symptoms, believing that “nothing [was] holding [him] down anymore.” At the same time, he talked about setting up a comfortable personal space in the shed in his backyard, some distance away from the main house, as the first step toward having his “own space,” both literally and metaphorically.

It’s almost like I got a monkey off my back. A lot of the stuff that was pulling me down isn’t holding me down anymore. So now I feel free to do what I need to and want to do. Part of that is having my own space away from my parents.

8.2.4.2. Navigating romantic relationships.

8.2.4.2.1. Managing current conflicts. After the first dosing session, Kenneth developed the insight about needing to change his patterns of communicating with Paula. Specifically, he described
choosing to appropriately convey his thoughts and feelings to her instead of ignoring her, and viewed this approach as the best way to improve his relationship with her. Whenever they felt “stuck,” he would often ask for a “timeout” to allow themselves to calm down. He was also willing to accommodate her preferences when going out together, and overall, seemed to display interpersonal effectiveness in his relationship with her.

We both decided that it’s not useful to just ignore each other if we’re mad at each other. So I suggested that we talk it out until our argument is resolved. If we couldn’t get a solution then, we would both call a ceasefire and set another time to talk about it. It would either be in person, or we’d set up another time after we’ve had some time to think about it, and then figure things out.

8.2.4.2.2. Insights about past relationships. Prior to his third dosing session, Kenneth agreed to Paula’s request to end the relationship. Kenneth explained that he agreed to break up with her due to a vision he had during the second dosing session, in which he experienced wrestling with a lion that then transformed into Paula. He viewed this vision as a culmination of their arguments, misunderstandings, and unsuccessful attempts to reach a compromise during their disagreements. Essentially, he perceived this ongoing ‘wrestling’ as symbolic of her hesitation to commit to him, and his persistence in wanting to make the relationship ‘work.’

In the session, I was wrestling with a lion for a while. From what I remember I got on top of the lion and I won but I looked down and it was just [Paula] and I was like, “Oh.” I just remember that image because it was the most powerful one. Her hair is kind of red, so it’s like a lion’s mane. It reminded me of our arguments, and how she wasn’t ready to commit.

After the breakup, Kenneth became introspective about his past romantic relationships, which incidentally had mostly been with females who had suffered from mental health issues and dysfunctional family patterns. As a result of this realization, he expressed a desire to explore what it would be like to date females with different attributes and backgrounds. Nonetheless, he expressed gratitude and appreciation for his past relationships as helping him discover his preferences in relationships.

I don’t know what it is, but a lot of girls I always seem to end up dating always seem to kind of come out of a phase, like depression or some other problems in their life. I always seem to “find” them. I’ve never dated a normal girl, in the sense that her life is fine, and her family doesn’t have any serious problems going on.
8.2.4.2.3. Thinking about future relationships. Fueled by the breakup, his desire to date “different kinds of girls,” and his current abstinence from alcohol or substances, Kenneth discussed his intention to explore a new approach to asking females out on dates. His preferences have shifted to females who are intelligent, driven, and involved in social justice activities, attributes that he identified with as well.

I don’t typically ask out girls in person while sober. That is a new thing especially like in a normal, non-party environment, you know? And I think the girls that I’m interested in now seem to also be different. They are like me, they’re focused. They prioritize their work more than they prioritize their social life, and so I think my approach to asking them out has to also be different. As for what that looks like, I’m still figuring that out.

8.2.4.3. Navigating friendships.

8.2.4.3.1. Feeling distant from certain friends. After the third dosing session, Kenneth also expressed feeling disconnected from people he attempted to hang out with before the start of the study. Kenneth believed this distance stemmed from differences in interests from those friends. This feeling of disconnection was perhaps linked to his desire to create his own ‘tribe’ (see section 8.2.4.3.2.).

I’ve been feeling distant from some of my friends since the end of last year. They’re just not very much into a lot of the same stuff I’m into. There’s also a lot of drama that’s very annoying that I don’t like to deal with.

8.2.4.3.2. Creating own tribe. Building on his increasing awareness of his preferences for friends after the third dosing session, Kenneth detailed his aspiration and plans for creating “[his] own tribe” by blending his different friend groups, especially those who shared his interests, and physically bringing them together for shared activities. While he realized that this goal would be pragmatically difficult to achieve, he was nonetheless determined to try.

During the [third dosing] session, I dropped in on a planet where I was literally a part of a little tribe. Like tents and spears and everything. And then I went through a jungle at one point and I got kind of lost and emerged in the Sahara Desert. And I thought to myself, “Why are these two scenarios mixing?” Like environmentally speaking, that doesn’t make sense. It didn’t feel like I was in a hot and dry place, nor did it feel like I was in a cool or humid place. It felt like I was somewhere in between. And I took that to mean that I need to blend both situations together in creating my own tribe. It’s like collecting a tribe from different groups of people and building a crew from that. Which is why I’m trying to do more of the activism work because it’s with people who
have the same schedules, who have the same type of stuff going on and likely have the same problem and will likely understand. I think I have connections with people in different groups, but actually physically bringing them all together is the hard part, because they're in different places and stuff. But yeah, I'm exploring ideas of what it means to have a tribe.

8.3. Correlations

Table 10 displays significant zero-order correlations between percentage use of different linguistic variables and Kenneth’s CAPS-5 and PCL-5 scores. Greater use of terms signalling authenticity, lower use of the second-person pronoun ‘you,’ and greater use of temporal terms (e.g., ‘until,’ ‘meanwhile,’ ‘occasionally’) were all significantly correlated with lower PTSD symptom severity on the CAPS-5 and PCL-5, all ps < .05. Additionally, shorter transcripts (i.e., lower word count) and less use of male references (e.g., ‘his,’ ‘him’) were significantly correlated with lower CAPS-5 scores, both ps < .05. Lastly, greater use of adjectives, less use of causal terms (e.g., ‘because’), and more body-focused references (e.g., ‘arm,’ ‘leg’) were all significantly correlated with lower PCL-5 scores, all ps < .05.

9. Discussion

With the aid of a mixed-methods approach, the present case study was able to offer rich insights into the interwoven effects and mechanisms of action of MDMA-assisted psychotherapy for an ethnoracial minority participant in the MP-16 trial. While this case study aimed to provide a detailed and destigmatizing report of a successful course of MDMA-assisted psychotherapy for a participant of color, it remains possible that this participant’s experiences might have been wholly different than those of other ethnoracial minority participants in the MP-6/17 trial, as a function of his age, gender, race, etc. Nonetheless, this case study provided a comprehensive examination of the complex routes through which PTSD symptom recovery was achieved for the participant in question.

Certain themes illustrated MDMA’s ability to dampen fear and anxiety related to traumatic memories so as to facilitate traumatic re-processing (Mithoefer, 2016). After the first dosing, Kenneth was able to face and develop healthier perceptions of his past traumas, viewing them as events in his past that had no real influence on his present safety. Indeed, Kenneth was able to describe his trauma
memories as neatly organized in the “filing cabinet” that is his mind after the first dosing session, akin to metaphorical descriptions of how PE for PTSD works in Foa et al. ’s (2019) manual. Because MDMA allowed him to “dive deeper” into his traumas than he ever did before, he was also able to experience the integration of his pre-, peri-, and posttraumatic selves. This is similar to the goal of internal family systems (IFS) therapy, which assumes that there are internal parts within each individual that take on different roles (e.g., ‘exiles’ that contain painful past experiences, ‘managers’ that attempt to maintain everyday functioning, and ‘firefighters’ that respond actively to imminent threats or crises; Schwartz, Schwartz, & Galperin, 2009). According to the IFS approach, optimal functioning is achieved when each internal part is recognized, validated, and valued, instead of being perceived as problematic or needing to be repressed (Green, 2008). This allows them to function as a cohesive whole. Therefore, through this integration of his various selves, Kenneth recognized the value of his “angsty teenager” in helping him cope with the sexual trauma, and was able to allow each of his internal parts to coexist without any part dominating the way he behaved or perceived the world, thus helping him make the most of the present moment. Additionally, Kenneth was able to identify and challenge cognitive distortions that would often leave him feeling upset or “stuck,” and felt sufficiently resourced after the third dosing to navigate future challenges without worrying excessively about their outcomes.

The remaining mechanistic themes also overlapped in several ways with correlational findings from Study 1. In Study 1, improvements in alexithymic tendencies, emotion regulation ability, and self-compassion were significantly associated with reductions in PTSD symptoms for the entire modified ITT sample. Similarly, after the first dosing session, Kenneth reported increased awareness of negative and positive emotions, choosing to acknowledge their presence instead of minimizing them or “bottling them up.” Additionally, after the first dosing session, Kenneth also increased his use of healthy emotion regulation strategies (e.g., responding with affection, meditation, stretching) during times of stress or conflict. Furthermore, after the first dosing session, Kenneth developed a softer, more compassionate inner voice to help defuse from situations that would otherwise frustrate him, and was even able to develop compassion toward his perpetrator and his
parents. These changes preceded his reductions PTSD symptoms, and were also reflected in his improved alexithymic tendencies, emotion regulation ability, and self-compassion. Kenneth’s reported themes of PTSD symptom recovery also reflected these synergistic processes of internal change.

There were additional similarities between other themes in this case study and those from Barone et al.’s (2019) study. For example, Kenneth’s improved ability to effectively reconnect with his parents while setting personal boundaries for independence and autonomy were consistent with Barone et al.’s (2019) observations of improved relationships and social skills among previous Phase 2 participants. While he decided to end his relationship with Paula during the course of the study, he was introspective about his preferences for a romantic partner, as well as who he would like in his friend group (i.e., “creating a tribe”), and indication of desire for social connection. Another similarity with Barone et al.’s study was Kenneth’s increased motivation to engage in various new activities which aligned with his academic and social justice aspiration (i.e., “going for overkill”). A distinction, however, was that while his social justice initiatives allowed him to cultivate his interest in posttraumatic advocacy, Kenneth also experienced detrimental effects, such as occasional overuse of his ADHD medication to complete schoolwork, resultant insufficient sleep, as well as transient chest discomfort. Additionally, a distinct benefit was Kenneth’s reduced suicidality (cf. Barone et al., 2019), owing to his experience of seeing himself as a 60-year-old during the first dosing session. This was consistent with Kenneth’s reduced endorsement of suicidal ideation on the C-SSRS throughout the study.

Notably, Kenneth’s experience during the first dosing session demonstrated a link to his cultural and religious heritage. Specifically, Kenneth likened the merging of his selves to Krishna, a Hindu deity characterized by his multiple, integrated personas (Mahony, 1987). This integration of his selves, akin to Krishna’s personas, was pivotal, because it empowered Kenneth to “move forward” from his traumas, while allowing him to honor the pain that his younger self had endured. While there is documented evidence of transcultural, heightened spirituality induced by psychedelic experiences (Lerner & Lyvers, 2006), the emergence of idiosyncratic cultural iconography within psychedelic
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experiences is not a unique phenomenon. For example, Ching (2020) described similarly visions of culturally significant icons from his Southeast Asian heritage (e.g., native flora and fauna, Chinese calligraphy) catalyzing important insights during his MDMA experience from the MAPS-sponsored therapist training trial (i.e., MT-1; ClinicalTrials.gov identifier: NCT01404754). Additionally, in Wagner, Mithoefer, Mithoefer, and Monson’s (2019) case example of a religiously devout Christian couple (one partner with PTSD) who underwent MDMA-assisted cognitive-behavioral conjoint therapy (CBCT), there were significant visions of Jesus providing comforting gestures reported during the dosing sessions. All of these observations perhaps illustrate the importance of acknowledging how one’s cultural or religious heritage can enter the psychedelic experience to induce meaning-making processes that may be in turn related to recovery from pathological patterns of functioning. As such, when culturally and/or religiously salient psychedelic experiences emerge, it may be pertinent for therapists to respond in sensitive and attuned ways (e.g., expressing curiosity and supporting deeper exploration of emerging experiences while suspending stereotyped interpretations of the participant’s experience), so as to facilitate development of lasting insights.

Other parallels exist between Kenneth’s experiences during MDMA-assisted psychotherapy and core mechanisms of change for established psychological treatments for PTSD. For example, Brown, Zandberg, and Foa (2019) detailed mechanisms of change in PE for PTSD, including the reduction of negative trauma-related cognitions that in turn help introduce more adaptive associations between the trauma and one’s life, future, and the world. In fact, improvements in dysfunctional trauma-related cognitions were shown to be a pervasive mechanism of change across diverse psychological interventions for adults and children who have experienced traumatic stress (Kangaslampi & Peltonen, 2019). Additionally, reductions in trauma-related cognitive appraisals have been shown to precede sudden gains in PTSD symptom improvement in routine care for individuals with PTSD (Wiedemann et al., 2020). These findings reflect what was observed for Kenneth, in that his alterations in dysfunctional, trauma-related cognitions (e.g., self-blame, perfectionism) after the first dosing session preceded the clinically significant drop in his CAPS-5 score after the second dosing session. Indeed, Kenneth no longer met DSM-5 diagnostic criteria for PTSD after the second
dosing session. Furthermore, other research has shown evidence for reduction in experiential avoidance – or, attempts to avoid unwanted thoughts, feelings, memories, physical sensations, and other internal experiences – preceding symptom improvement in CBT for various behavioural disorders, including PTSD (Eustis et al., 2019; Hayes, Wilson, Gifford, Follette, & Strosahl, 1996). This is similar to how Kenneth was able to “survey” his past traumatic experiences without avoidance of emerging memories and feelings during the first dosing session, continue to approach trauma reminders after the first dosing, and experience clinically significant improvement in PTSD symptoms after the second dosing session. The aforementioned observations lend support to why MDMA-assisted psychotherapy might be comparable with, if not more efficacious than, for example, PE for PTSD (Amoroso & Workman, 2016), as there might be similar mechanisms of change involved.

At the same time, there were procedural distinctions between MDMA-assisted psychotherapy and CBT for PTSD. First, therapists in the MP-16/17 trial underwent the MDMA-assisted psychotherapy training program, which included an experiential component of a single dosing session. This depth of training is perhaps distinct from CBT training programs for PTSD, in which therapists’ prior experience in receiving, for example, PE, is not required for administering the treatment (Foa et al., 2019). This level of immersion in MDMA-assisted psychotherapy training might have also allowed for the therapists to better understand the spectrum of experiences that might emerge for participants during dosing sessions, which might in turn strengthen the relational bond with participants, crucial for retaining participants of color who might be at higher risk for dropping out (Lester et al., 2010). Nonetheless, it may be impossible given the present data to attribute certain change processes (e.g., cognitive change) as specific to MDMA-assisted psychotherapy, given overlap with CBT for PTSD. As such, future research should attempt to dismantle mechanistic processes of MDMA-assisted psychotherapy in order to better understand its distinctions from and commonalities with CBT approaches for treating PTSD.

Our correlational findings also revealed meaningful associations between change in Kenneth’s use of certain linguistic terms and decreases in his PTSD symptoms. Kenneth’s increased use of terms signalling authenticity, adjectives, and temporal terms over the course of the study might
have indicated an improved ability to describe in detail difficult trauma-related memories with honesty, self-compassion, and compassion for others (including the sexual perpetrator), perhaps with an accurate understanding of the sexual trauma as an event in his personal history that he could overcome. Kenneth also used fewer causal terms over the course of the study, perhaps indicating an adaptive abandonment of the belief that he was to blame for the sexual assault, or that he could have done something to prevent the assault (cf. Jelinek et al., 2010). Additionally, Kenneth used more body-focused references over the course of the study, which might be related to his descriptions of somatic relief from trauma (e.g., physical stretching as a means of relieving tension built up in his muscles over the years since the sexual trauma). Furthermore, Kenneth’s speech portions reduced in word count over the course of the study, alongside reductions in his use of ‘you.’ The former might have signalled a more relaxed, hence less verbose, engagement in treatment as his PTSD symptoms improved (see Fernández-Lansac & Crespo, 2015), while the latter might have indicated a reduced tendency to experientially avoid or psychologically distance himself from discussions of trauma-related problems with the use of the second-person pronoun (see Dunnack & Park, 2009). Interestingly, no correlations were observed between Kenneth’s use of positive and negative emotion words and his PTSD symptoms, unlike robust findings in the PTSD literature (Greenhoot et al., 2013; Wardecker et al., 2017). Additionally, it was not clear why Kenneth’s decreased use of male references was correlated with reduced PTSD symptoms. Perhaps because Kenneth was victimized by a male, there was a decrease in psychological salience of males as threatening figures after MDMA-assisted psychotherapy, which contributed to decreased use of male references. Nonetheless, quantitative linguistic analysis was helpful in this case study to provide further nuanced insights into the role of language in Kenneth’s recovery from PTSD. As such, Phase 3 studies could continue to analyze session transcripts leading up to each primary outcome assessment interval to see if different linguistic variables would predict PTSD symptom change.

It is hoped that the themes gleaned from this case study would inform future research in various ways, for example, development of measures that assess these mechanisms of change during MDMA-assisted psychotherapy, as well as larger-scale analysis of transcripts
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from other participants to converge on commonly experienced effects. More importantly, this case study offered a culturally sensitive lens into an ethnoracial minority participant’s recovery from PTSD with MDMA-assisted psychotherapy, and hopefully would serve to inform readers and potential participants of color about the utility of this treatment for addressing their own PTSD-related problems. It appeared that Kenneth’s experience with MDMA-assisted psychotherapy for treatment-resistant PTSD was overall a positive and beneficial one, despite multiple past and ongoing cultural and familial barriers to psychotherapy. However, Kenneth remained unable to disclose both his sexual trauma and his participation in the study to his family, due to their stigmatizing attitudes toward mental illness and mental health treatment. For many ethnoracial minority participants, these barriers might mean the difference between continuing in treatment or dropping out, or even refusing to begin treatment altogether (Gary, 2005). Therefore, the need for culturally responsive strategies to circumvent these barriers becomes ever more urgent, as trials for MDMA-assisted psychotherapy for PTSD move into Phase 3 prior to eventual submission for FDA approval (Burge, 2017).

10. General Discussion

In summary, Study 1 found no ethnoracial differences in efficacy and safety outcomes of MDMA-assisted psychotherapy for treatment-resistant PTSD, in an open-label trial (MP-16/17) that recruited proportionately more ethnoracial minority participants than previous trials. Large effect sizes were found for primary and most of the secondary outcomes, with recovery rates of 73% and 92%, respectively, in terms of CAPS-5 and PCL-5 scores. Preliminary evidence was also found for the potential mechanistic roles of emotion awareness and regulation, and self-compassion. In Study 2, a mixed-method case study was conducted on an ethnoracial minority participant (Kenneth) in the MP-16 trial, highlighting culturally salient aspects of his recovery from PTSD, as well as similar mechanisms of change from Study 1, and nuanced linguistic markers of change.

However, in both studies, participant diversity could still be expanded along additional parameters. For example, in Study 1, ethnoracial minority participants were significantly younger than their non-Hispanic White counterparts in the modified ITT set. Thus, generational stigma toward the
use of MDMA for healing among older ethnoracial minority participants was a persistent barrier to diverse recruitment. In Study 2, despite his overall beneficial experience during the trial, Kenneth remained averse to disclosing his sexual trauma and treatment to his parents, indicative of strong family stigma toward mental illness and mental health treatment.

In conclusion, more strategies need to be explored to ensure that Phase 3 trials can continue to diversify their participant pool, so as to allow further examination of ethnoracial differences in efficacy and safety. Importantly, these strategies need to be cognizant of the aforementioned (and more) barriers to recruitment from underrepresented populations. Williams et al. (2020) documented multiple culturally responsive modifications to the MP-16/17 study design and protocol which are, thus, worth revisiting here as final recommendations for Phase 3 trials. These include:

- Intentional diversification of study staff (i.e., principal investigators, co-investigators, study therapists, overnight attendants, and independent raters of different races and ethnicities), to make ethnoracial minority participants feel more invested and comfortable participating in the study (see also Williams, Proetto, Casiano, & Franklin, 2012), and to improve the study team’s ability to understand, appreciate, and address participants’ culturally relevant concerns about participating (e.g., possible generational stigma about drug use, family stigma).

- Using culturally responsive recruitment materials that contain pictures of and information about study staff, psychoeducation about PTSD and possible causes (e.g., racially motivated violence), clear and detailed language about common to rare side effects of MDMA, and emphasis on the team’s dedication to cultural humility, so as to assuage initial fear or stigma about participating among ethnoracial minority individuals (see also Avery, Hernandez, & Hebl, 2004).

- Conducting psychoeducational outreach to important leaders and organizations within target communities, so that information about the study can be effectively disseminated via word-of-mouth (see also Williams, Beckmann-Mendez, & Turkheimer, 2013).

- Providing equitable incentives/compensation to participants from marginalized communities, who may have other responsibilities (e.g., working multiple jobs, going to school,
transportation issues, and/or taking care of family members) that limit their availability, ability, and willingness to participate (see also Fisher et al., 2002). Doing so conveys a sense of respect and appreciation for the participant’s time and effort in the study.

- Dedicating more time to potential participants – particularly with ethnoracial minority individuals – during phone screenings to reduce wariness and build rapport, prior to eliciting information about their traumas and symptoms. It is also necessary to provide psychoeducation about PTSD symptoms to individuals with lower mental health literacy to help determine eligibility, which requires more time (see also Cheng, Wang, McDermott, Kridel, & Rislin, 2018).

- Modifying language in the informed consent document in a culturally responsive manner (e.g., replacing ‘investigation’ with ‘study,’ and ‘experimental session’ to ‘overnight session’), so as to not activate implicit stigma and negative stereotypes against medical research and drug use among ethnoracial minority individuals.

- Providing accurate and detailed information (e.g., giving exact percentages) on the side effects of MDMA when used in a therapeutic context during the informed consent process, to alleviate ethnoracial minority participants’ potential concerns about death, disability, and addiction (see also Rigg & Lawental, 2018).

- Assessing for race-based stress and trauma (e.g., with the UConn Racial/Ethnic Stress & Trauma Survey [UnRESTS]; Williams, Metzger, Leins, & DeLapp, 2018) to signal to ethnoracial minority participants that the therapists are ready to support discussions of such topics should they emerge in preparatory, dosing, and/or integration sessions.

- Introducing diversity in artwork, reading materials, decorations, and music selections may help explicitly communicate to ethnoracial participants that individuals from all cultures are welcomed and respected in the therapeutic space (c.f., Purdie-Vaughns, Steele, Davies, Ditlmann, & Crosby, 2008).

It is hoped that these recommendations will continue to be implemented in Phase 3 trials to diversify the MDMA-assisted psychotherapy participant pool. The validity of these recommendations
can also be tested empirically. For example, a study can be designed to examine differences in inclination to participate in MDMA-assisted psychotherapy between ethnoracial minority participants who received a psychoeducational message containing the phrase “experimental session” and those seeing the phrase “overnight session.” Because communities of color have been excluded from these trials for so long, we must endeavor to increase access to this promising novel treatment for all communities, so that everyone has an equitable chance to recover from treatment-resistant PTSD. Perhaps once FDA approval is gained, MDMA-assisted psychotherapy clinical trial inclusion criteria can be modified to be more inclusive and less stringent, thereby allowing highly marginalized and traumatized individuals with multiple comorbid psychiatric disorders a chance to access this treatment.
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Table 1.

MP-16/17 study schedule

<table>
<thead>
<tr>
<th>Duration</th>
<th>2-6 weeks</th>
<th>1-11 weeks</th>
<th>About 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits</td>
<td>Informed consent</td>
<td>Independent rater</td>
<td>Enrollment (Visit 0)</td>
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<tr>
<td>LEC-5</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PCL-5</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CAPS-5</td>
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<td>✓</td>
<td></td>
</tr>
<tr>
<td>AUDIT</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUDIT</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI-II</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS-Lifetime</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>C-SSRS-Since Last Visit</td>
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<td></td>
</tr>
<tr>
<td>C-SSRS-Pre- and Post-Drug</td>
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<td></td>
</tr>
<tr>
<td>IPF</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>SCS</td>
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Table 1.

MP-16/17 study schedule (continued)

<table>
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<th>Duration</th>
<th>About 4 weeks</th>
<th>About 4 weeks</th>
<th>About 6 weeks</th>
</tr>
</thead>
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<tr>
<td>Visits</td>
<td>MDMA session 2 (Visit 10)</td>
<td>Integration session 2.1 (Visit 11)</td>
<td>Phone call 1</td>
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</tr>
<tr>
<td>PCL-5</td>
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</tr>
<tr>
<td>CAPS-5</td>
<td>✓</td>
<td></td>
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</tr>
<tr>
<td>AUDIT</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>DUDIT</td>
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<tr>
<td>BDI-II</td>
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<tr>
<td>C-SSRS-Lifetime</td>
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<td></td>
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<tr>
<td>C-SSRS-Since Last Visit</td>
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<td>C-SSRS-Pre-and Post-Drug</td>
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<td>IASC-AD</td>
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<tr>
<td>SCS</td>
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</tbody>
</table>

Note. Each MDMA dosing session lasts approximately 8 hours. All preparatory and integration sessions are approximately 1.5 hours each. LEC-5 = Life Events Checklist for DSM-5; PCL-5 = Posttraumatic Symptom Checklist for DSM-5; CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; AUDIT = Alcohol Use Disorders Identification Test; DUDIT = Drug Use Disorders Identification Test; BDI-II = Beck Depression Inventory-Second Edition; C-SSRS = Columbia Suicide Severity Rating Scale; IPF = Inventory of Psychosocial Functioning; IASC-AD = Inventory for Altered Self-Capacities – Affect Dysregulation scale; TAS-20 = Toronto Alexithymia Scale, 20-item version; SCS = Self-Compassion Scale.
### Table 2.

Demographic characteristics of recruited sample split by participation status and ethnoracial group

<table>
<thead>
<tr>
<th>Site</th>
<th>Total (N = 42)</th>
<th>Non-Hispanic White (completed; n = 25)</th>
<th>Ethnoracial minority (completed; n = 11)</th>
<th>Non-Hispanic White (pre-dosing termination; n = 3)</th>
<th>Ethnoracial minority (pre-dosing termination; n = 2)</th>
<th>Non-Hispanic White (post-dosing termination; n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site Charleston, SC</td>
<td>3 (7.1%)</td>
<td>1 (2.4%)</td>
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<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Site Boulder, CO</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Site Fort Collins, CO</td>
<td>3 (7.1%)</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Site Los Angeles, CA</td>
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<td>2 (4.8%)</td>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Site New Orleans, LA</td>
<td>3 (7.1%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Site University of California – San Francisco, CA</td>
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<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Site San Francisco, CA</td>
<td>3 (7.1%)</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>Site University of Connecticut, CT</td>
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<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>1 (2.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Site University of Wisconsin – Madison, WI</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Site New York University, NY</td>
<td>1 (2.4%)</td>
<td>2 (4.8%)</td>
<td>-</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Site New York, NY</td>
<td>1 (2.4%)</td>
<td>1 (2.4%)</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Site Boston, MA</td>
<td>1 (2.4%)</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>1 (2.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Site Vancouver, BC</td>
<td>2 (4.8%)</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Site Montreal, QC</td>
<td>-</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Age (years)**

- 37.60 (11.62)
- 30.27 (5.88)
- 49.33 (18.56)
- 26.50 (2.12)
- 31

**Gender**

- Female: 16 (38.1%)
- Male: 9 (21.4%)

**Race**

- Native American/Alaskan Native: -
- Asian/Asian American: 6 (14.3%)
- Black/African American: 1 (2.4%)
- White: 25 (59.5%)
- Multiracial: -

**Ethnicity**

- Hispanic/Latino: 2 (4.8%)
- Not Hispanic/Latino: 25 (59.5%)

**Marital status**

- Never married: 9 (21.4%)
- Married/living with partner: 13 (31.0%)
- Separated: 2 (4.8%)
- Divorced: 1 (2.4%)
- Did not report: -

**Employment**

- Full-time: 15 (35.7%)
- Regular part-time: 4 (9.5%)
- On disability: 3 (7.1%)
- Unemployed: 2 (4.8%)
- Student/in training program: -
- Other: 1 (2.4%)
- Did not report: -

**Note.** Hispanic/Latino White participants were categorized as part of the ethnoracial minority group. Percentages (in parentheses) throughout are based on cell counts divided by entire recruited sample size. Mean age in years at enrollment are displayed (except for the participant terminated post-dosing, whose age is simply shown), with standard deviations accompanying in parentheses.
Table 3.

LEC-5 index/worst traumatic events in recruited sample at screening split by participation status and ethnoracial group

<table>
<thead>
<tr>
<th>LEC-5 index/worst trauma</th>
<th>Non-Hispanic White (completed; (n = 25))</th>
<th>Ethnoracial minority (completed; (n = 11))</th>
<th>Non-Hispanic White (pre-dosing termination; (n = 3))</th>
<th>Ethnoracial minority (pre-dosing termination; (n = 2))</th>
<th>Non-Hispanic White (post-dosing termination; (n = 1))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural disaster</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>1 (%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fire/explosion</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Transportation accident</td>
<td>2 (4.8%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serious accident (work/home/recreation)</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Exposure to toxic substance</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Physical assault</td>
<td>2 (4.8%)</td>
<td>3 (7.1%)</td>
<td>-</td>
<td>1 (2.4%)</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td>Assault with weapon</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sexual assault</td>
<td>9 (21.4%)</td>
<td>5 (11.9%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other unwanted/uncomfortable sexual experience</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Combat/exposure to war zone</td>
<td>2 (4.8%)</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Captivity</td>
<td>2 (4.8%)</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Life-threatening illness/injury</td>
<td>-</td>
<td>-</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Severe human suffering</td>
<td>-</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sudden violent death</td>
<td>4 (9.5%)</td>
<td>-</td>
<td>-</td>
<td>1 (2.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Sudden accidental death</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Serious harm/injury or death caused to others</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any other stressful event(^a)</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>1 (2.4%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note. The event can either have happened to the participant directly, or the participant can have witnessed it, learned about it happening to a close family member or close friend, or experienced repeated exposure to aversive details about it as part of their first responder job. Hispanic/Latino White participants were categorized as part of the ethnoracial minority group. Percentages (in parentheses) throughout are based on cell counts divided by entire recruited sample size.

\(^a\) Identified events, in order from left to right, were: having an abortion alone in a foreign country; and homelessness.
Table 4.

Post-baseline LEC-5 stressors across assessment intervals split by participation status and ethnoracial group in modified intent-to-treat (ITT) set

<table>
<thead>
<tr>
<th>Total (N = 37)</th>
<th>LEC-5 stessor</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>V09</td>
<td>V14</td>
<td>V18</td>
<td>V20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>Missing</td>
<td>Yes</td>
<td>Missing</td>
<td>Yes</td>
<td>Missing</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-Hispanic White (completed; n = 25)</td>
<td>9 (24.3%)</td>
<td>1 (2.7%)</td>
<td>2 (5.4%)</td>
<td>3 (8.1%)</td>
<td>5 (13.5%)</td>
<td>0 (0%)</td>
<td>4 (10.8%)</td>
</tr>
<tr>
<td>Ethnoracial minority (completed; n = 11)</td>
<td>1 (2.7%)</td>
<td>0 (0%)</td>
<td>1 (2.7%)</td>
<td>3 (8.1%)</td>
<td>3 (8.1%)</td>
<td>1 (2.7%)</td>
<td>1 (2.7%)</td>
</tr>
<tr>
<td>Non-Hispanic White (post-dosing termination; n = 1)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note. Endorsement of post-baseline stressors on the LEC-5 across assessment intervals in the modified intent-to-treat (ITT) set. V09 = third integration session after first dosing; V14 = third integration after second dosing; V18 = third integration after third dosing; V20 = study termination. Hispanic/Latino White participants were categorized as part of the ethnoracial minority group. Percentages (in parentheses) throughout are based on cell counts divided by modified ITT set size.
Table 5.
Percentage endorsement of reliable change index (RCI) categories of primary outcome measures for non-Hispanic White \( (n = 26) \) and ethnoracial minority participants \( (n = 11) \) in modified intent-to-treat (ITT) set

<table>
<thead>
<tr>
<th>Measure</th>
<th>RCI</th>
<th>Deterioration</th>
<th>Unreliable change</th>
<th>Reliable improvement – PTSD present</th>
<th>Recovery – PTSD absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPS-5</td>
<td>10.79</td>
<td>Non-Hispanic White</td>
<td>0 (0%)</td>
<td>5 (13.5%)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethnoracial minority</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (5.4%)</td>
</tr>
<tr>
<td>PCL-5</td>
<td>10.4</td>
<td>Non-Hispanic White</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ethnoracial minority</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

*Note. CAPS-5 = Clinician-Administered PTSD Scale for DSM-5; PCL-5 = Posttraumatic Symptom Checklist for DSM-5. The dichotomous diagnostic scoring system was used to determine whether there was a diagnosis of PTSD or not at study termination for both measures. Percentages (in parentheses) throughout are based on cell counts divided by modified ITT set size.*
MDMA-ASSISTED PSYCHOTHERAPY FOR PTSD

Table 6.

Percentage endorsement of reliable change index (RCI) categories of secondary outcome measures for non-Hispanic White \((n = 26)\) and ethnoracial minority participants \((n = 11)\) in modified intent-to-treat (ITT) set

<table>
<thead>
<tr>
<th>RCI</th>
<th>Non-Hispanic White</th>
<th>Ethnoracial minority</th>
<th>Unreliable change</th>
<th>Reliable improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI-II</td>
<td>8.89</td>
<td>0 (0%)</td>
<td>6 (16.2%)</td>
<td>20 (54.1%)</td>
</tr>
<tr>
<td></td>
<td>Ethnoracial minority</td>
<td>0 (0%)</td>
<td>3 (8.1%)</td>
<td>8 (21.6%)</td>
</tr>
<tr>
<td>AUDIT</td>
<td>4.99</td>
<td>0 (0%)</td>
<td>26 (70.3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td></td>
<td>Ethnoracial minority</td>
<td>0 (0%)</td>
<td>9 (24.3%)</td>
<td>4 (10.8%)</td>
</tr>
<tr>
<td>DUDIT</td>
<td>5.64</td>
<td>1 (2.7%)</td>
<td>22 (59.5%)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td></td>
<td>Ethnoracial minority</td>
<td>1 (2.7%)</td>
<td>7 (18.9%)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>IPF</td>
<td>14.37</td>
<td>0 (0%)</td>
<td>10 (27.0%)</td>
<td>16 (43.2%)</td>
</tr>
<tr>
<td></td>
<td>Ethnoracial minority</td>
<td>0 (0%)</td>
<td>5 (13.5%)</td>
<td>6 (16.2%)</td>
</tr>
<tr>
<td>IASC-AD</td>
<td>6.77</td>
<td>0 (0%)</td>
<td>9 (24.3%)</td>
<td>17 (45.9%)</td>
</tr>
<tr>
<td></td>
<td>Ethnoracial minority</td>
<td>0 (0%)</td>
<td>4 (10.8%)</td>
<td>7 (18.9%)</td>
</tr>
<tr>
<td>TAS-20</td>
<td>11.88</td>
<td>1 (2.7%)</td>
<td>12 (32.4%)</td>
<td>13 (35.1%)</td>
</tr>
<tr>
<td></td>
<td>Ethnoracial minority</td>
<td>1 (2.7%)</td>
<td>6 (16.2%)</td>
<td>4 (10.8%)</td>
</tr>
<tr>
<td>SCS</td>
<td>0.48</td>
<td>0 (0%)</td>
<td>4 (10.8%)</td>
<td>22 (59.5%)</td>
</tr>
<tr>
<td></td>
<td>Ethnoracial minority</td>
<td>1 (2.7%)</td>
<td>4 (10.8%)</td>
<td>8 (21.6%)</td>
</tr>
</tbody>
</table>

Note. BDI-II = Beck Depression Inventory – Second Edition; AUDIT = Alcohol Use Disorders Identification Test; DUDIT = Drug Use Disorders Identification Test; IPF = Inventory of Psychosocial Functioning; IASC-AD = Inventory for Altered Self-Capacities – Affect Dysregulation scale; TAS-20 = Toronto Alexithymia Scale, 20-item version; SCS = Self-Compassion Scale. Percentages (in parentheses) throughout are based on cell counts divided by modified ITT set size.
Table 7.

Zero-order correlations between pre-post difference scores on primary outcome measures and measures of affect dysregulation, alexithymia, and self-compassion

<table>
<thead>
<tr>
<th></th>
<th>IASC-AD_{diff}</th>
<th>TAS-20_{diff}</th>
<th>SCS_{diff}</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPS-5_{diff}</td>
<td>.55***</td>
<td>.41*</td>
<td>-.52***</td>
</tr>
<tr>
<td>PCL-5_{diff}</td>
<td>.39*</td>
<td>.59***</td>
<td>-.49**</td>
</tr>
</tbody>
</table>

*Note.* CAPS-5_{diff} = difference scores on Clinician-Administered PTSD Scale for DSM-5; PCL-5_{diff} = difference scores on Posttraumatic Symptom Checklist for DSM-5; IASC-AD_{diff} = difference scores on Inventory for Altered Self-Capacities – Affect Dysregulation scale; TAS-20_{diff} = difference scores on Toronto Alexithymia Scale, 20-item version; SCS_{diff} = difference scores on Self-Compassion Scale. All pre-post difference scores were calculated subtracting baseline scores from scores at study termination. *p < .05; **p < .01; ***p < .001 (two-tailed).
Table 8.

Vitals and other biometrics for case study participant

<table>
<thead>
<tr>
<th></th>
<th>Informed consent</th>
<th>MDMA session 1 (Visit 5) – Pre-dose</th>
<th>MDMA session 1 (Visit 5) – Interim</th>
<th>MDMA session 1 (Visit 5) – Endpoint</th>
<th>MDMA session 2 (Visit 10) – Pre-dose</th>
<th>MDMA session 2 (Visit 10) – Interim</th>
<th>MDMA session 2 (Visit 10) – Endpoint</th>
<th>MDMA session 3 (Visit 15) – Pre-dose</th>
<th>MDMA session 3 (Visit 15) – Interim</th>
<th>MDMA session 3 (Visit 15) – Endpoint</th>
<th>MDMA session 3 (Visit 15) Study termination (Visit 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>77.8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>80.7</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>164</td>
</tr>
<tr>
<td>BMI</td>
<td>28.9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30.1</td>
</tr>
<tr>
<td>BP&lt;sub&gt;systolic&lt;/sub&gt; (mmHg)</td>
<td>126</td>
<td>141</td>
<td>142</td>
<td>127</td>
<td>141</td>
<td>142</td>
<td>127</td>
<td>141</td>
<td>142</td>
<td>127</td>
<td>137</td>
</tr>
<tr>
<td>BP&lt;sub&gt;diastolic&lt;/sub&gt; (mmHg)</td>
<td>66</td>
<td>75</td>
<td>72</td>
<td>72</td>
<td>75</td>
<td>72</td>
<td>72</td>
<td>75</td>
<td>72</td>
<td>72</td>
<td>90</td>
</tr>
<tr>
<td>Pulse (bpm)</td>
<td>57</td>
<td>61</td>
<td>102</td>
<td>67</td>
<td>61</td>
<td>102</td>
<td>67</td>
<td>61</td>
<td>102</td>
<td>67</td>
<td>59</td>
</tr>
<tr>
<td>Temperature (℃)</td>
<td>36.2</td>
<td>37.0</td>
<td>37.2</td>
<td>37.2</td>
<td>37.0</td>
<td>37.2</td>
<td>37.2</td>
<td>37.0</td>
<td>37.2</td>
<td>37.2</td>
<td>36.2</td>
</tr>
</tbody>
</table>

*Note. Each MDMA dosing session lasts approximately 8 hours. BMI = body mass index; BP<sub>systolic</sub> = systolic blood pressure; BP<sub>diastolic</sub> = diastolic blood pressure.*
Table 9.

Significant zero-order correlations between case study participant’s scores on primary outcome measures and average frequencies on linguistic variables from preceding transcripts ($N = 4$)

<table>
<thead>
<tr>
<th></th>
<th>Word count</th>
<th>Authenticity</th>
<th>Second person pronouns</th>
<th>Common adjectives</th>
<th>Male references</th>
<th>Causation</th>
<th>Body references</th>
<th>Temporal terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPS-5</td>
<td>.95*</td>
<td>-1.00**</td>
<td>.98*</td>
<td>-.92</td>
<td>.99**</td>
<td>.67</td>
<td>-.70</td>
<td>-.99**</td>
</tr>
<tr>
<td>PCL-5</td>
<td>.84</td>
<td>-.95*</td>
<td>.99**</td>
<td>-.97*</td>
<td>.87</td>
<td>1.00**</td>
<td>-.95*</td>
<td>-.97*</td>
</tr>
</tbody>
</table>

Note. CAPS-5 = participant’s scores on Clinician-Administered PTSD Scale for DSM-5; PCL-5 = participant’s scores on Posttraumatic Symptom Checklist for DSM-5, except for informed consent interval; All linguistic variables were derived from the Linguistic Inquiry and Word Count 2015 software (LIWC; Pennebaker, Booth et al., 2015). *$p < .05$; **$p < .01$ (two-tailed).
Figure 1. CONSORT flow diagram for the multisite, single-arm, open-label MP-16/17 clinical trial for MDMA-assisted psychotherapy for PTSD. No follow-up section shown since data were only available for the primary endpoint; discontinued participation integrated into allocation section.

*a* Four participants did not receive the intervention (i.e., pre-dosing termination) due inclusion criteria not being met at enrollment confirmation. One other participant, although eligible to participate at enrollment confirmation, did not receive the intervention (i.e., pre-dosing termination) due to premature site closure. These participants’ data were excluded from all analyses because they did not complete the first dosing session.
One participant chose to discontinue participation after the second dosing session due to self-reported lack of symptom improvement. This participant’s data were included as part of the modified intent-to-treat (ITT) set.
Figure 2. Changes in mean Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) scores for non-Hispanic White \((n = 26)\) and ethnoracial minority participants \((n = 11)\) across sessions. Error bars represent +/-1SD for each ethnoracial group. Visit 3 refers to the baseline CAPS-5 assessment before the third preparatory session. Visit 8 occurred after the second integration session after the first dosing session. Visit 13 occurred after the second integration session after the second dosing session. Visit 19 occurred after the second integration session after the third dosing session.
Figure 3. Changes in mean Posttraumatic Symptom Checklist for DSM-5 (PCL-5) scores for non-Hispanic White (n = 26) and ethnoracial minority participants (n = 11) across sessions. Error bars represent +/-1SD for each ethnoracial group. Baseline PCL-5 assessment occurred at the informed consent visit. Visit 4 refers to the preparatory session prior to the first dosing session. Visit 9 refers to the third integration session after the first dosing session, prior to the second dosing session. Visit 14 refers to the third integration session after the second dosing session, prior to the third dosing session. Visit 20 refers to study termination.
Figure 4. Changes in mean Beck Depression Inventory – Second Edition (BDI-II) scores for non-Hispanic White (n = 26) and ethnoracial minority participants (n = 11) from baseline to study termination. Error bars represent +/- 1SD for each ethnoracial group. Baseline assessment occurred at Visit 4, the preparatory session prior to the first dosing session, while post-treatment assessment occurred at study termination (Visit 20).
Figure 5. Changes in mean Alcohol Use Disorder Identification Test (AUDIT) scores for non-Hispanic White ($n = 26$) and ethnoracial minority participants ($n = 11$) from baseline to study termination. Error bars represent +/-1SD for each ethnoracial group. Baseline assessment occurred at the informed consent visit, while post-treatment assessment occurred at study termination (Visit 20).
Figure 6. Changes in mean log-transformed Drug Use Disorder Identification Test (DUDIT) scores for non-Hispanic White (n = 26) and ethnoracial minority participants (n = 11) from baseline to study termination. Error bars represent +/-1SD for each ethnoracial group. Baseline assessment occurred at the informed consent visit, while post-treatment assessment occurred at study termination (Visit 20).
Figure 7. Changes in mean Inventory of Psychosocial Functioning (IPF) scores for non-Hispanic White (n = 26) and ethnoracial minority participants (n = 11) from baseline to study termination. Error bars represent +/-1SD for each ethnoracial group. Baseline assessment occurred at Visit 4, the preparatory session prior to the first dosing session, while post-treatment assessment occurred at study termination (Visit 20).
**Figure 8.** Changes in mean Inventory for Altered Self-Capacities – Affect Dysregulation (IASC-AD) scale scores for non-Hispanic White \((n = 26)\) and ethnoracial minority participants \((n = 11)\) from baseline to study termination. Error bars represent +/-1SD for each ethnoracial group. Baseline assessment occurred at Visit 4, the preparatory session prior to the first dosing session, while post-treatment assessment occurred at study termination (Visit 20).
Figure 9. Changes in mean Toronto Alexithymia Scale, 20-item version (TAS-20) scores for non-Hispanic White ($n = 26$) and ethnoracial minority participants ($n = 11$) from baseline to study termination. Error bars represent +/-1SD for each ethnoracial group. Baseline assessment occurred at Visit 4, the preparatory session prior to the first dosing session, while post-treatment assessment occurred at study termination (Visit 20).
Figure 10. Changes in mean Self-Compassion Scale (SCS) scores for non-Hispanic White (n = 26) and ethnoracial minority participants (n = 11) from baseline to study termination. Error bars represent +/-1SD for each ethnoracial group. Baseline assessment occurred at Visit 4, the preparatory session prior to the first dosing session, while post-treatment assessment occurred at study termination (Visit 20).
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(A)

Percentage Endorsement of Positive Ideation on C-SSRS

Visit Number

Informed Consent
Independent Rater
4 - Pre-Dosing
5 - Post-Dosing
6 - Phone Call 1
7 - Phone Call 2
8 - 10 - Pre-Dosing
9 - Post-Dosing
11 - Phone Call 1
12 - Phone Call 2
13 - 15 - Pre-Dosing
14 - Post-Dosing
16 - Phone Call 1
17 - Phone Call 2
18
19
20

- Non-Hispanic White
- Ethnoracial Minority
MDMA-ASSISTED PSYCHOTHERAPY FOR PTSD

(B)

![Percentage Endorsement of Serious Ideation on C-SNRS](chart)

- **Non-Hispanic White**
- **Ethnoracial Minority**

Visit Number:
- Informed Consent
- Independent Rater
- 4
- 5 - Pre-Dosing
- 5 - Post-Dosing
- 6
- Phone Call 1
- Phone Call 2
- 7
- 9
- 10 - Pre-Dosing
- 10 - Post-Dosing
- 11
- Phone Call 1
- Phone Call 2
- 12
- 14
- 15 - Pre-Dosing
- 15 - Post-Dosing
- 16
- Phone Call 1
- Phone Call 2
- 17
- 18
- 20
Figures 11A-C. Changes in percentage endorsement (i.e., ‘yes’) of positive ideation (A), serious ideation (B), and positive behavior (C) on the C-SSRS for non-Hispanic White and ethnoracial minority participants across all assessment intervals. The Lifetime version of the C-SSRS was administered at informed consent, while all subsequent administrations used the Since Last Visit version, which assesses suicidal ideation and behavior since the most recent previous
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assessment. Subsample sizes for non-Hispanic White and ethnoracial minority participants ranged from 21 to 29 for positive ideation, serious ideation, and positive behavior. Subsample sizes for ethnoracial minority participants ranged from 5 to 13 for positive ideation, serious ideation, and positive behavior.
Figure 12. Change in case study participant’s Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) score across sessions. Visit 3 refers to the baseline CAPS-5 assessment before the third preparatory session. Visit 8 occurred after the second integration session after the first dosing session. Visit 13 occurred after the second integration session after the second dosing session. Visit 19 occurred after the second integration session after the third dosing session. Based on the CAPS-5 dichotomous diagnostic scoring system, the participant did not meet DSM-5 criteria for PTSD at Visit 13, and maintained recovery at Visit 19.
**Figure 13.** Change in case study participant’s Posttraumatic Symptom Checklist for DSM-5 (PCL-5) score across sessions. Baseline PCL-5 assessment occurred at the informed consent and initial screening visit. Visit 4 refers to the preparatory session prior to the first dosing session. Visit 9 refers to the third integration session after the first dosing session, prior to the second dosing session. Visit 14 refers to the third integration session after the second dosing session, prior to the third dosing session. Visit 20 refers to study termination. Based on the PCL-5 dichotomous diagnostic scoring system, the participant did not meet DSM-5 criteria for a provisional diagnosis of PTSD at Visit 9, and maintained recovery at Visits 14 and 20.
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Mechanisms of change

- Trauma reprocessing
  - Revisiting index trauma without being overwhelmed
  - Revisiting other traumas without being overwhelmed
  - Merging parts of self

- Cognitive change
  - Identifying cognitive distortions
  - Challenging cognitive distortions
  - Self-efficacy against future stressors

- Emotional awareness and regulation
  - Experiencing emotions in their fullness
  - De-escalating negative situations
  - Meditation and stretching
  - Compassion toward self and others
Figure 14. Subthemes (Trauma reprocessing; Cognitive change; and Emotional awareness and regulation) of the master theme, Mechanisms of change.
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Reduced PTSD symptoms

- Reduced intrusions
  - Reduced flashbacks
  - Reduced nightmares
- Reduced avoidance
  - Reduced avoidance of trauma memories
  - Reduced avoidance of trauma reminders
- Improved cognitions and mood
  - Complete index trauma memory
  - Resolution
  - Feeling happy
- Reduced vigilance and arousal
  - Reduced vigilance
  - Somatic relaxation
  - Restful sleep
Figure 15. Subthemes (*Reduced intrusions; Reduced avoidance; Improved cognitions and mood;* and *Reduced vigilance and arousal*) of the master theme, *Reduced PTSD symptoms*
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Additional effects

Reduced suicidality
- Vision of future self
- Reduced suicidal ideation

Reduced substance use
- Appreciating potential of psychedelics
- Reduced desire for marijuana

Pursuing priorities
- Hypermotivated
- Posttraumatic advocacy

Negative effects
- Sleep deprivation
- Chest discomfort
Figure 16. Subthemes (Reduced suicidality; Reduced substance use; Pursuing priorities; and Negative effects) of the master theme, Additional effects.
Navigating interpersonal relationships

- Navigating relationship with parents
  - Non-disclosure
  - Reconnecting while setting boundaries
  - Freedom and autonomy

- Navigating romantic relationships
  - Managing current conflicts
  - Insights about past relationships
  - Thinking about future relationships

- Navigating friendships
  - Feeling distant from certain friends
  - Creating own tribe
Figure 17. Subthemes (Navigating relationship with parents; Navigating romantic relationships; and Navigating friendships) of the master theme, Navigating interpersonal relationships.