Efficacy of Psychotherapy-Supported MDMA in the Treatment of Complex Posttraumatic Stress Disorder

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EFFICACY OF PSYCHOTHERAPY-SUPPORTED MDMA IN THE TREATMENT OF COMPLEX POSTTRAUMATIC STRESS DISORDER

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The Faculty of the School of Medicine
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LIST OF ABBREVIATIONS

APA: American Psychological Association
BAI: Beck Anxiety Inventory
BDI: Beck Depression Inventory
BIPOC: Black, Indigenous, and People of Color
BP: Borderline Personality Disorder
CAPS: Clinician-Administered PTSD Scale for DSM
CBC: Complete Blood Count
CBT: Cognitive Behavioral Therapy
CPT: Cognitive Processing Therapy
CI: Confidence Interval
CMHC: Connecticut Mental Health Center
CMP: Complete Metabolic Panel
CPTSD: Complex Posttraumatic Stress Disorder
C-SSRS: Columbia-Suicide Severity Rating Scale
DES: Dissociative Experiences Scale
DSM: Diagnostic and Statistical Manual of Mental Disorders
DSO: Disturbances of Self-Organization
EKG: Electrocardiogram
EMDR: Eye Movement Desensitization and Reprocessing
FDA: Food and Drug Administration
fMRI: Functional Magnetic Resonance Imaging
GAD-7: Generalized Anxiety Disorder scale
GAF: Global Assessment of Functioning
HIC: Human Investigations Committee
HIPAA: Health Insurance Portability and Accountability Act
ICD: International Classification of Diseases
IES-R: Impact of Events Scale-Revised
IND: Investigational New Drug
IRB: Institutional Review Board
ITQ: International Trauma Questionnaire
LOCF: Last Observed Carried Forward
MAPS: Multidisciplinary Association of Psychedelic Studies
MMRM: Mixed Models for Repeated Measures
NEO-PI-R: Neuroticism, Extraversion, Openness – Personality Inventory
OC: Observed Case
PCL: Posttraumatic Stress Disorder Checklist
PDS: Posttraumatic Diagnostic Scale
PET: Positron Emission Tomography
PSQI: Pittsburgh Sleep Quality Index
PTGI: Posttraumatic Growth Inventory
PTSD: Posttraumatic Stress Disorder
RCT: Randomized Controlled Trial
SD: Standard Deviation
ABSTRACT

Complex Posttraumatic Stress Disorder is a debilitating psychiatric disorder with no approved treatment options despite the high symptom burden and diminished quality of life. Randomized controlled trials have shown robust attenuation of posttraumatic stress disorder symptomatology using treatment with 3,4-Methylenedioxymethamphetamine (MDMA) plus psychotherapy, but individuals with complex traumatization have not been studied explicitly. Prior trials primarily utilized an inactive placebo group, undermining the interpretation of the results due to concern for unblinding of subjects. The proposed study is the first to utilize an active comparator to test a key hypothesis related to MDMA’s mechanism of action and to preserve blinding. This proposed randomized, double-blind, controlled trial will explore the efficacy of psychotherapy-supported MDMA in reducing trauma-related symptom severity, depression, and anxiety in the treatment of adults with Complex Posttraumatic Stress Disorder (n = 64) when compared to an active comparator, methylphenidate.
CHAPTER 1: INTRODUCTION

1.1 What is Complex Posttraumatic Stress Disorder?

Complex Posttraumatic Stress Disorder (CPTSD) is a debilitating psychiatric disorder that typically develops following a prolonged series of interpersonally traumatic events. CPTSD is characterized by six distinct symptom clusters, encompassing the three main posttraumatic stress disorder (PTSD) clusters as well as three clusters related to disturbances in self-organization (DSO). The PTSD symptom clusters include the re-experiencing of past traumatic events, avoidance of reminders linked to these events, and a state of persistent hypervigilance or increased startle response due to current stimuli. Disturbances of self-organization include affect dysregulation, persistent beliefs about oneself as worthless associated with guilt or shame, and difficulty sustaining close interpersonal relationships. Currently, the 5th revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the primary diagnostic reference in the United States, does not differentiate CPTSD as a separate entity from PTSD. In contrast to the World Health Organization’s (WHO) recognition of Complex PTSD as a distinct disorder in the 11th revision of the International Classification of Diseases (ICD-11) in July 2018, this discrepancy raises noteworthy considerations.

1.2 The Debate About Complex PTSD as a Distinct Disorder

The classification and conceptualization of psychiatric disorders have long been a subject of debate and revision. One such area of contention involves the distinction of CPTSD as a distinct entity from DSM-5 PTSD comorbid with borderline personality disorder (BPD). Since the publication of the ICD-11, an increasing number of studies
have supported CPTSD’s validity as a distinct symptom profile. However, the debate remains ongoing, and subsequently, there are a very limited number of randomized controlled trials that have studied this specific population. Recognition and understanding of trauma-related disorders have evolved in recent decades, with PTSD first being introduced into the DSM during its third edition in 1980. Critics argued that PTSD’s diagnostic criteria did not fully encompass the complete spectrum of symptoms observed in those with chronic, interpersonal trauma who consistently exhibit clusters of distinctive features. In response to this debate, the DSM-5 incorporated disturbances of self-organization and a dissociative subtype into its criteria attempting to better represent the symptom profile of those with complex traumatization. However, several studies have indicated that patients with a history of complex interpersonal trauma, particularly those with childhood developmental trauma and those who experience dissociative symptoms, tend to derive less benefit from existing treatments and are often considered to be treatment-resistant. Establishing Complex PTSD as a distinct disorder, as has been done in the ICD-11, would allow for inclusion in more empirical studies. This inclusion could lead to improved treatment outcomes for a population that currently faces limited efficacious treatment options.

A primary argument against recognizing CPTSD as a distinct psychiatric disorder focuses on the overlapping features it shares with borderline personality disorder. Specifically, areas such as affect dysregulation, interpersonal relationship disturbances, and negative self-concept are commonly affected in both conditions. Additionally, childhood trauma exposure, which is central to the diagnosis of CPTSD, is also a known risk factor in BPD. Proponents of this view contend that the symptoms observed in
individuals with complex trauma that fall outside of the traditional PTSD framework are adequately captured within the BPD diagnosis. However, if this classification were sufficient, one would expect that guideline-directed BPD treatment would be similarly efficacious in those meeting the CPTSD profile, but existing evidence does not support this assumption. While BPD and CPTSD share similar symptom dimensions and can exist comorbidly, research has highlighted key phenomenological differences between the two conditions.  

Studies have utilized latent class analyses to identify distinct symptom profiles within populations of individuals who have experienced complex trauma. For example, Cloitre et al. conducted a latent class analysis on childhood abuse victims and identified four latent classes, which included CPTSD, BPD, PTSD, and a baseline/low symptoms class. Similarly, a latent class analysis by Frost et al. in an adult sample of sexual trauma survivors identified a distinct CPTSD symptom class. This class was associated with repeated childhood trauma, further supporting the differentiation of CPTSD as a distinct diagnosis. Furthermore, network analysis conducted on an adult sample of institutional childhood abuse survivors revealed that BPD symptoms were not strongly interconnected to others within the analysis. This suggests that BPD symptomatology is distinct from that of PTSD and CPTSD.

One such distinction emerges in relationship disturbances that are observed in each condition. In BPD, relationship patterns typically involve chaotic cycles of idealization and devaluation. Individuals with CPTSD are often chronically avoidant and fearful of social relationships. Additionally, while BPD is associated with an unstable
self-concept, individuals with CPTSD are commonly marked by a persistently negative view of themselves. Furthermore, while both disorders are strongly associated with difficulty regulating emotions, suicidality and self-injury are much more common in individuals with BPD.\textsuperscript{12} BPD also often presents with unique symptoms that are typically absent in CPTSD including impulsivity, paranoid dissociation, drastic efforts to avoid real or perceived abandonment, and chronic feelings of emptiness. BPD treatment often prioritizes reducing the risk of self-harm and reducing dependence on others. In contrast, patients with CPTSD may be more likely to benefit from focusing on improving self-concept, reducing fear surrounding social engagement, and processing traumatic memories.\textsuperscript{29}

1.3 How is Complex PTSD Currently Treated?

There is a debate in the literature about whether CPTSD is better treated with trauma-focused therapies (like classic PTSD) or with a phase-based model. Proponents of the phase-based model argue that first improving disturbances of self-organization and dissociative symptoms equips the patient with better emotional regulation and interpersonal skills before engaging in trauma-focused therapies, thus improving treatment outcomes.\textsuperscript{15,52} A randomized controlled trial (RCT) by Cloitre et al. investigated the impact of the phase-based treatment method compared to supportive counseling followed by narrative therapy in the severity of PTSD and dissociative symptoms.\textsuperscript{17} A later analysis found that those who did not first undergo “Skills Training in Affective and Interpersonal Regulation” (STAIR) before narrative therapy experienced a worsening of symptoms during the follow-up period. Participants randomized to receive the phase-based model, which included STAIR followed by narrative therapy,
experienced a significant improvement in dissociative symptoms which continued during the 6-month follow-up period.\textsuperscript{15}

Those supporting the trauma-focused model argue that the acute stabilization phase may not be necessary\textsuperscript{18} and could instead cause detrimental treatment delays.\textsuperscript{21} Since patients with complex trauma have a very high incidence of co-occurring psychiatric conditions, another approach has been treating comorbid symptom profiles which include substance use disorder\textsuperscript{64} and borderline personality disorder.\textsuperscript{33} Meta-analysis by Melton et al. found that neither approach was superior to the other in those with symptom clusters associated with CPTSD, and identified DSO improvement of only borderline significance. However, both types of interventions were found to be superior to control groups in reducing symptoms of depression and anxiety.\textsuperscript{61} This suggests that there may be some utility of phase-based and trauma-focused interventions in CPTSD populations with comorbid psychiatric disorders like depression and anxiety.

One potential barrier to utilizing trauma narrative-based therapies in the treatment of CPTSD is that they require sustained attention and emotional engagement with distressing memories while in a subjectively safe therapeutic environment. This may be exceedingly difficult in patients who dissociate in response to reminders of trauma. For those who can remain engaged, narrative-based therapy approaches allow the reprocessing of traumatic memories within a more objective framework than was possible during the original event, which can promote an emotionally corrective experience. This integration promotes the inclusion of distressing memories into one's self-concept and allows for increased feelings of emotional safety and improved self-efficacy.\textsuperscript{15}
1.4 The Role of Shame

Historically, PTSD has been conceptualized as a primarily fear-based disorder, but a growing body of research suggests that there are other significant factors at play. Many studies have suggested that shame is a significant affective disturbance in PTSD. This research has included data based on self-report measures, physiological data, and observation-based studies. Meta-analysis of the relationship between trauma-related shame and psychopathology, including PTSD, trauma-related distress, and depression symptoms revealed a robust association. Shame is a socially rooted, primary emotion that is based on human evolution. Shame is a judgment of the self as “bad” which includes a perceived loss of dignity and power, an inability to behave in line with one’s core values, learned helplessness, and an inability to control one’s life. Shame tends to be most prominent in those who have experienced interpersonal trauma, which is a key diagnostic criterion and risk factor in CPTSD. The highest incidence of shame was associated with interpersonal violence, specifically sexual abuse, and repeated traumatic exposures. Toxic shame inhibits recovery by blocking the integration of traumatic memories into one's core identity.

Various measures of shame have been utilized in research, with a main distinction being “state shame” vs. “dispositional shame” (shame proneness that persists across situations). Dispositional shame in traumatized individuals has been defined as a “negative evaluation of the self in the context of trauma with a painful affective experience, and a behavioral tendency to hide and withdraw from others to conceal one’s own perceived deficiencies.” Øktedalen and colleagues created a Trauma-Related Shame Inventory (TRSI) and their psychometric analysis supported construct validity and
internal reliability\textsuperscript{75} which has since been validated in other studies.\textsuperscript{97} Our study will investigate the mean change in dispositional shame as measured by the TRSI.

1.5 What is MDMA?

3,4-methylenedioxymethamphetamine (MDMA) is a powerful central nervous system stimulant and atypical psychedelic phenethylamine compound, belonging to the amphetamine class of drugs. Unlike hallucinogenic drugs, MDMA acts as an “entactogen” or “empathogen” which is defined as a class of drugs that “promotes affiliative social behavior, has acute anxiolytic effects, and can lead to profound states of introspection and personal reflection.”\textsuperscript{72} For these reasons, MDMA has shown therapeutic promise since the 1970s when it was used as a tool in psychotherapy. However, this halted in 1985 when the Drug Enforcement Administration classified it as a Schedule I substance. The same year, the Multidisciplinary Association of Psychedelic Studies (MAPS) filed a Federal Drug Administration (FDA) application to conduct clinical research on psychotherapy-supported MDMA in the treatment of posttraumatic stress disorder. Since its designation as an illicit substance, MDMA more commonly became known to many as the party drug “ecstasy” and research investigating its therapeutic potential was strictly prohibited. In 2021, the FDA granted MDMA a Breakthrough Therapy Designation in the treatment of PTSD.

MDMA’s empathogenic and prosocial effects are thought primarily to result from an increased release of serotonin and inhibition of serotonin reuptake, leading to heightened activity at the 5-HT\textsubscript{2A} and 5-HT\textsubscript{1B} receptors.\textsuperscript{93} The increase in serotonin levels is also believed to lead to improved cognitive flexibility, increase responsiveness to positive
emotions, and decreased sensitivity to negative emotions, including fear, anger, and sadness.\textsuperscript{39} MDMA also heightens dopamine and norepinephrine activity by inhibiting reuptake at the post-synaptic cleft. Dopamine is known to induce feelings of euphoria and norepinephrine is primarily responsible for MDMA’s stimulant effects including increased alertness, heart rate, and blood pressure. MDMA’s complex mechanism of action is reported to cause enhanced feelings of well-being, increased desire for interpersonal closeness, increased empathy for oneself and others, and increased emotional openness. It is also reported to reduce distress in response to perceived social rejection and enhance introspection and self-awareness. Additionally, MDMA downregulates amygdala activity, which is responsible for the processing of fear, making it of great interest in PTSD, a disorder that is believed to “hijack” the amygdala.\textsuperscript{39,47}

1.6 Statement of the Problem

Since the concept of CPTSD was first introduced in 1992,\textsuperscript{35} there has since been extensive debate about its classification and existence as a distinguishable disorder. Research has been largely limited on the topic until the publication of the World Health Organization’s 11\textsuperscript{th} revision of the International Classification of Diseases in 2018 with the inclusion of Complex PTSD as a distinct disorder. Karatzias et al. conducted a systematic review and meta-analysis of randomized controlled trials of psychological interventions for PTSD where participants displayed clinically significant levels of one or more Complex PTSD symptom clusters. As previously outlined, these symptom clusters include affect dysregulation, negative self-concept, and interpersonal relationship disturbances. The analysis found that cognitive behavioral therapy, exposure therapy, and eye movement desensitization and reprocessing (EMDR) were superior to standard care
for classic PTSD but that those with a history of childhood abuse consistently
experienced less symptom improvement. Childhood abuse is one of the known primary
risk factors for CPTSD and the results of the meta-analysis suggested these participants
were more likely to have the full CPTSD symptom profile.\textsuperscript{46}

Epidemiological studies, albeit limited due to the recency of the official diagnosis,
have estimated that 3.8\% of people within the United States meet the criteria for CPTSD,
compared to 3.4\% meeting the criteria for ICD-11 PTSD.\textsuperscript{14} This suggests that
approximately 12.5 million people within the United States may currently meet the
criteria for CPTSD, without any reliable, efficacious treatment options. Probable CPTSD
is significantly more prevalent than the ICD-11 conceptualization of PTSD in patients
with lived experience of psychiatric disorders, particularly in those with high levels of
depression and anxiety.\textsuperscript{14} One cohort study identified that 12.72\% of the sample of
patients with lived experience of psychiatric disorder(s) (n = 1305) met the criteria for
CPTSD, with 78\% of them reporting not receiving a relevant diagnosis by a mental
health professional.\textsuperscript{54}

Given that the DSM-5 is the current diagnostic gold standard in the United States,
most clinical research is based on these criteria, which some argue is too heterogeneous.
Relying largely on this broad diagnostic category as the primary basis for most trials may
be contributing to suboptimal care for those with a history of complex traumatization.
There is currently an imminent need to identify robust treatment options for those
matching the CPTSD profile and psychotherapy-supported MDMA treatment may be a
novel option.
1.7 Goals and Objectives

The primary goal of the study is to test the efficacy of psychotherapy-supported MDMA treatment in adult patients with Complex Posttraumatic Stress Disorder as defined by changes in PTSD symptom severity. Additionally, our proposed study design will test a key hypothesis related to MDMA’s mechanism of action by being the first to utilize an active comparator, specifically the stimulant methylphenidate. MDMA is thought to produce distinctive efficacy in the treatment of PTSD due to its high potency for blocking the serotonin transporter, relative to the norepinephrine and dopamine transporters. The proposed design will test this hypothesis given methylphenidate’s very low potency at the serotonin receptor.

Additional goals and objectives include testing the impact of psychotherapy-supported MDMA treatment on changes in depression symptoms, anxiety symptoms, sleep disturbance, and quality of life in this population. Novel objectives of this study include the impact of this treatment on Complex PTSD symptom severity score, as defined by the 12-item International Trauma Questionnaire (ITQ), a self-report measure of CPTSD symptom severity created by the World Health Organization that is emerging as a repeatedly validated tool. Our study will also set out to investigate the potential relationship of CPTSD symptom improvement with change in dispositional shame (shame proneness) score, as defined by the Trauma-Related Shame Inventory (TRSI).

1.8 Hypothesis

We hypothesize that the mean change in CAPS-5, BDI-II, and GAD-7 scores will be statistically significantly larger among adults with Complex PTSD who receive
psychotherapy-assisted MDMA treatment compared to the mean change in CAPS-5, BDI-II, and GAD-7 scores among adults with Complex PTSD who receive psychotherapy-assisted methylphenidate treatment.

1.9 Definitions

- **Complex Posttraumatic Stress Disorder (CPTSD):** unless otherwise specified, anytime the term complex posttraumatic stress disorder is used, it refers to the disorder meeting ICD-11 criteria CPTSD criteria. This term is used interchangeably with CPTSD and Complex PTSD
- **Posttraumatic Stress Disorder (PTSD):** unless otherwise specified, anytime the term posttraumatic stress disorder is used, it refers to the disorder meeting DSM-5 PTSD criteria. This term is used interchangeably with PTSD
- **Psychotherapy-supported MDMA:** this term is used interchangeably with the term “MDMA-assisted psychotherapy”
- **Clinically significant improvement:** for purposes of this study, clinically significant improvement is defined as a decrease of ≥30% in CAPS-5 score
- **Loss of diagnosis:** no longer meets DSM-5 criteria for PTSD
- **Remission:** loss of diagnosis and no symptoms have greater than mild severity
REFERENCES

57. Maples-Keller JL, Norrholm SD, Burton M, et al. A randomized controlled trial of 3,4-methylenedioxymethamphetamine (MDMA) and fear extinction in
CHAPTER 2: REVIEW OF THE LITERATURE

2.1 Literature Search Criteria

A comprehensive literature search was conducted between July 2022 to June 2023 utilizing the databases Scopus, PubMed, Cochrane Reviews, and clinicaltrials.gov. Searches utilized combinations of the following keywords that were included within the article title, abstract, and tagged keywords: “PTSD”, “post-traumatic stress disorder”, “posttraumatic stress disorder”, “post traumatic stress disorder”, “Complex PTSD”, “CPTSD”, “C-PTSD”, “complex post-traumatic stress disorder”, “complex posttraumatic stress disorder”, “complex post traumatic stress disorder”, “3,4-methylenedioxymethamphetamine”, “MDMA”, “ecstasy”, “efficacy”, “safety”, “adult”, “randomized controlled trial”, “International Trauma Questionnaire”, “shame”, “depression”, “anxiety”, and “quality of life”. Study titles and abstracts were reviewed for relevancy and priority was given to high-quality empirical studies including appropriately powered randomized controlled trials, systematic reviews, and meta-analyses.

2.2 Current Pharmacological Treatments for PTSD and Complex PTSD

Since there are currently no FDA-approved pharmacological treatments specifically for ICD-11 Complex PTSD, options are limited to approved medications for DSM-5 PTSD. The FDA has approved two selective serotonin reuptake inhibitors (SSRIs), sertraline and paroxetine, for the pharmacological treatment of PTSD. Additionally, fluoxetine (another SSRI) and venlafaxine, a serotonin and norepinephrine
reuptake inhibitor (SNRI), are recommended by the American Psychological Association and the Veterans Administration Department of Defense’s PTSD guidelines. Multiple systematic reviews and meta-analyses have investigated available pharmacotherapy in the treatment of PTSD and have found similar modest efficacy among SSRIs and SNRIs when compared to placebo. One meta-analysis by Huang et al. found both medication classes reduced symptoms of re-experiencing, hypervigilance, depression, and anxiety with a standardized mean difference of -0.33 (95% CI, -0.43 to -0.23)\(^{37}\). However, there is an increasing body of evidence suggesting that these pharmacological treatment options are less efficacious in some subpopulations, particularly those with childhood trauma and veterans. There are currently no pharmacological interventions available for PTSD that induce remission, which underscores the imminent need for advancement within this field of study.\(^{49}\)

2.2.1 Sertraline

Smith et al. reviewed the results of four phase III clinical trials of sertraline for severe PTSD and only two out of four found a statistically significant difference between the experimental group and the placebo group. One such study with 208 participants had a 6.8-unit reduction in CAPS-II score (\(p = .043\)) and the other with 183 participants had a 9.8-unit reduction (\(p = .016\)). Notably, these studies had a 28% and 29% dropout rate, respectively, which introduces the question of attrition bias which can arise when there is a differential loss of participants. This can limit the internal validity of the study by introducing a source of bias that also compromises the generalizability of the results. A
pooled analysis also found that a decrease in PTSD symptom severity was only significant in female participants.25,86

2.2.2 Paroxetine

Three 12-week phase III clinical trials were conducted evaluating the efficacy of paroxetine (dosages ranging from 20-50mg/day) to inactive placebo. The primary outcome measure used to assess changes in PTSD symptom severity was the Clinician-Administered PTSD Scale-II (CAPS-II) score. In the first trial, with a sample size of 551 participants, results showed the experimental group had a 14-unit greater reduction (p < .001) than the placebo group, with a calculated effect size of 0.56. The results were statistically significant in the last observed carried forward (LOCF) method and the observed case (OC) method. These results suggested paroxetine may be an efficacious treatment for PTSD, but it is important to note a dropout rate of 36% which could skew results. If there are characteristics of a participant that makes them more likely to drop out or if dropping out was related to the effects of the intervention, this could overestimate treatment effects.25,86

Similarly, in the second trial involving 307 participants with PTSD, the CAPS-II scores significantly decreased by 11 units (p < .001), compared to the placebo group, with a calculated effect size of 0.45. Results were statistically significant for both the LOCF and OC groups. The dropout rate in this trial was also high at 39% raising similar concerns about internal validity and generalizability to those discussed above. In the third trial involving 332 participants, there was a CAPS-II score reduction of 6 units (p = .047) compared to the placebo, with a small, calculated effect size of 0.09. Additionally, results
were only statistically significant using the LOCF method but not the OC method, which raises significant concerns about data validity. This discrepancy suggests the missing data points may have influenced the outcome, which could falsely inflate treatment effects or reduce the variability of the data set. Like the other trials, the dropout rate was high at 33%.\textsuperscript{25,86}

2.2.3 Fluoxetine

Two clinical trials investigated the efficacy of fluoxetine compared to placebo in the treatment of PTSD. One open prospective trial, studying combat-related PTSD (n = 19) showed a significant decrease in CAPS-II score of 21.8 units (p < .001) following 10 weeks of treatment with 20 – 80mg of fluoxetine. However, the study had a remarkably high dropout rate of 47%, which significantly increases the chance of attrition bias. Additionally, 37% of participants reported not receiving any benefit from treatment.\textsuperscript{71}

One RCT with 47 participants demonstrated a mean reduction in CAPS-II score of 12.59 (p = .0106) when treated with 20 – 60mg of fluoxetine over 5 weeks. Similar to other SSRI trials, this RCT had a high dropout rate of 27%.\textsuperscript{92}

2.2.4 Venlafaxine

In a randomized controlled trial evaluating the efficacy of venlafaxine, an SNRI, vs. placebo in a sample of 329 participants with PTSD, there was a higher reduction in symptom severity in those treated with venlafaxine. This was measured with CAPS-4 and the mean difference between groups was a reduction of 8.9 units (p = .006) with a mild-to-moderate effect size of 0.31. This study did have a 30.4% dropout rate, but it was
similar between groups.\textsuperscript{20} This reduces the likelihood that dropout significantly skewed the results but does indicate that many participants did not experience noticeable benefits.

\section*{2.3 Current Non-Pharmacological Treatments for PTSD and Complex PTSD}

Given the complex symptomology associated with posttraumatic stress disorder, the condition poses significant challenges to mental health providers and often requires the use of non-pharmacological interventions. Many types of psychotherapy have been studied in PTSD with variable levels of efficacy.\textsuperscript{7,53} As previously discussed, Complex PTSD is often less responsive to both pharmacological and non-pharmacological treatment options. This underscores the novelty of our study as there are currently no robust treatment options available for Complex PTSD.

\subsection*{2.3.1 Cognitive Behavioral Therapy: Exposure Therapy and Cognitive Processing Therapy}

Exposure therapy has accrued substantial empirical evidence of its efficacy in treating PTSD. Several randomized controlled trials\textsuperscript{79,83} and meta-analyses\textsuperscript{60,91} have demonstrated the effectiveness of exposure therapy in reducing symptom severity, avoidance behavior, and overall life functioning. However, findings suggest that patients with a complex trauma history tend to require additional therapeutic interventions to experience an impactful level of improvement. Exposure therapy involves confronting distressing situations or traumatic memories to ultimately promote desensitization to triggers and reduce symptoms. Exposure therapy is believed to facilitate fear extinction and prevents the reconsolidation of traumatic memories. Research suggests exposure therapy is efficacious in reducing fear responses in PTSD which sustain lasting benefits.
However, exposure therapy has some disadvantages including the risk of temporary symptom exacerbation if an exposure becomes too distressing which can ultimately lead to retraumatization.\textsuperscript{60}

Cognitive processing therapy (CPT) has emerged as a widely recognized, evidence-based treatment for PTSD\textsuperscript{27,91} and comorbid conditions like depression and anxiety.\textsuperscript{79} CPT involves addressing trauma-related cognitive distortions and maladaptive thoughts and beliefs that contribute to distressing symptoms. This approach aims to develop healthy coping strategies to reduce the symptom burden. However, this form of psychotherapy typically requires a significant time commitment to see measurable benefits. Cognitive processing therapy posits that PTSD symptoms result from distorted cognition and beliefs and that modifying these beliefs should improve symptoms.

2.3.2 Eye Movement Desensitization and Reprocessing

Eye movement desensitization and reprocessing (EMDR) is a psychotherapy approach with a growing body of evidence, including multiple RCTs and systematic reviews\textsuperscript{91}, supporting its efficacy in the treatment of PTSD. EMDR involves bilateral brain stimulation, through actions such as eye movements, while processing traumatic memories in a safe therapeutic environment. Theory suggests that bilateral brain stimulation enhances the integration of adapted traumatic memories within the memory network. Several studies have established the efficacy of EMDR in alleviating PTSD symptoms by targeting specific distressing memories. However, EMDR is generally avoided in some comorbid conditions due to an increased risk of retraumatization.\textsuperscript{19,36}
2.3.3 Sensorimotor Psychotherapy

Sensorimotor psychotherapy is an emerging treatment approach involving the mind-body connection, which has shown limited, preliminary benefits in treating PTSD and Complex PTSD. Some studies have found that targeting unresolved somatic and psychological trauma has contributed to improvements in PTSD symptoms, dissociation, and somatic symptoms. One advantage of sensorimotor psychotherapy is that it addresses the physiological and sensory components of trauma by improving body awareness and emotional regulation. Sensorimotor psychotherapy utilizes an integrated approach that encompasses somatic experiencing, body movement, and mindfulness. Classen et al. conducted a pilot randomized controlled trial investigating the efficacy of body-oriented group therapy in the treatment of women with Complex PTSD and found improvements in body awareness (d = .91; p = .007), anxiety symptoms (d = .81; p = .02), and receptiveness to soothing techniques (d = 1.12; p = .001) when compared to the control group. It’s important to note that the sample size was small, consisting of only 32 participants so these results require replication within larger samples to better assess generalizability.11

2.4 Psychotherapy-Supported MDMA: “Breakthrough” Therapy Designation by the FDA

2.4.1 Theories about Mechanism

On August 16, 2017, the United States Food and Drug Administration (FDA) designated psychotherapy-supported MDMA treatment as a “breakthrough therapy” for posttraumatic stress disorder. In recent years, multiple randomized controlled trials have
demonstrated a robust attenuation of PTSD symptomology along with favorable safety outcomes.\textsuperscript{65-68,74,77}

There are various proposed theories about MDMA’s mechanism with one being that the benefits are related to an improved ability to trust and be emotionally open with the treatment team. Additionally, MDMA reduces anxiety and panic which may allow patients to access traumatic memories and process them within a safe therapeutic setting. MDMA also reduces activity in the amygdala which regulates the fear response and contributes to the storing of traumatic memories. Research suggests that reducing activity in this region, while subsequently increasing responsiveness to positive emotions, allows for reprocessing of these memories within a less fearful framework.\textsuperscript{50}

\textit{2.4.2 Safety Concerns and MDMA’s Adverse Effects}

Research into the adverse effects of MDMA is best outlined by considering it within two distinct contexts: use as an illicit substance and therapeutic use within a controlled clinical setting. It is important to achieve a comprehensive view of all possible complications to continue to optimize safety protocols. Given the relative recency of MDMA’s use in a therapeutic setting, there is a larger abundance of literature outlining its risks when used as an illicit substance. These include some severe disturbances to the body’s homeostasis including hyperthermia, hyponatremia, hypertension, and tachycardia. The various disturbances to homeostasis can contribute to the development of severe and/or life-threatening complications including rhabdomyolysis, renal injury, and acute cardiovascular events including arrhythmias. Using this substance in an
uncontrolled, non-therapeutic setting also raises the risk of becoming a victim of physical or sexual violence, as the user's objectivity can be greatly compromised.\textsuperscript{45,63}

In therapeutic settings, adverse effects commonly observed have generally been less severe and non-life-threatening. These effects include anxiety, nausea, bruxism, reduced appetite, dizziness, muscle tightness, and dysphoric mood.\textsuperscript{40,86} Unfortunately, the presence of a therapeutic setting has not always guaranteed protection against victimization during prior MDMA trials. There have been reported allegations of sexual assault by a therapist in British Columbia, highlighting the vulnerability of patients who are under the influence of psychedelic medications, like MDMA.\textsuperscript{90} To mitigate this risk in future trials, the MAPS protocol now requires a two-person therapy team for all psychotherapy sessions. This team-based approach aims to improve oversight, enhance safety, and reduce the risk of revictimization for patients undergoing psychotherapy-supported MDMA treatment.

2.4.3 Cost Effectiveness

Apart from the substantial efficacy of psychotherapy-supported MDMA treatment, research has also highlighted its cost-effectiveness, providing further impetus to expand its use. Avancena et al. analyzed monetary costs, deaths averted, and quality-adjusted life years. The findings suggested that providing access to patients with severe PTSD could prevent up to 106,000 deaths and could net hundreds of billions of dollars in healthcare system savings\textsuperscript{5}. Moreover, an analysis by Marseille et al. suggested that on average, third-party insurance payers would achieve cost savings within three years of
covering psychotherapy-supported MDMA treatment, which could provide a strong financial incentive for widespread implementation by insurance companies.58

2.5 Review of Possible Confounding Variables

Feduccia et al. pooled data from four phase II psychotherapy-supported MDMA trials and the analysis revealed that a recent taper from an SSRI or SNRI reduced the treatment response. After accounting for participant demographics, baseline PTSD score, and depression severity, researchers found that 63.6% of the non-taper group no longer met PTSD criteria at the primary endpoints vs. 25.0% of the taper group. Additionally, the non-taper group had a lower depression score (mean = 12.7, SD = 10.17; p = 0.010) at the primary endpoint compared to the taper group (mean = 22.6, SD = 16.69; p = 0.32).24 This suggests that recent exposure to anti-depressants, particularly monoamine reuptake inhibitors, may interfere with treatment response.

Various possible confounding variables have been considered in previous trials but Mitchell et al.’s phase III trial was the only RCT large enough to appropriately evaluate subgroups within the study sample. Surprisingly, the presence of dissociative symptoms, severe childhood trauma, comorbid substance use, or alcohol use disorder did not significantly impact the outcome. Additionally, the analysis did not find any demographic information to be confounding variables.65

2.6 Review of Relevant Methodology

2.6.1 Study Design

To date, there have been six Phase II clinical trials and one Phase III clinical trial investigating psychotherapy-supported MDMA in the treatment of posttraumatic stress
disorder which have collectively demonstrated a robust treatment benefit. Aside from one small pilot study, all studies have employed a randomized, double-blind design to study the efficacy and safety of the treatment. The Phase III trial by Mitchell et al. utilized an inactive placebo-controlled design and one Phase II trial utilized very low-dose MDMA as an active comparator. Other Phase II studies utilized a randomized dose-response design. Our study design will be most like the Phase III trial by Mitchell et al.

2.6.2 *Methylphenidate as an Active Comparator*

One major limitation of prior psychotherapy-supported MDMA trials is that most have compared MDMA to an inactive placebo, which introduces a significant risk of bias due to unblinding, as MDMA’s apparent psychogenic effects make it obvious to participants if they are in the experimental group. Some phase II studies utilized low-dose MDMA as a control group, but this does not allow for true isolation of MDMA’s effects as participants may experience some benefit from even low doses.

The current study focuses on identifying the impact of the serotonin-releasing component of MDMA. This focus enables us to protect the integrity of blinding by comparing MDMA to an active comparator, methylphenidate, optimal active control for MDMA. MDMA has a similar affinity for norepinephrine and serotonin transporters and approximately four-fold lower potency at dopamine transporters, making it among the most potent amphetamine derivates at the serotonin transporter. In contrast, methylphenidate has the lowest affinity for the serotonin transporter among the common amphetamine derivates and it has more than 100-fold greater affinity for dopamine and norepinephrine transporters. Thus, both mechanistically and psychologically,
methylphenidate is an optimal comparator for MDMA.\textsuperscript{32} Our goal is to significantly improve the blinding process, by limiting both participants and investigators from guessing treatment group assignments.

Furthermore, selecting an active comparator with an optimal psychological side effect profile is crucial to avoid or limit detrimental emotional processing effects. Previous studies conducted on healthy subjects have favored methylphenidate as a preferred comparator to other stimulants, specifically modafinil. In a randomized controlled trial with a cross-over design, fMRI analysis was conducted on 22 participants exposed to fearful faces in MDMA (125mg), methylphenidate (60mg), and modafinil (600mg) groups. The modafinil group, but not the methylphenidate group exhibited increased amygdala activity and activation within the limbic-cortical-striatal-pallidal-thalamic circuit when exposed to fearful faces, which correlated with increased subjective feelings of fearfulness (Z = 4.367; p = .0016) and depressiveness (Z = 4.258; p = .0012) in the modafinil group.\textsuperscript{82} However, this study’s generalizability may be limited given its small sample size and exclusion of subjects with psychiatric disorders.

Notably, another cross-over study in healthy subjects (n = 24) investigated the emotional, autonomic, and endocrine effects of MDMA, methylphenidate, modafinil, and placebo. Results indicated that methylphenidate had increased subjective anxiety levels. In the proposed study, we aim to mitigate adverse psychological effects by utilizing lower doses of methylphenidate, with an initial dose of 10-20mg with an additional 10mg supplemental dose.\textsuperscript{23}
2.6.3 Racial Disparities Within Clinical Trials

Another limitation of previous clinical trials of psychotherapy-supported MDMA treatment of PTSD is that there was a notable lack of racial diversity, with an overrepresentation of white participants. Historically, there have been well-documented racial disparities in the diagnosis and treatment of PTSD.\textsuperscript{6,10,62,95} Given that minoritized groups are at a higher risk of severe PTSD,\textsuperscript{62} it is essential to make a concerted effort to minimize these disparities going forward, and this begins with improved representation within clinical trials. This involves the inclusion of BIPOC individuals in research personnel, specifically within the team of therapists. Williams et al. defined racial trauma as “the severe mental and emotional injury caused by the cumulative traumatic effects of racism experienced throughout one’s life.”\textsuperscript{96} One black female participant of a MAPS-sponsored MDMA trial reported that when racial trauma wounds emerged within treatment sessions, she did not receive empathy and understanding from her therapists, which she felt deepened the disconnection between her mind and body.\textsuperscript{85} Our study will prioritize outreach to communities with a higher prevalence of minority races to better represent the PTSD population at large.

2.6.4 Study Population and Selection Criteria

All RCTs investigating the efficacy of psychotherapy-supported MDMA treatment were performed in adults meeting the DSM-4 or DSM-5 criteria for PTSD. All studies included participants with moderate to severe PTSD, with most requiring at least 6 months of symptoms. In Mitchell et al.’s phase III trial, moderate PTSD severity was defined as a CAPS-5 score $\geq 35$. However, one phase II study specifically studied adults
with PTSD related to military service or being a crime victim, with at least 5 years of symptoms. All phase II studies required participants to have failed at least one treatment to become eligible.

2.6.5 Interventions

The intervention and control protocols are outlined in detail in Table 1 for all randomized controlled trials studying psychotherapy-supported MDMA in the treatment of PTSD (excluding one pilot study that was terminated).

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcomes</th>
<th>Intervention and Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03537014</td>
<td><strong>Primary:</strong> CAPS-V</td>
<td><strong>Experimental Group:</strong></td>
</tr>
<tr>
<td>Phase 3</td>
<td><strong>Secondary:</strong> SDS</td>
<td><strong>Session 1:</strong> MDMA 80mg + supplement MDMA 40mg 1.5-2.5 hours later</td>
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<td></td>
<td><strong>Exploratory:</strong> BDI-II</td>
<td><strong>Session 2:</strong> MDMA 120mg + supplement MDMA 60mg 1.5-2.5 hours later if tolerated</td>
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<td></td>
<td></td>
<td><strong>Session 3:</strong> MDMA 120mg + supplement MDMA 60mg 1.5-2.5 hours later if tolerated</td>
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<td></td>
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<td><strong>Control Group:</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>Session 1:</strong> MDMA 80mg + supplement MDMA 40mg 1.5-2.5 hours later</td>
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<td></td>
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<td><strong>Session 2:</strong> MDMA 120mg + supplement MDMA 60mg 1.5-2.5 hours later if tolerated</td>
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<td></td>
<td><strong>Session 3:</strong> MDMA 120mg + supplement MDMA 60mg 1.5-2.5 hours later if tolerated</td>
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<td></td>
<td></td>
<td>• Sessions were spaced 4 weeks apart</td>
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<td></td>
<td></td>
<td>• Three 8-hour inner-directed manualized psychotherapy performed by two-person therapy team, beginning after initial medication administration</td>
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<td></td>
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<td>• Three 90-minute integration sessions following each session</td>
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<td>• 1st: morning after session</td>
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<td>• 2nd: 3-4 weeks after session</td>
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<td></td>
<td></td>
<td>• 3rd: 3-4 weeks after session</td>
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</tbody>
</table>

<p>| NCT00090064 | <strong>Primary:</strong> CAPS-IV | <strong>Experimental Group:</strong>                                      |
| Phase 2     | <strong>Secondary:</strong> IES-R | <strong>Session 1:</strong> MDMA 125mg + supplement MDMA 62.5mg 1.5-2.5 hours later |
|             |                    | <strong>Session 2:</strong> MDMA 125mg + supplement MDMA 62.5mg 1.5-2.5 hours later |
|             |                    | <strong>Control Group:</strong>                                            |
|             |                    | <strong>Session 1:</strong> Placebo 125mg + supplement placebo 62.5mg 1.5-2.5 hours later |</p>
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Phase</th>
<th>Primary Measures</th>
<th>Secondary Measures</th>
<th>Experimental Group</th>
<th>Active Control</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>NCT01793610</td>
<td>Phase 2</td>
<td>CAPS-IV</td>
<td>BDI-II, PSQI</td>
<td>Session 2: Placebo 125mg + supplemental placebo 62.5mg 1.5-2.5 hours later</td>
<td>Two 8-hour inner-directed manualized psychotherapy performed by a two-person therapy team, beginning after initial medication administration&lt;sup&gt;68,69&lt;/sup&gt;</td>
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<td>Full-dose MDMA:</td>
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<td>Sessions 1 &amp; 2: MDMA 125mg + supplemental MDMA 62.5mg 1.5-2.5 hours later</td>
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<td>Medium-dose MDMA:</td>
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<td>Sessions 1 &amp; 2: MDMA 100mg + supplemental MDMA 50mg 1.5-2.5 hours later</td>
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<td>Low-dose MDMA:</td>
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<td></td>
<td>Sessions 1 &amp; 2: Placebo 40mg + supplemental placebo 20mg 1.5-2.5 hours later</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>• Two 8-hour inner-directed manualized psychotherapy performed by a two-person therapy team, beginning after initial medication administration&lt;sup&gt;67&lt;/sup&gt;</td>
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<tr>
<td>NCT01211405</td>
<td>Phase 2</td>
<td>CAPS-IV</td>
<td>GAF, PTGI, BDI-II, DES-II, PSQI, NEO-PI-R</td>
<td>Full-dose MDMA: Sessions 1 &amp; 2: MDMA 125mg + supplemental MDMA 62.5mg 1.5-2 hours later</td>
<td>Medium-dose MDMA: Sessions 1 &amp; 2: MDMA 75mg + supplemental MDMA 37.5mg 1.5-2 hours later</td>
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<td>Low-dose MDMA:</td>
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<td></td>
<td>Sessions 1 &amp; 2: Placebo 30mg + supplemental placebo 15mg 1.5-2 hours later</td>
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<td></td>
<td></td>
<td>• Two 8-hour inner-directed manualized psychotherapy performed by a two-person therapy team, beginning after initial medication administration&lt;sup&gt;67&lt;/sup&gt;</td>
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<tr>
<td>NCT00353938</td>
<td>Phase 2</td>
<td>CAPS-IV</td>
<td>PDS</td>
<td>Experimental Group: Sessions 1 &amp; 2: MDMA 125mg + supplemental MDMA 62.5mg 2.5 hours later if tolerated</td>
<td>Active Control: Sessions 1 &amp; 2: MDMA 25mg + supplemental MDMA 12.5mg 2.5 hours later if tolerated</td>
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<tr>
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<td></td>
<td></td>
<td>• Two 8-hour inner-directed manualized psychotherapy performed by a two-person therapy team, beginning after initial medication administration&lt;sup&gt;74&lt;/sup&gt;</td>
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<tr>
<td>NCT01689740</td>
<td>Phase 2</td>
<td>CAPS-IV</td>
<td>BDI-II, GAF, PDS, PSQI</td>
<td>Experimental Group: Sessions 1 &amp; 2: MDMA 125mg + supplemental MDMA 62.5mg 1.5-2.5 hours later</td>
<td>Active Control: Sessions 1 &amp; 2: MDMA 25mg + supplemental MDMA 12.5mg 1.5-2.5 hours later</td>
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</tbody>
</table>
2.6.6 Outcomes and Variable Measurements

All prior studies have elected to use change in PTSD symptom severity from baseline to the primary endpoint as the primary outcome, as measured by the fourth or fifth versions of the Clinician-Administered PTSD Scale for DSM (CAPS-4 or CAPS-5), which are comparable by conversion. Given CAPS-5 has undergone extensive psychometric testing and has been repeatedly validated as an assessment tool, our study will utilize this scale as the primary outcome measure to maximize data reliability and validity. Similarly to previous studies, we will also utilize the CAPS-5 scale to measure the change in PTSD symptom severity from baseline to subsequent follow-up assessments, extending past the primary endpoint. Our data collection strategy will parallel that used in Mitchell et al.’s Phase III trial given an analysis of the methodology revealed its validity and reliability. Independent raters who were unaware of the details of the study conducted all outcome assessments. Researchers found diagnostic concordance between raters, with a Cohen’s kappa coefficient of 0.94, and established data reliability with a Spearman correlation coefficient of 0.98 (p < 0.0001).
The studies employed secondary outcome measures including various psychological constructs including functional impairment, depression symptoms, dissociative symptoms, sleep disturbance, post-traumatic growth, personality change, and subjective distress related to traumatic events, (see Table 2 for variable operationalization). Two studies also included the Posttraumatic Diagnostic Scale (PDS) as a secondary outcome, measuring PTSD symptom severity.\textsuperscript{66,74} Although studies had mixed results about the impact on depression and anxiety symptoms, studies suggest that comorbid depression and anxiety are more prevalent among those with probable CPTSD, compared to the ICD-11 PTSD conceptualization.\textsuperscript{54}

<table>
<thead>
<tr>
<th>Table 2: Secondary Outcome Operationalization in Prior MDMA Trials</th>
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<tbody>
<tr>
<td><strong>Secondary Outcome</strong></td>
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<tr>
<td>Functional Impairment</td>
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<tr>
<td>Depression Symptoms</td>
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<td>Anxiety Symptoms</td>
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<tr>
<td>Dissociative Symptoms</td>
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<tr>
<td>Sleep Disturbance</td>
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<tr>
<td>Post-Traumatic Growth</td>
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<tr>
<td>Quality of Life</td>
</tr>
<tr>
<td>Personality Change</td>
</tr>
<tr>
<td>Subjective Distress Related to Traumatic Events</td>
</tr>
</tbody>
</table>
2.6.7 Safety Concerns

Previous investigations have implemented rigorous safety protocols with comprehensive monitoring strategies which will serve as the foundation for the proposed study’s safety protocol. Notably, there were no severe adverse events reported in any of the studies, with the predominant reported adverse effects being anxiety, low mood, nausea, and jaw clenching.\textsuperscript{40} Furthermore, two long-term follow-up studies examining psychotherapy-supported MDMA treatment did not demonstrate any evidence of enduring harmful effects including drug dependency.\textsuperscript{44,94}

Safety protocols encompass thorough medical and psychiatric assessments as well as pre-enrollment testing to exclude those at higher risk of serious safety events. These include pre-existing cardiovascular conditions or psychotic disorders (see specific selection criteria in the section outlined in section 3.2 for a detailed account of exclusion criteria). Considering the established risk of cardiovascular adverse effects with the use of MDMA, protocols incorporated frequent vital sign monitoring including blood pressure, heart rate, and body temperature. Suicidality was also repeatedly assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS).

2.6.8 Follow-Up

To date, long-term outcomes are only available for phase II studies. Jerome et al. performed a pooled analysis of treatment outcomes at 12 months following the last experimental session. The analysis indicated that at the 12-month follow-up point, 67% of MDMA participants no longer met DSM-5 criteria for PTSD, which is an increase from 56% in these same participants at the primary study endpoint.\textsuperscript{44} Participants did not report any severe adverse effects in the 12 months following the primary endpoint.\textsuperscript{66}
2.6.9 Statistical Analysis

Similarly to the phase III clinical trial, our study will utilize mixed models for repeated measures (MMRM) to perform efficacy analyses of the primary, secondary, and exploratory outcomes. MMRM has shown superiority in analyzing data sets that use repeated measures within the same research subject. Unlike other methods, MMRM can account for missing data without diminishing the quality of the analysis. Baseline characteristics between study groups will be analyzed using a t-test for continuous variables and a chi-square t-test for categorical variables.65

2.6.10 Conclusion

Posttraumatic stress disorder is a debilitating psychiatric disorder with current treatment options that are moderately efficacious for some but fail to offer relief to many others. Despite the notable progress in the field of PTSD neuroscience, the development of novel PTSD therapies has stalled. Recent research progress includes an advanced understanding of underlying genetics and epigenetics, identification of molecular targets in the brain with positron emission tomography (PET), molecular analyses of postmortem brain tissue, and improved understanding of neural circuitry through structural and functional brain magnetic resonance imaging.

Meta-analyses comparing the efficacy of SSRIs to psychotherapy-supported MDMA treatment have demonstrated substantial differences between the two. Psychotherapy-supported MDMA treatment has resulted in robust symptom improvement, with Cohen’s $d$-effect size of 0.9, with only 2-3 treatment sessions. Many participants have entered remission and no longer meet the criteria for PTSD which was
sustained in long-term follow-up. SSRIs, which require daily dosing, provide only a modest symptom improvement for some, and no benefit for many. Paroxetine had an effect size between 0.45-0.56 and sertraline had an effect size between 0.31-0.37.25

As previously outlined, those meeting the criteria for Complex PTSD are more likely to be resistant to treatment. Given the recent emergence of psychotherapy-supported MDMA as a potential breakthrough treatment in PTSD, this may hold promise in the CPTSD population. Since multiple RCTs have included participants with severe childhood trauma, which is one of the hallmarks of the disorder, it's reasonable to hypothesize that it could emerge as the first treatment approved for CPTSD. The participants in our study will meet DSM-5 PTSD criteria in addition to the three symptom clusters encompassing disturbances of self-organization. Therefore, the methodology for our study will be based on an analysis of RCTs investigating psychotherapy-supported MDMA treatment in participants with severe PTSD.
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69. Mithoefer MC, Wagner MT, Mithoefer AT, et al. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4- methylenedioxymethamphetamine-assisted psychotherapy: A


CHAPTER 3: STUDY METHODS

3.1 Study Design

This trial will investigate the efficacy and safety of the use of psychotherapy-supported MDMA in the treatment of adults with ICD-11 Complex Posttraumatic Stress Disorder, also meeting the DSM-5 criteria for moderate to severe posttraumatic stress disorder, as defined by a CAPS-5 score of 35 or greater. The proposed study will be a randomized, double-blind, controlled trial across two institutional Yale-New Haven Healthcare System clinical sites utilizing active comparator, methylphenidate with psychotherapy as a control. The study design is based on a modified version of the protocol created by the Multidisciplinary Association for Psychedelic Studies (MAPS) in conjunction with the Food and Drug Administration. The experimental sessions will span across 12 weeks, with three 8-hour sessions spaced 4 weeks apart. The primary endpoint will be 4 weeks after the third experimental session. There will be a follow-up open-label extension trial following the proposed study for participants previously randomly assigned to the control group.

3.2 Study Population, Inclusion, and Exclusion Criteria

The study population will include adults between the ages of 18-65 years old who meet the criteria for ICD-11 Complex Posttraumatic Stress Disorder, as established by the International Trauma Questionnaire (see Appendix A) and meet the criteria for DSM-5 PTSD, as defined by a baseline CAPS-5 score ≥ 35. Participants will be required to have experienced at least one year of symptoms. Participants will be required to meet all inclusion criteria and cannot have any exclusion criteria, both defined in detail below in
Table 3. Inclusion and exclusion data will be obtained via various screening measures (detailed in section 3.3) and baseline assessments before study enrollment. The sample size will include 64 participants, with 32 randomly assigned to the experimental group and 32 assigned to the control group. This randomization will be performed using a third-party randomization software to protect the blinding of group assignments.

<table>
<thead>
<tr>
<th>Table 3: Inclusion and Exclusion Criteria</th>
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<tbody>
<tr>
<td><strong>Inclusion Criteria</strong></td>
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<tr>
<td>• Adults between 18-65 years old</td>
</tr>
<tr>
<td>• Meets ICD-11 criteria for Complex Posttraumatic Stress Disorder (see appendix A for diagnostic scoring criteria)</td>
</tr>
<tr>
<td>• Meets DSM-5 criteria for moderate or severe PTSD, as demonstrated by baseline CAPS-5 score ≥ 35</td>
</tr>
<tr>
<td>• Has experienced PTSD symptoms for ≥ 1 year</td>
</tr>
<tr>
<td>• If a participant is of childbearing potential, they must have a negative pregnancy test before each session and use at least one adequate birth control method</td>
</tr>
<tr>
<td>• Are able and willing to undergo a psychotropic medication taper and washout period of one month if applicable</td>
</tr>
<tr>
<td>• Can swallow pills</td>
</tr>
<tr>
<td>• Are able and willing to provide an emergency contact</td>
</tr>
<tr>
<td><strong>Exclusion Criteria</strong></td>
</tr>
<tr>
<td>• Has a past medical history of cardiovascular disease, including myocardial infarction, cerebrovascular accident, an arrhythmia, or heart failure</td>
</tr>
<tr>
<td>• Has baseline QT/QTc interval prolongation, exceeding 450 milliseconds</td>
</tr>
<tr>
<td>• Has uncontrolled hypertension, with baseline blood pressure exceeding 120/80</td>
</tr>
<tr>
<td>• Has a history of a significant medical condition that could convey potential increased risk for adverse events including, but not limited to active liver disease</td>
</tr>
<tr>
<td>• Weighs less than 48kg</td>
</tr>
<tr>
<td>• Has a primary psychotic disorder or an affective disorder with psychotic features</td>
</tr>
<tr>
<td>• Has a history of suicide attempt, suicidal behavior, active suicidal ideation, or a psychiatric hospitalization within the past year</td>
</tr>
<tr>
<td>• Has an active moderate or severe cannabis use disorder (as defined by DSM-5 criteria)</td>
</tr>
<tr>
<td>• Has an active moderate or severe alcohol use disorder (as defined by DSM-5 criteria)</td>
</tr>
<tr>
<td>• Tests positive on urine toxicology screening for illicit substances</td>
</tr>
<tr>
<td>• Is pregnant or lactating</td>
</tr>
<tr>
<td>• Is unable to provide informed consent</td>
</tr>
</tbody>
</table>
3.3 Screening, Recruitment, and Randomization

3.3.1 Screening

After building a pool of potential participants, they will be phone screened utilizing the Posttraumatic Stress Disorder Checklist (PCL-5). Participants meeting the criteria for moderate to severe PTSD will be screened in person via an initial psychiatric diagnostic interview including the brief psychiatric psychosis interview. Screening tests will include a physical exam, vitals monitoring, an EKG, BMI calculation, complete blood count (CBC) with differential, complete metabolic panel (CMP), and urine toxicology. The Sobell Timeline Followback (TLFB) will be used in the screening period and for subsequent monitoring throughout the study to assess alcohol, illicit drug, and cannabis use. If there is evidence of illicit drug use on the baseline urine toxicology screening, this individual will be excluded from the study. Individuals with mild cannabis use disorder or mild alcohol use disorder, as outlined by DSM-5 criteria, will be permitted to participate in the study. If a research subject tests positive on one of the urine toxicology screenings performed before 8-hour sessions, the participant will not be permitted to receive MDMA, methylphenidate, or an inactive placebo. The participant will be permitted to undergo the psychotherapy session. The Fagerström smoking scale will be assessed at baseline and monitored throughout the study to assess nicotine use, which will be investigated as a potential covariate. However, nicotine use will not be utilized to determine if a participant meets inclusion or exclusion criteria. Participants must be willing to undergo a psychotropic medication washout period, with a one-month abstinence period following a medication taper.
3.3.2 Recruitment

Participants will be recruited via print and online advertisements, by provider treatment referral, and by word of mouth over a 16-month recruitment period. We will utilize resources from Yale-New Haven Healthcare System (YNHHS), the VA National Center for PTSD, and the Connecticut Mental Health Center (CMHC) by informing psychiatric clinicians within these clinical sites and requesting referrals for potentially eligible patients who express interest. Print advertisements will be distributed throughout New Haven and surrounding communities with an emphasis on community centers frequently accessed by minority populations to improve outreach to these communities for more equitable access to this study.

3.3.3 Sampling and Randomization

If more than 64 participants meet the study criteria, 64 will be randomly selected via third-party randomization software. Following study enrollment, participants will be randomized to either the intervention or control group via web-based randomization software. 32 participants will be assigned to the experimental group and 32 will be assigned to the active comparator group. They will be matched by the sex assigned at birth and the presence or absence of childhood trauma history.

3.4 Subject Protection and Confidentiality

Before study initiation, ethical approval will be obtained by the Yale Human Investigations Committee’s (HIC) institutional review board (IRB) at Yale School of Medicine and Yale New Haven Health System (YNHHS). Following IRB approval, an Investigational New Drug (IND) application will be submitted. Before any participation
in the study’s protocol, written informed consent will be obtained from all participants in accordance with Yale’s IRB. The consent form includes an overview of the goals and objectives of the research study, contains a detailed study description including the timeline, methods to protect the confidentiality, possible treatment benefits, and adverse effects, and a statement explaining that a participant may withdraw at any time or be removed from the study at the discretion of the investigators.

This consent form will be reviewed with each potential participant in detail by HIPAA-trained research personnel and participants will be given ample opportunity to ask questions and discuss any concerns that may arise. The collection, storage, and analysis of all patient information will comply with privacy standards as outlined in the Health Insurance Portability and Accountability Act (HIPAA). 84

3.5 Timeline and Resources

The entirety of the study will take place within a 23–24-month timeframe. Recruitment, screening, and enrollment will span 16 months to achieve the target sample size of 64 participants meeting the study criteria. There will be an allotted 6-week period to perform psychotropic medication tapers when applicable. Specific tapering schedules will be informed by society guidelines for the specific medications. If a participant cannot safely taper off their psychotropic medication within these 6 weeks, they will not be enrolled in the study. Following this tapering period, there will be a 4-week medication washout period. Following the washout period, participants will undergo three 90-minute preparatory psychotherapy sessions, across the span of 4 weeks. Following the preparation phase, the experimental sessions will span 12 weeks. The primary, secondary,
and exploratory outcome endpoints of the study will be assessed 4 weeks after the third experimental session.

This study will take place at two outpatient clinical sites throughout the Yale-New Haven Healthcare System. There will be two principal investigators, one being a physician and the other being an advanced practice provider (APP). The APP will conduct the pre-study physical exam and review medical information to determine eligibility. Each study site will require two clinical psychologists to perform psychotherapy and assess outcome data, a research coordinator, a research assistant, and a research analyst for data entry.

3.6 Study Protocol

Following a medication washout period, requiring all participants to be abstinent from psychotropic medications for at least one month, all will undergo three 90-minute preparatory psychotherapy sessions with a two-person therapy team to begin to establish a therapeutic alliance and to prepare participants for the potential distressing emotions and memories that could arise during future sessions.

Regardless of group assignment, participants will be required to fast for 10 hours before the administration of either MDMA or methylphenidate. This includes nicotine, caffeine, alcohol, illicit substances, and prescription or over-the-counter medications (unless otherwise approved by the investigators). Following drug administration, all participants will undergo three 8-hour manualized, inner-directed psychotherapy sessions using the protocol that the Multidisciplinary Association for Psychedelic Studies (MAPS)
created in conjunction with the FDA. These sessions will be one month apart.

3.6.1 Experimental Intervention

Before the first experimental 8-hour psychotherapy session, blinded investigators will administer 80mg of MDMA in oral tablet form. A supplemental dose of 40mg will be administered between 2-2.5 hours later if safety precautions are met (outlined in detail in section 3.7) and the participant consents. Prior to the second and third experimental 8-hour psychotherapy sessions (all sessions spaced one month apart), blinded investigators will administer 120mg of MDMA in oral tablet form. A supplemental dose of 60mg will be administered between 2-2.5 hours later if safety precautions are met and the participant consents. MDMA will be obtained from the Yale Investigational Pharmacy and consumed with at least 50 mL of water.

3.6.2 Active Control

Before the first 8-hour psychotherapy session, blinded investigators will administer 10mg of methylphenidate in oral tablet form. This tablet and those used before the sessions will be identical in appearance and taste to the MDMA tablet given to the experimental group. A supplemental dose of 10mg will be administered between 2-2.5 hours later if safety precautions are met (outlined in detail in section 3.7) and the participant consents. Prior to the second and third 8-hour psychotherapy sessions, blinded investigators will administer 20mg of methylphenidate in oral tablet form. A supplemental dose of 10mg will be administered between 2-2.5 hours later if safety precautions are met and the participant consents.
Table 4: Medication Administration Protocols Before 8-hour Psychotherapy Sessions

<table>
<thead>
<tr>
<th>Session</th>
<th>Experimental Group</th>
<th>Active Comparator Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Session 1</td>
<td>80mg MDMA + supplemental 40mg dose 2-2.5 hours later</td>
<td>10mg methylphenidate + supplemental 10mg dose 2-2.5 hours later</td>
</tr>
<tr>
<td>Session 2</td>
<td>120mg MDMA + supplemental 40mg dose 2-2.5 hours later</td>
<td>20mg methylphenidate + supplemental 10mg dose 2-2.5 hours later</td>
</tr>
<tr>
<td>Session 3</td>
<td>120mg MDMA + supplemental 40mg dose 2-2.5 hours later</td>
<td>20mg methylphenidate + supplemental 10mg dose 2-2.5 hours later</td>
</tr>
</tbody>
</table>

Note: all supplemental dose administrations for both groups are contingent on meeting safety precautions outlined in section 3.7

3.7 Safety Monitoring

In addition to the baseline assessments outlined in section 3.3, all participants will be monitored for serious adverse events throughout the course of the study. Before medication administration, vital signs will be assessed including blood pressure, heart rate, and body temperature. If blood pressure is not below the threshold of 140/90, heart rate is not below the threshold of 120 bpm, and body temperature is not below 100.4°F (38°C), MDMA or methylphenidate will not be administered. Participants will be screened for suicidal ideation and behavior before and following each psychotherapy session using the C-SSRS. Furthermore, participants will be encouraged to report any symptoms experienced during the entire duration of the experiment which will be reported with the study findings. Following the completion of the study, during the endpoint analysis one month after the third session, an EKG will be done to compare to the pre-study baseline.

3.8 Outcome Assessment and Operationalization

3.8.1 Data Collection
All primary, secondary, and exploratory outcome data collection throughout the course of the study will be performed by the psychotherapy team. The team will conduct outcome assessments at three points during the study. The first two outcome assessments will occur approximately 3 weeks after the first two 8-hour sessions. The third assessment will occur 4 weeks after the final 8-hour session, which is the study’s primary endpoint. These assessments will include CAPS-5, ITQ, BDI-II, GAD-7, TRSI, PSQI with PTSD addendum, and QHOQOL-BREF.

3.8.2 Primary Outcome

The primary outcome being assessed is the change in PTSD symptom severity from baseline to the primary endpoint (4 weeks post-third psychotherapy session), as defined by the change in CAPS-5 score.

3.8.3 Secondary Outcomes

As a secondary outcome, we will assess the change in Complex PTSD symptom severity from baseline to the primary endpoint, as defined by the change in ITQ score. We will also measure the change in depression symptom severity, as defined by the change in BDI-II score. Furthermore, we will measure the change in anxiety symptom severity, as defined by the change in GAD-7 score.

3.8.4 Exploratory Outcomes

We will investigate the change in dispositional shame levels from baseline to the primary endpoint, as defined by the change in the Trauma-Related Shame Inventory (TRSI)\textsuperscript{75} score. We will also assess change in the quality of life, as defined by the
WHOQOL-BREF, and change in sleep quality, as defined by the PSQI with the PTSD nightmare addendum, from baseline to the primary endpoint.

### 3.9 Statistical Analysis

Primary, secondary, and exploratory outcome efficacy analyses will be performed utilizing a mixed effects model for repeated measures (MMRM) using both the intention-to-treat and per-protocol methods. This will include outcome data collected during baseline assessments and following the three 8-hour sessions for the following continuous, parametric variables listed in Table 4. Statistical significance will be defined as $p \leq 0.05$. Additionally, using the change in CAPS-5 score from baseline to the primary endpoint, we will classify participants as having clinically significant improvement, loss of diagnosis, remission, or not clinically improved. Clinically significant improvement will be defined as a $\geq 30\%$ improvement in CAPS-5 score and not clinically improved will be any change below this threshold. Loss of diagnosis is defined as no longer meeting the criteria for DSM-5 PTSD. Remission is defined as loss of diagnosis and the absence of any symptoms with greater than mild severity. This outcome is categorical and will therefore be analyzed via the chi-square method.
### Table 5: Operationalization of Parametric, Continuous Study Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Operationalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD symptom severity</td>
<td>Mean change in CAPS-5 score</td>
</tr>
<tr>
<td>CPTSD symptom severity</td>
<td>Mean change in ITQ score</td>
</tr>
<tr>
<td>Depression symptom severity</td>
<td>Mean change in BDI-II score</td>
</tr>
<tr>
<td>Anxiety symptom severity</td>
<td>Mean change in GAD-7 score</td>
</tr>
<tr>
<td>Dispositional shame</td>
<td>Mean change in TRSI score</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Mean change in QHOQOL-BREF</td>
</tr>
<tr>
<td>Sleep quality</td>
<td>Mean change in PSQI</td>
</tr>
</tbody>
</table>

Several baseline characteristics will be analyzed to ensure there are no significant differences between treatment groups and identify covariates to include in our primary analysis. Continuous variables including baseline PTSD symptom severity (CAPS-5 score), BMI, baseline quality of life (QHOQOL-BREF score), baseline depression severity (BDI-II score), baseline anxiety severity (GAD-7 score), alcohol use (number of heavy alcohol use days on timeline followback), cannabis use (number of cannabis use days on timeline followback), and the mean number of packs of cigarettes consumed per day. These variables will be reported as a mean and standard deviation and analyzed with a student t-test to determine if there are statistically significant differences between study groups. We will perform a multiple linear regression analysis including these continuous variables to assess for possible covariates to account for in the model. Categorical variables including the presence or absence of a medication washout, the presence or absence of the dissociative subtype, and socioeconomic status will be reported as a proportion and analyzed via a chi-square test. We will perform a multiple logistic regression analysis including these categorical variables to assess for possible covariates to include as fixed effects.
3.10 Sample Size Calculation

Sample size calculations were based on data from Mitchell et al.’s phase 3 clinical trial. Prior psychotherapy-supported MDMA randomized controlled trials experienced dropout rates of ≤ 7.6%. Conservatively, our study estimates a dropout rate of 10%. We propose a study with a power of 80%, β = 0.02, and α = 0.05 for the primary outcome. We applied the Bonferroni adjustment for the 3 secondary outcomes in our study; this results in α = 0.017. Conservatively, we rounded this down to α = 0.01, producing a sample size of n = 58. When adjusted to account for an expected 10% dropout rate, the final sample size needed was n = 64.
REFERENCES


CHAPTER 4: CONCLUSION

4.1 Advantages and Disadvantages

To our knowledge, this study will be the first randomized controlled trial to study a pharmacological therapy in the treatment of Complex Posttraumatic Stress Disorder. Additionally, our study will be the first to utilize a non-MDMA active comparator group in trials investigating the efficacy of psychotherapy-supported MDMA treatment for PTSD. This novel design is advantageous because it directly addresses one of the central limitations of prior studies. Given the strong psychogenic effects of MDMA, critics have argued that using an inactive placebo significantly compromises the quality of double-blinding as participants and investigators can readily observe the clear subjective and objective effects of the experimental group. Using methylphenidate, a stimulant medication, as the control group should significantly improve the blinding process, which improves the validity and reliability of the results. Additionally, since our study will prioritize recruiting a more racially diverse sample population than prior trials which included predominantly white participants, this improves generalizability to the general Complex PTSD population.

Our proposed study's limitations are important to acknowledge, specifically the relatively small sample size. This limitation is like prior psychotherapy-supported MDMA trials which have all utilized sample sizes of less than 100 participants. Although effect sizes have been large and statistically significant, there is an undoubted benefit in testing novel interventions in larger samples. Additionally, while using methylphenidate as an active comparator should improve blinding, some participants and investigators
may still correctly determine which intervention was administered. Methylphenidate will control for the stimulant-like effects of MDMA given its activity at norepinephrine and dopamine transporters. While this will control for MDMA’s effects on norepinephrine and dopamine transporters, if the blockade contributes to MDMA’s therapeutic effect, this may underestimate the MDMA’s efficacy compared to an inactive placebo. Therefore, the absence of an inactive placebo group could be a potential limitation as it could minimize MDMA’s apparent effects.

4.2 Clinical and Public Health Significance:

In recent years, the clinical and public health significance of studying psychotherapy-supported MDMA treatment has gained increasing recognition. Given the relatively limited amount of existing research studying CPTSD, there are notable gaps in the literature regarding effective treatment approaches. The recognition of CPTSD as a distinct diagnosis in 2018 has prompted a growing interest in exploring potential treatment options. Given the profound impact of CPTSD on the health and quality of life of those affected, there is an urgent need to identify and study efficacious treatment strategies. The proposed study seeks to fill this treatment gap by investigating psychotherapy-supported MDMA as a potential novel treatment option for adults with complex trauma and to provide preliminary evidence of efficacy and safety in this population. This study also intends to build upon previous successes of randomized controlled trials studying psychotherapy-supported MDMA for the treatment of DSM-5 PTSD to further expand this knowledge base. If the results of the proposed study demonstrate robust efficacy like PTSD, this would represent a significant advancement within the field of psychiatry and specifically trauma-related disorders. This outcome
could also encourage future research and investment in a previously neglected patient population.

From a broader public health perspective, it is essential to identify effective treatment options for individuals with PTSD, particularly those with complex trauma. The impact of trauma extends far beyond the individual and affects families and society at large. Unaddressed trauma can have intergenerational effects which can perpetuate suffering for decades or even centuries. Additionally, significant functional improvements within this population would yield substantial benefits for society. When individuals with PTSD experience substantial recovery, they can reintegrate themselves as active and productive members of society. In conclusion, the investigation of psychotherapy-supported MDMA as a novel treatment option for CPTSD holds profound clinical and public health significance. By advancing our understanding of psychological trauma, this study’s findings could contribute to the broader field of trauma research and ultimately help pave the way for healing.
REFERENCES


APPENDICES

APPENDIX A: International Trauma Questionnaire and Scoring Guidelines

**International Trauma Questionnaire**

**Instructions:** Please identify the experience that troubles you most and answer the questions in relation to this experience.

Brief description of the experience _______________________________________

When did the experience occur? (circle one)
- a. less than 6 months ago
- b. 6 to 12 months ago
- c. 1 to 5 years ago
- d. 5 to 10 years ago
- e. 10 to 20 years ago
- f. more than 20 years ago

Below are a number of problems that people sometimes report in response to traumatic or stressful life events. Please read each item carefully, then circle one of the numbers to the right to indicate how much you have been bothered by that problem **in the past month**.

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1. Having upsetting dreams that replay part of the experience or are clearly related to the experience?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>P2. Having powerful images or memories that sometimes come into your mind in which you feel the experience is happening again in the here and now?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>P3. Avoiding internal reminders of the experience (for example, thoughts, feelings, or physical sensations)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>P4. Avoiding external reminders of the experience (for example, people, places, conversations, objects, activities, or situations)?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>P5. Being “super-alert”, watchful, or on guard?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>P6. Feeling jumpy or easily startled?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>P7. Affected your relationships or social life?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>P8. Affected your work or ability to work?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>P9. Affected any other important part of your life such as parenting, or school or college work, or other important activities?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Below are problems that people who have had stressful or traumatic events sometimes experience. The questions refer to ways you typically feel, ways you typically think about yourself and ways you typically relate to others. Answer the following thinking about how true each statement is of you.

<table>
<thead>
<tr>
<th>How true is this of you?</th>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1. When I am upset, it takes me a long time to calm down.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>C2. I feel numb or emotionally shut down.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>C3. I feel like a failure.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>C4. I feel worthless.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>C5. I feel distant or cut off from people.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>C6. I find it hard to stay emotionally close to people.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

In the past month, have the above problems in emotions, in beliefs about yourself and in relationships:

| C7. Created concern or distress about your relationships or social life?                | 0          | 1           | 2           | 3           | 4         |
| C8. Affected your work or ability to work?                                              | 0          | 1           | 2           | 3           | 4         |
| C9. Affected any other important parts of your life such as parenting, or school or college work, or other important activities? | 0          | 1           | 2           | 3           | 4         |
1. Diagnostic scoring for PTSD and CPTSD

**PTSD**
- If P1 or P2 ≥ 2 criteria for Re-experiencing in the here and now (Re_dx) met
- If P3 or P4 ≥ 2 criteria for Avoidance (Av_dx) met
- If P5 or P6 ≥ 2 criteria for Sense of current threat (Th_dx) met
- AND
- At least one of P7, P8, or P9 ≥ 2 meets criteria for PTSD functional impairment (PTSDFI)
- If criteria for ‘Re_dx’ AND ‘Av_dx’ AND ‘Th_dx’ AND ‘PTSDFI’ are met, the criteria for PTSD are met.

**CPTSD**
- If C1 or C2 ≥ 2 criteria for Affective dysregulation (AD_dx) met
- If C3 or C4 ≥ 2 criteria for Negative self-concept (NSC_dx) met
- If C5 or C6 ≥ 2 criteria for Disturbances in relationships (DR_dx) met
- AND
- At least one of C7, C8, or C9 ≥ 2 meets criteria for DSO functional impairment (DSOFI)
- If criteria for ‘AD_dx’ AND ‘NSC_dx’ AND ‘DR_dx’, and ‘DSOFI’ are met, the criteria for DSO are met.

PTSD is diagnosed if the criteria for PTSD are met but NOT for DSO.
CPTSD is diagnosed if the criteria for PTSD are met AND criteria for DSO are met.
Not meeting the criteria for PTSD or meeting only the criteria for DSO results in no diagnosis.

2. Dimensional scoring for PTSD and CPTSD.

Scores can be calculated for each PTSD and DSO symptom cluster and summed to produce PTSD and DSO scores.

**PTSD**
- Sum of Likert scores for P1 and P2 = Re-experiencing in the here and now score (Re)
- Sum of Likert scores for P3 and P4 = Avoidance score (Av)
- Sum of Likert scores for P5 and P6 = Sense of current threat (Th)
- PTSD score = Sum of Re, Av, and Th

**DSO**
- Sum of Likert scores for C1 and C2 = Affective dysregulation (AD)
- Sum of Likert scores for C3 and C4 = Negative self-concept (NSC)
- Sum of Likert scores for C5 and C6 = Disturbances in relationships (DR)
- DSO score = Sum of AD, NSC, and DR

---

### APPENDIX B: The Trauma-Related Shame Inventory

<table>
<thead>
<tr>
<th>Statement</th>
<th>Not true of me</th>
<th>Somewhat true of me</th>
<th>Mostly true of me</th>
<th>Completely true of me</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. As a result of my traumatic experience, I have lost respect for myself.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>2. Because of what happened to me, others find me less desirable.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>3. I am ashamed of myself because of what happened to me.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>4. As a result of my traumatic experience, others have seen parts of me</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>that they want nothing to do with.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>5. As a result of my traumatic experience, I cannot accept myself.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>6. If others knew what happened to me, they would view me as inferior.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>7. If others knew what happened to me, they would be disgusted with me.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>8. I am ashamed of the way I behaved during my traumatic experience.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>9. I am so ashamed of what happened to me that I sometimes want to escape</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>from myself.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>10. As a result of my traumatic experience, I find myself less desirable.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>11. I am ashamed of the way I felt during my traumatic experience.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>12. If others knew what had happened to me, they would look down on me.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>13. As a result of my traumatic experience, there are parts of me that I</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>want to get rid of.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. If others knew what happened to me, they would not like me.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>15. Because of my traumatic experience, I feel inferior to others.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>16. If others knew what happened to me, they would be ashamed of me.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>17. If others knew what happened to me, they would find me unacceptable.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>18. As a result of my traumatic experience, a part of me has been exposed</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>that others find shameful.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. If others knew how I behaved during my traumatic experience, they</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>would be ashamed of me.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. My traumatic experience has revealed a part of me that I am ashamed</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>of.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. As a result of my traumatic experience, I don’t like myself.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>22. If others knew how I felt during my traumatic experience, they would</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>be ashamed of me.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. Because of what happened to me, I am disgusted with myself.</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>24. I am so ashamed of what happened to me that I sometimes want to</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>become invisible to others.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

APPENDIX C: ICD-11 Criteria for Complex Posttraumatic Stress Disorder

6B41 Complex post traumatic stress disorder

Parent
Disorders specifically associated with stress

Description
Complex post traumatic stress disorder (Complex PTSD) is a disorder that may develop following exposure to an event or series of events of an extremely threatening or horrific nature, most commonly prolonged or repetitive events from which escape is difficult or impossible (e.g. torture, slavery, genocide campaigns, prolonged domestic violence, repeated childhood sexual or physical abuse). All diagnostic requirements for PTSD are met. In addition, Complex PTSD is characterised by severe and persistent 1) problems in affect regulation; 2) beliefs about oneself as diminished, defeated or worthless, accompanied by feelings of shame, guilt or failure related to the traumatic event; and 3) difficulties in sustaining relationships and in feeling close to others. These symptoms cause significant impairment in personal, family, social, educational, occupational or other important areas of functioning.

Exclusions
- Post traumatic stress disorder (6B40)

Diagnostic Requirements

Essential (Required) Features:
- Exposure to an event or series of events of an extremely threatening or horrific nature, most commonly prolonged or repetitive events from which escape is difficult or impossible. Such events include, but are not limited to, torture, concentration camps, slavery, genocide campaigns and other forms of organized violence, prolonged domestic violence, and repeated childhood sexual or physical abuse.
- Following the traumatic event, the development of all three core elements of Post-Traumatic Stress Disorder, lasting for at least several weeks:
  - Re-experiencing the traumatic event after the traumatic event has occurred, in which the event(s) is not just remembered but is experienced as occurring again in the here and now. This typically occurs in the form of vivid intrusive memories or images; flashbacks, which can vary from mild (there is a transient sense of the event occurring again in the present) to severe (there is a complete loss of awareness of present surroundings), or repetitive dreams or nightmares that are thematically related to the traumatic event(s). Re-experiencing is typically accompanied by strong or overwhelming emotions, such as fear or horror, and strong physical sensations. Re-experiencing in the present can also involve feelings of being overwhelmed or immersed in the same intense emotions that were experienced during the traumatic event, without a prominent cognitive aspect, and may occur in response to reminders of the event. Reflecting on or ruminating about the event(s) and remembering the feelings that one experienced at that time are not sufficient to meet the re-experiencing requirement.
Deliberate avoidance of reminders likely to produce re-experiencing of the traumatic event(s). This may take the form either of active internal avoidance of thoughts and memories related to the event(s), or external avoidance of people, conversations, activities, or situations reminiscent of the event(s). In extreme cases the person may change their environment (e.g., move house or change jobs) to avoid reminders.

Persistant perceptions of heightened current threat, for example as indicated by hypervigilance or an enhanced startle reaction to stimuli such as unexpected noises. Hypervigilant persons constantly guard themselves against danger and feel themselves or others close to them to be under immediate threat either in specific situations or more generally. They may adopt new behaviours designed to ensure safety (not sitting with ones' back to the door, repeated checking in vehicles' rear-view mirror). In Complex Post-Traumatic Stress Disorder, unlike in Post-Traumatic Stress Disorder, the startle reaction may in some cases be diminished rather than enhanced.

- Severe and pervasive problems in affect regulation. Examples include heightened emotional reactivity to minor stressors, violent outbursts, reckless or self-destructive behaviour, dissociative symptoms when under stress, and emotional numbing, particularly the inability to experience pleasure or positive emotions.

- Persistent beliefs about oneself as diminished, defeated or worthless, accompanied by deep and pervasive feelings of shame, guilt or failure related to the stessor. For example, the individual may feel guilty about not having escaped from or succumbing to the adverse circumstance, or not having been able to prevent the suffering of others.

- Persistent difficulties in sustaining relationships and in feeling close to others. The person may consistently avoid, deride or have little interest in relationships and social engagement more generally. Alternatively, there may be occasional intense relationships, but the person has difficulty sustaining them.

- The disturbance results in significant impairment in personal, family, social, educational, occupational or other important areas of functioning. If functioning is maintained, it is only through significant additional effort.

76. Organization WH. 6B41: Complex post traumatic stress disorder. 
https://icd.who.int/browse11/l-m/en
APPENDIX D: Compound Authorization and Consent Form

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH PROJECT
200 FR. 4 (2016-2)

YALE UNIVERSITY SCHOOL OF MEDICINE
YALE-NEW HAVEN HOSPITAL

Study Title: Efficacy of Psychotherapy-Supported MDMA in the Treatment of Complex Posttraumatic Stress Disorder: A Randomized Controlled Trial

Study Arms: Psychotherapy-supported MDMA vs. psychotherapy plus methylphenidate

Principal Investigator: Danielle Dubois, PA-II and John Krystal, MD

Invitation to Participate and Description of Project

You are invited to take part in a research study designed to look at the effects of psychotherapy-supported MDMA treatment on Complex Posttraumatic Stress Disorder (CPTSD) symptoms. You have been asked to take part because you meet the criteria for moderate or severe CPTSD. This study will include 64 total participants and will take place at two clinical sites.

To decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Description of Procedures

If you decide to participate in this study, you will first undergo interviews and be asked a series of questions related to your mental health, psychiatric history, medical history, substance/alcohol use, and demographic information. If the interview and questionnaires suggest that you may meet the study criteria, you will need to undergo a medical exam and have testing performed to ensure it is safe for you to participate in the study. This will include a physical exam by a PA/APRN, lab work including a urine toxicology screening, and an EKG.

If you are determined to be a candidate for the study and are selected via a random sampling method, you will be enrolled in the study. Prior to beginning additional assessments, you will be asked to taper off psychiatric medications, if applicable. Tapering means that you slowly reduce your medication dose to reduce side effects until you are no
longer taking the medication. If you are not able or willing to do so, you will not be considered a candidate for this study. If you choose to undergo a medication taper, this will be performed safely under the supervision of a physician and PA/APRN. After you complete this taper, you will need to be without these psychiatric medications for one month.

After one month, you can have baseline assessments performed and you will undergo further interviews with the clinical team to do so. Before beginning the study, you will undergo three 90-minute psychotherapy sessions to prepare you for the intensive future 8-hour psychotherapy sessions. These sessions will help to prepare you for what to expect if you are administered MDMA or methylphenidate and how to handle difficult emotions and traumatic memories if they arise during therapy sessions.

You will be randomly assigned to receive either MDMA or methylphenidate using a computer program that will be unknown to you and all members of the research team until after the study is complete. If you do not receive MDMA, you will have the option to enroll in an open-label trial extension after the study is complete so you can be treated with psychotherapy-supported MDMA if you choose. We offer this option because many people with PTSD in previous trials have had significant improvements in their symptoms and we would like to give all participants this opportunity for healing. Therapy sessions will always be conducted by a two-person therapy team, and you will receive support throughout the entirety of the sessions.

Prior to the 8-hour sessions, you will have your vitals checked and a urine toxicology screening. If your vitals are within a healthy range and your urine test is negative for illegal drugs, you will be able to proceed with the treatment. You will be administered a pill that will either be MDMA or methylphenidate, and you will not be informed which you have been given.

You will then participate in an 8-hour psychotherapy session with two therapists where you will guide the process and work through your emotions in a safe environment. 2-2.5 hours into the session, you will have your vitals checked again and if they are within a safe range, you will have the option to receive another half-dose of MDMA or methylphenidate. Again, you will not be told which medication you have received. You will then complete the remainder of the session. In total, there will be three medication administrations with 8-hour psychotherapy sessions, and these will be spaced 4 weeks apart. At any point during the study, if you experience bothersome symptoms, you are encouraged to report it to the therapy team and the principal investigators.

Three times throughout the study period, your therapy team will conduct assessments that will be used as data in the study. There will also be three 90-minute integration sessions between the 8-hour sessions to help you process what you have experienced. You will return to have another assessment 4 weeks after your final 8-hour session to collect data for the study. We will perform another EKG at the end of the study to compare it to the EKG at the beginning of the study.

A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. You will be told of any significant new findings that are developed during the course of your participation in this study that may affect your willingness to continue to participate.
Risks and Inconveniences

➢ MDMA is a psychoactive drug that is known to affect chemical messengers in the brain, and often produces positive emotions and increased empathy in those who take it. MDMA can make it easier to trust yourself and your therapy team. MDMA has shown promise in previous trials in treating people with moderate or severe PTSD. There are some risks associated with MDMA but in previous clinical trials, these have all been mild and resolved relatively quickly (less than one week). These effects include an increase in blood pressure, an increase in heart rate, an increase in body temperature, anxiety, nausea, jaw clenching, reduced appetite, dizziness, muscle tightness, and temporary low mood. There is a risk of drug dependence, but this has not occurred in any prior MDMA trials. The risk of many of these effects is lowered by tapering off medications. If you choose to participate, you will have your vitals monitored regularly to check for changes.

➢ Methylphenidate is a stimulant medication that will be considered an active “placebo”. A placebo is a medication that is used in a study to compare the main drug being tested. The reason for using a placebo group is that believing you are receiving treatment can influence your results. Methylphenidate can cause side effects but most of them are mild and short-lived. These include an increase in blood pressure, an increase in heart rate, reduced appetite, difficulty sleeping, anxiety or irritability, nausea, headache, dizziness, or temporary mood changes.

➢ Throughout the study period, you may experience difficult emotions as you work through traumatic memories. This is a normal part of the treatment process, and the therapy team will be there to support you to work through these emotions.

There is a federal law called the Genetic Information Nondiscrimination Act (GINA) that, in general, makes it illegal for health insurance companies, group health plans, and most employers, except those with fewer than 15 employees, to discriminate against you based on your genetic information. However, it does not protect you against discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

Benefits

➢ In previous trials like this one, many participants have had a significant reduction in their PTSD symptoms. Many individuals no longer met the criteria for PTSD at the end of the study due to the amount of improvement.

➢ You may also experience improvements in depression, anxiety, quality of life, and sleep quality.

Economic Considerations
There will be no costs that you will be responsible for related to this study. You will be compensated for any costs that you incur involving transportation to and from the clinical sites. According to the guidelines of the International Revenue Service (IRS), payments that you receive may be considered taxable income. All costs of medical testing, procedures, and treatments will be covered by the study.

**Treatment Alternatives/Alternatives**

- The current medications that are approved by the United States Food and Drug Administration (FDA) are sertraline and paroxetine. These are selective serotonin reuptake inhibitors (SSRIs).
- The current psychotherapy options available for PTSD include but are not limited to cognitive behavioral therapy (CBT) including exposure therapy and cognitive processing therapy (CPT), eye movement desensitization and reprocessing (EMDR), dialectical behavioral therapy (DBT), and sensorimotor psychotherapy.

**Confidentiality and Privacy**

Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all of your providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g. health insurance company, disability provider.)

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as permitted by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. Any identifiable information that is collected will be stored in a secure database that meets the requirements for patient health information. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

We understand that information about you obtained in connection with your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researcher will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name, demographic information, medical information, psychiatric history, substance and alcohol use, biological data collected from testing, and any material that is disclosed during psychotherapy sessions.

This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your identifying information with a code that does not directly identify you. The principal investigator will keep a link that identifies you to your coded information, and this link will be kept secure and available only to the PI or selected
members of the research team. Any information that can identify you will remain confidential. The research team will only give this coded information to others to carry out this research study.

The information about your health that will be collected in this study includes:

- Medical and psychiatric history
- Medication history
- Demographic information
- Biological data including blood tests, urine tests, EKG, and vitals
- Substance and alcohol use history
- Tobacco use history
- Information disclosed during psychotherapy sessions

Information about you and your health which might identify you may be used by or given to:

- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those providers who are participants in the Electronic Medical Record (EMR) system.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigators
- The U.S. Food and Drug Administration (FDA) This is done so that the FDA can review information about the new drug product [or device] involved in this research. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- Health care providers who provide services to you in connection with this study.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study

By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.
All healthcare providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale-New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

You have the right to review and copy your health information in your medical record in accordance with institutional medical records policies. However, by deciding to take part in a single or double-blinded treatment study and signing this permission form, you will not be allowed to look at or copy your study-related information until after the research is completed.

This authorization to use and disclose your health information collected during your participation in this study will never expire.

**In Case of Injury**

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

If you become ill or are physically injured due to the study drug MDMA or methylphenidate or any investigational procedure specifically required by the plan for this study, you will not be responsible for the costs required to diagnose or treat such injury. The costs of diagnosis and medical care for any complication, injury, or illness caused by the study drugs or properly performed non-standard of care investigational procedure required by the study will be covered by the study as long as you have followed the directions of the study doctor.

If you receive a bill for any costs related to the diagnosis or treatment of your injury, please contact the study doctor.

You will not receive any other kind of payment. There are no plans to pay you for such things as lost wages, disability, or discomfort as part of this study.

You do not give up any of your legal rights by signing this consent form.

**Voluntary Participation and Withdrawal**

Participating in this study is voluntary. You are free to choose not to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your
health care, and your health care benefits). However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow the use of your information as part of this study.

**Withdrawing From the Study**

If you do become a subject, you are free to stop and withdraw from this study at any time during its course. To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

The researchers may withdraw you from participating in the research if necessary. This includes but is not limited to no longer being compliant with the study’s inclusion and exclusion criteria or if you experience severe adverse effects.

Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale-New Haven Hospital.

**Withdrawing Your Authorization to Use and Disclose Your Health Information**

You may withdraw or take away your permission to use and disclose your health information at any time.

If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

**Questions**

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision.

**Authorization and Permission**

I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the particulars of my involvement and
possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

By signing this form, I give permission to the researchers to use and distribute information about me for the purposes described in this form. By refusing to give permission, I understand that I will not be able to be in this research.

Name of Subject:_____________________________

Signature:___________________________________

Date:_______________________________________

Signature of Principal Investigator Date

or

Signature of Person Obtaining Consent Date

If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at 203/432-5919.

If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator, John Krystal, MD. If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688.
APPENDIX E: Sample Size Calculation

<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Study Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Mean, group 1</td>
</tr>
<tr>
<td>Group 2</td>
<td>Mean, group 2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>Alpha</td>
</tr>
<tr>
<td></td>
<td>Beta</td>
</tr>
<tr>
<td></td>
<td>Power</td>
</tr>
</tbody>
</table>

This calculation of sample size is the raw estimate. See section 3.10 for corrected calculation.

Power Calculation

\[
k = \frac{n_2}{n_1} = 1
\]

\[
n_1 = \frac{(\sigma_1^2 + \sigma_2^2/K)(z_{1-\alpha/2} + z_{1-\beta})^2}{\Delta^2}
\]

\[
n_1 = \frac{(11.6^2 + 11.6^2/1)(2.58 + 0.84)^2}{10.5^2}
\]

\[
n_1 = 29
\]

\[
n_2 = K \times n_1 = 29
\]

\[
\Delta = |\mu_2 - \mu_1| = \text{absolute difference between two means}
\]

\[
\sigma_1, \sigma_2 = \text{variance of mean #1 and #2}
\]

\[
n_1 = \text{sample size for group #1}
\]

\[
n_2 = \text{sample size for group #2}
\]

\[
\alpha = \text{probability of type I error (usually 0.05)}
\]

\[
\beta = \text{probability of type II error (usually 0.2)}
\]

\[
z = \text{critical Z value for a given } \alpha \text{ or } \beta
\]

\[
k = \text{ratio of sample size for group #2 to group #1}
\]

15. Cloitre M, Petkova E, Wang J, Lu F. An examination of the influence of a sequential treatment on the course and impact of dissociation among women with PTSD


32. Han DD, Gu HH. Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs. Article. *BMC Pharmacology*. 2006;66. doi:10.1186/1471-2210-6-6


67. Mithoefer MC, Mithoefer AT, Feduccia AA, et al. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised,


