MDMA-Assisted Psychotherapy for Treatment of Post-Traumatic Stress Disorder (PTSD)

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Most Americans experience stress in their daily lives (American Psychological Association, 2017). Thus, an important goal of psychological research is to evaluate techniques that promote stress reduction and relaxation. MDMA (3,4- methylenedioxymethamphetamine)-assisted psychotherapy may help people who have experienced psychological trauma and who have not been able to resolve their problems through existing treatments.

Effective psychotherapy may hinge on patients' openness with therapists, willingness to confront and examine discomfort, and competence in processing emotion. In some patients, however, arousal quickly rises above psychological control and triggers sympathetic nervous system arousal (Mithoefer et al., 2017). This kind of arousal is common among people with Posttraumatic Stress Disorder (PTSD) and often leads patients to avoid the triggering thought or emotion. The pattern of experiencing emotionally charged content, encountering excitement, and immediately rehearsing avoidance may deliver psychotherapy perplexing and disappoint patients. Other patients may attempt to remain somewhat calm in order to process triggering content, but the experience may be more painful than helpful (Amoroso & Workman, 2016; Eftekhari et al., 2013). What arises between the lower threshold for arousal and upper threshold for panic, is a level of emotional engagement that is favorable for processing emotions. This zone is called the optimal arousal. People who suffer from trauma-related disorders such as PTSD often struggle to remain within the state of optimal arousal (Mithoefer, 2013). One of the most popular treatments for PTSD is exposure therapy, in which a patient recalls a trauma in the therapeutic setting (Oehen et al., 2013). While recalling a traumatic experience in detail, a patient may consciously associate the safety and calm of the therapy setting with the memory. This treatment alone is effective for many people with PTSD but not all; sometimes, recall triggers

such a high level of arousal that the arousal itself distracts from any intervention (Mithoefer et al., 2011). In other cases, even patients who seek treatment avoid disclosing personal memories, thoughts, and feelings (Oehen et al., 2013). These factors contribute to the prevalence of chronic, treatment-resistant PTSD (Buoso et al., 2008; Oehen et al., 2013).

The current methods for PTSD in psychopharmacology are strongest for the selective serotonin reuptake inhibitors (SSRIs): sertraline, paroxetine and fluoxetine as well as the selective serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine. Currently only sertraline (Zoloft) and paroxetine (Paxil) are approved by the Food and Drug Administration (FDA) for PTSD. (APA.ORG). The high incidence of PTSD and the limited effectiveness of existing treatments combine to create an urgent need for the development of new treatments. PTSD is typically a chronic illness associated with high rates of psychiatric and medical comorbidity, disability, suffering, drug abuse, and suicide.

One solution to the difficulties with exposure therapy for people with PTSD is MDMA, which is a psychedelic that produces feelings of empathy, intimacy, affection, and trust (Hysek et al., 2014; Wardle & de Wit, 2014). Phase I clinical trials have demonstrated that MDMA can be administered without evidence of harm to pre-screened subjects and induces a 2–4-h experience typically characterized by euphoria, increased well being, sociability, self-confidence, and extroversion (Mithoefer et al., 2011). The effects of MDMA can lift a user's mood by boosting the positive impact of positive facial expressions and memories while simultaneously softening the negative impact of negative facial expressions and memories. Recalling emotional memories while under the comforting influence of MDMA, weakens the memory power to induce fear. Thus, MDMA-assisted psychotherapy may promote especially effective and durable fear memory extinction in exposure therapy (Mithoefer et al., 2013). The effects of MDMA

distinguish it as a potentially efficacious drug adjunct for psychotherapy, especially in the treatment of PTSD (Mithoefer et al., 2011). The difference between harmful and helpful effects of the drug lies in controlled dosage and pairing of drug use with psychotherapy.

However, much more research is needed. Partly due to abuse of the drug among recreational users, concerns about post-treatment substance abuse. Some researchers have warned against aggressive behavior, depression, and other side effects of long-term MDMA abuse. Carefully administered doses of MDMA with psychotherapy may benefit people with chronic PTSD because it improves mood and strengthens the therapeutic alliance. Preliminary results regarding MDMA assisted psychotherapy for PTSD look promising and warrant further investigation. If future phase-three trials may indeed replicate these findings, implication of an efficient adjunct to psychotherapy would be considered crucial. MDMA may provide a bridge to effectively overcome the gap between psychotherapy and psychopharmacology, thereby facilitating the combination of a more holistic approach to psychopathology. Future studies using clinically relevant doses can further elucidate the role of MDMA in emotional memory processing and delineate specific mechanisms of MDMA-assisted psychotherapy for reducing symptoms of PTSD (Mithoefer et al. 2018). MDMA therapy is not a quick fix for PTSD. It involves a high degree of commitment from the patient and a willingness to undergo therapy in addition to using the substance. Finally, research on MDMA-assisted psychotherapy provides an overview of some challenges in psychotherapy for PTSD, including the debilitating mood symptoms of PTSD, challenges with forming an effective therapeutic alliance, and interruptions in fear memory extinction caused by hyperarousal**.** Therefore, I end by pointing out limitations in the existing literature and exploring potential directions for future research. These considerations lead to the hypothesis that MDMA can be administered in conjunction with psychotherapy in

order to significantly reduce the symptoms of patients with chronic and treatment-resistant PTSD when compared to the same psychotherapy combined with an inactive placebo.

Methods

Participants

A total of 30 participants (14 men and 16 women) will be recruited from social media advertisements. The participants ranged from ages 20 to 40 years (M=29.3, SD = 5.84), with previous inadequate response to at least one pharmacotherapy and/or psychotherapy. The mean level of education was M=33, post-secondary level education. Recruitment for the study was done through referrals from healthcare professionals, and from advertisements placed in therapy offices in the province. Participants underwent extensive screening by independent examiners, including psychological assessments, physical ex aminations to identify any possible contraindications to receiving MDMA. The Structured Clinical Interview for DSM-IV Axis I Disorders—Research Version (SCID-I-RV) or the SCID-II was used during screening to detect comorbid disorders, and medical and therapy records from outside providers were reviewed (Mithoefer et al. 2019). Exclusion criteria included presence of major medical conditions, past or current psychotic disorder, pregnancy or lactation, and weight under 48 kg. Participants could not have a diagnosis of substance abuse disorders within 60 days of screening for five studies and within 6 months for one study (Mithoefer et al. 2019).

Measure

Severity of PTSD symptoms - The CAPS is a widely used structured interview for quantifying PTSD symptoms that has excellent psychometric properties of reliability and validity (Weathers et al., 2001). This measure produces a global symptom severity score as well as a

categorical ranking as to whether a subject meets DSM-IV-R criteria for PTSD. An inadequate response to previous treatment was concluded if participants had a CAPS-IV total score indicating moderate to extreme PTSD at screening. (Mithoefer et al. 2019)

In terms of our primary measure we plan to use the Clinician Administered PTSD Scale (CAPS-IV). This takes the form of semi-structured interview that is conducted by the clinician. It includes severe indices for PTSD symptom cluster; exposure to a traumatic event, re-experiencing of a traumatic event, avoidance, negative mood, and increased arousal; and a diagnostic score. The clinician scores, the frequency and intensity of each criterion, in which higher scores are indicative of more frequent and severe symptoms of PTSD. The primary outcome measure we will be using will be mean scores of the MDMA and inactive placebo group.

Our secondary testing instrument for symptoms of PTSD is the measuring of heart rate reactivity since this is a hallmark predictor of PTSD (difference in resting heart rate and heart rate after presentation of an external stressor). In this case we would be looking for decreased heart rate reactivity following exposure to treatment. The dichotomous diagnostic score (Weathers et al., 2001), and ⩾30% drop in CAPS-IV total scores were used to evaluate clinically significant changes in PTSD symptoms. The therapists consider physiological measures (blood pressure, pulse, and temperature) and self reported distress and mental state to make a clinical judgment concerning the participant's stability and the waning of drug effects.

These secondary measures being: Neurocognitive test: The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) tests attention and processing speed, expressive language, visual-spatial and constructional abilities, and memory. Physiological test: blood pressure, pulse, and temperature were monitored during all experimental sessions

(Mithoefer et al. 2019). The Beck Depression Inventory—II (BDI-II)**,** an established 21-item measure of self-reported depression symptoms (Beck et al. 1996), was administered. Responses are made on a four-point Likert scale and summed to produce an overall score.

Procedures

All participants confirmed comprehension of study procedures would ask them for written informed consent. Participants were randomized through a web-based system to receive blinded doses of placebo/control, control group or active doses of MDMA, experimental group. Participants were randomized for when doses were administered during two 8-h psychotherapy sessions spaced one month apart. Following the conclusion of the last 8 hour psychotherapy session, participants who were in the placebo group had the option of completing a non-blinded MDMA session as part of the crossover segment and those who were in the active group had the option to complete a third session of MDMA that was non-blinded (this crossover segment will not be included in our data analysis). Follow up would occur at 2 months following the final experimental session

In addition to CAPS-IV presented in paper, several secondary measures were administered to participants to gather data regarding efficacy and mechanisms of action of MDMA- assisted psychotherapy. The participant must commit to attending all preparatory, therapy, and follow-up sessions, completing the evaluation instruments, and complying with dietary and drug restrictions. The only exception to this would be if the participant has notified the therapists of a decision to withdraw consent and drop out of the study.

Participants were taught diaphragmatic breathing and other techniques to aid in the relaxation and self-soothing process. It is important to convey to participants that the experiences

catalyzed by MDMA- assisted therapy will likely continue to unfold and resolve over days or even weeks following the MDMA assisted sessions resulting in particular symptoms may even seem to get worse before improving (Mithoefer et al. 2017).While PTSD symptoms are the primary focus of outcome measures in this research, and processing traumatic experiences is an essential part of the psychotherapy, it is highly likely that the scope of the sessions will go beyond trauma processing to include exploration of other psychological, interpersonal and spiritual aspects of life (Mithoefer et al. 2017).

Results

Statistical Analysis

Because our hypothesis is centred around whether MDMA can result in a significant reduction in CAPS-IV scores, no correlation ($r = 0$) or a positive correlation of any given strength between CAPS-IV scores and time after exposure to 2-8 hour MDMA-assisted psychotherapy would not be in concordance with our expectations. In addition, a small-moderate negative correlation of up to $r = -0.49$ would not align with our expectations. Again, we are looking for clinical relevance. In this study we would expect there to be a strong negative correlation ($p < 0.05$) between CAPS-IV scores and time after exposure to MDMA-assisted psychotherapy. In addition, in order to assess clinical significance, we will use Cohen's d to compare the mean CAPS-IV score of the experimental group and control group. Any Cohen's d score below a 0.8 would not align with our expectations as we are looking for a large treatment effect. In conclusion, MDMA's unique pharmacological and psychological effects make it an excellent potential adjunct to psychotherapy and especially well-suited for treatment of PTSD.

Summary of Expected Results

First, the study confirms previous findings of clinically significant reductions in symptom severity following MDMA-assisted psychotherapy for individuals diagnosed with PTSD. These are important findings that indicate MDMA-assisted psychotherapy facilitates self-reported improvements in interpersonal relationships, spirituality, sense of possibility, assessment of personal strengths, and appreciation of life. After the first session, if active doses of MDMA combined with psychotherapy resulted in decreased PTSD symptom severity, these results at long-term follow-up suggest that these clinical improvements are durable. Importantly, safety outcomes of MDMA in a PTSD population demonstrated that limited doses of MDMA were safe to use in a controlled clinical setting. (Ingmar et al. 2020).

The pharmacological effects of MDMA in combination with the psychotherapeutic processing of trauma appear to have a synergetic effect to reduce PTSD symptoms.

Due to small sample sizes, reliability of effect size estimates from individual studies is unknown. Blinding of treatment assignment for psychoactive substances is a recognized challenge. A recognized limitation in clinical trials of all drugs with perceivable effects and in all psychotherapy studies where there is no possibility of effective blinding. At posttreatment assessment, perhaps, the MDMA group experienced larger reductions in PTSD symptom severity compared to the placebo group (Mithoefer et al 2019). Future research of MDMA-assisted psychotherapy should include robust measurement and analysis of posttraumatic growth as outcomes for treating PTSD.

Graph of expected Findings

In this graph by Wagner et al, we see scores for CAPS on the y-axis and time following treatment on the left, going up to two months following treatment. CAPS-IV total score least squared mean estimates at endpoints. The change in scores from baseline to post two experimental sessions were significantly different between MDMA and control groups. In this example, the correlation between time after exposure to 2-8 hour sessions of MDMA-assisted psychotherapy and CAPS-IV scores is significant ($p < 0.05$) indicating that CAPS-IV scores decrease as time after exposure to 2-8 hour MDMA-assisted psychotherapy sessions increases.

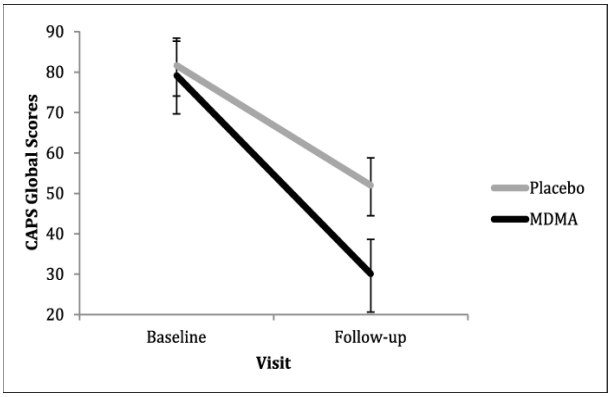

Figure-1 CAPS-IV score vs Placebo group /MDMA group

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Appendix of instruments

BDI – II

The Beck Depression Inventory (BDI, BDI-II), created by Dr. Aaron T. Beck, is a 21-question multiple-choice self-report inventory, one of the most widely used instruments for measuring the severity of depression. The questionnaire is composed of items relating to depression symptoms such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex. BDI-II, a revision of the BDI that was published in 1996. The BDI-II was a 1996 revision of the BDI, created to fall in line with the update DSM-IV criteria for depression. Items involving changes in body image, somatic preoccupation, and work difficulty were replaced. Also, sleep

loss and appetite loss items were revised to assess both increases and decreases in sleep and appetite.

The BDI-II contains 21 questions, each answer being scored on a scale value of 0 to 3. The cut-offs used differ from the original: 0-13 - minimal depression; 14-19 - mild depression; 20-28 -moderate depression; and 29-63 - severe depression. Higher total scores indicate more severe depressive symptoms.

Sample Questions

1. Sadness
0. I do not feel sad.
1. I feel sad much of the time.
2. I am sad all the time.
3. I am so sad or unhappy that I cannot stand it.

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2. Pessimism
0. I am not discouraged about my future.
1. I feel more discouraged about my future than I used to.
2. I do not expect things to work out for me.
3. I feel my future is hopeless and will only get worse.

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3. Past Failure
0. I do not feel like a failure.
1. I have failed more than I should have.
2. As I look back, I see a lot of failures.
3. I feel I am a total failure as a person.

CAPS-IV

The CAPS is a structured interview designed to make a categorical PTSD diagnosis, as well as to provide a measure of PTSD symptom severity.

The CAPS-5 is a 30-item structured interview that can be used to:

- Make current (past month) diagnosis of PTSD
- Make lifetime diagnosis of PTSD
- Assess PTSD symptoms over the past week

The CAPS-IV also inquires about associated features of guilt and dissociation; the latter allow the interview to be used for assessment of Acute Stress Disorder (e.g., Creamer et al., 2004; O'Donnell et al., 2004), although nothing has been published to date on the validity of this approach. It takes 30-60 minutes to administer, (depending on the level of psychopathology) and slightly less to score. Training is required to administer this test, although all the necessary information for self-learning is available for free. t is recommended that the "1, 2" rule be used to determine a diagnosis; that is, a frequency score of 1 and an intensity score of 2 is required for a particular symptom to meet criterion.

Inter-rater reliability is high, ranging from 0.92 to 1.00 for "Frequency" ratings and 0.93 to 0.98 for "Intensity" ratings; the global severity correlation was 0.89. (Hovens et.al., 1994). Kappa for a categorical PTSD diagnosis is often 1.0 (i.e., 100% agreement, e.g., Mueser et.al., 2001). Strong convergent validity has been demonstrated against the Structured Clinical Interview for DSM-IV (SCID) PTSD module (.83) and the PSS-I (.73) (Foa & Tolin, 2000).

Overall agreement between a clinician-rated diagnosis and CAPS diagnosis was 79%; sensitivity was .74, while specificity was .84 (Hovens et.al., 1994).

Sample Item

In the past month, have you had any unwanted memories of (EVENT) while you were awake, so not counting dreams?

How does it happen that you start remembering (EVENT)?

[If not clear:] (*Are these unwanted memories, or are you thinking about [EVENT] on purpose?)*

How much do these memories bother you?

Are you able to put them out of your mind and think about something else?

How often have you had these memories in the past month? (Weathers et al. 2013)