

Manual grant concept paper

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The Multidisciplinary Association for Psychedelic Studies (MAPS) is a membership-based non-profit organization founded in 1986 that supports research into the therapeutic potential of MDMA and psychedelic compounds. MAPS is developing 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy as an evidence-based treatment of posttraumatic stress disorder (PTSD) through pilot studies conducted in the US, Europe and the Middle East. After finding promising results from initial studies, MAPS is seeking to develop a manualized form of this psychotherapy. Manual development will include revising and completing a treatment manual for MDMA-assisted psychotherapy and refining and operationalizing adherence measures for the assessment of therapists' compliance with the manual. Successful development of a treatment manual for MDMA-assisted psychotherapy will aid in conducting the Phase 2 and Phase 3 studies needed to gain prescription approval for this technique from the Food and Drug Administration (FDA). The goal of submitting this grant concept paper is to solicit advice from the National Institute of Health on which RFAs would be able to fund this initiative.

PTSD is a debilitating psychiatric disorder that affects between 6% to 10% of the general population (Kessler et al., 2005). After experiencing a life-threatening event, people with PTSD continue to re-experience the event, avoid activities or locations that remind them of the event, feel emotionally detached or numb and remain anxious and hyper-vigilant. Recognized treatments for PTSD include psychotherapy and pharmacotherapy. However, a significant number of people do not respond to these treatments or cannot tolerate them (Ursano *et al.*, 2004; Foa *et al.*, 2009). The development of innovative, efficacious treatments for PTSD will benefit patients, their loved ones and society at large.

MDMA possesses unique pharmacology that may make it beneficial for treating PTSD. Early reports described its effect as reduction of fear in relation to emotionally threatening material (Greer and Tolbert 1986). MDMA reduces activity in the left amygdala (Gamma et al., 2000), potentially reducing strength of amygdalar reactivity to threatening stimuli (Phelps *et al.*, 2001; Rauch *et al.*, 2006). Bedi et al have observed that MDMA reduces sensitivity to fearful facial expressions and leads to people finding happy faces more rewarding (Bedi *et al.*, 2009; Bedi *et al.*, 2010). It is possible that this effect of MDMA could increase rapport between patient and therapist and reduce self-consciousness in therapy. Furthermore, MDMA is associated with an elevation in the neurohormone oxytocin, associated with affiliation and bonding in mammals (Dumont et al., 2009). MDMA produces a predominantly positive mood state, though with moderate anxiety and very mild perceptual effects. These effects may all contribute to its ability to enhance and support psychotherapy, permitting people with PTSD to confront emotionally upsetting material without fear and increasing trust between patient and therapist.

Prior to placement in the most restricted schedule of controlled substances, psychotherapists used MDMA in combination with psychotherapy to help treat various neuroses, relationship problems and PTSD (Greer & Tolbert, 1986; Stolaroff, 2004). These narrative reports offered initial support for using MDMA-assisted psychotherapy to treat PTSD. In their experience with MDMA-assisted psychotherapy published in 1986, Greer and Tolbert reported safely

administering MDMA to 29 participants with a variety of psychological problems or conditions (Greer & Tolbert, 1986). A MAPS-sponsored clinical study in Spain of placebo, 50 and 75 mg MDMA in six women with PTSD arising from sexual assault reported that these doses of MDMA could be safely administered in this population. Bouso and colleagues note that none of the participants reported an increase in re-experiencing, and observed signs of improvement in participants given MDMA (Bouso et al., 2008). Findings from a clinical study in the US suggest that MDMA-assisted psychotherapy may be a promising treatment for PTSD that can be performed without occurrence of any drug-related serious adverse events (Mithoefer et al., 2010). Mithoefer and colleagues reported findings from a study comparing MDMA with inactive placebo in 20 participants with chronic, treatment-resistant PTSD, with 12 assigned to receive MDMA and eight receiving inactive placebo. They reported that two months after two sessions of psychotherapy with MDMA or placebo, participants given MDMA experienced a significant decline in Clinician-Administered PTSD Scale (CAPS) scores compared to participants in the placebo group receiving the same psychotherapy, as well as reductions in Impact of Events (IES) scores, with a treatment effect size of 1.24. When symptoms were assessed at least 12 months later (at an average of 41 months later), the effects of this treatment appear to be maintained in most subjects, with average CAPS scores of 17 out of the 20 subjects remaining statistically equivalent (Mithoefer et al., Unpublished).

MDMA-assisted psychotherapy first appeared in the mid to late 1970s, prior to the scheduling of the drug. Methods include a team of a male and a female therapist, use of music, and attention to the internal and external environment surrounding the psychotherapy (set and setting). Other elements of MDMA-assisted psychotherapy include use of introspection and confrontation with trauma-related memories, feelings or thoughts (a type of exposure), integrating the material in subsequent conventional (non-drug) psychotherapy sessions, encouraging creative expression, and learning relaxation and self-soothing techniques. However, there were no formal descriptions of the therapy techniques in use at the time. Mithoefer and colleagues made use of these techniques in their study. They also used selected techniques drawn from cognitive behavioral therapy (including prolonged exposure) and psychodynamic therapy.

The sponsor and the investigator began developing a treatment manual prior to and during the start of the pilot study in the US (Ruse *et al.*, 2005; 2010). The manual was created and developed by the principal investigator (PI) and co-investigator in the US study of MDMA-assisted psychotherapy, a psychotherapist with experience in manual development, an expert in the literature on MDMA and an expert on the history and development of MDMA-assisted psychotherapy. Work began in 2002 and continues through 2011. The manual has undergone several revisions informed by the experience conducting the US study. In addition to providing detailed guidance on conducting MDMA-assisted psychotherapy sessions, the manual addresses methods for conducting preparatory and integrative psychotherapy before and after MDMA-assisted sessions, as well as specific instructions concerning working with MDMA.

Treatment adherence criteria have been developed that permit observers to rate the degree to which a therapist follows the manualized treatment. MAPS staff and Clinical Investigators have developed a training program to instruct interested psychotherapists in the manualized treatment method. Measures of adherence criteria include ratings of a team of therapists during each type of session and checklists for ratings of overall adherence to the treatment manual. These were

developed through examining the literature, including narrative and research reports and observations of recordings of sessions from the pilot study in the US. In order to gather data for manual development, video recordings from a second pilot study of MDMA-assisted psychotherapy in Switzerland were collected. The cost of transcription, translation and subtitling of a single MDMA-assisted psychotherapy session recording is \$1100. For assessment of adherence to the treatment manual, 20% of sessions need to be analyzed (Falsetti, 2011). We wish to demonstrate that therapists will be able to follow the treatment manual.

The proposed program of research will permit further development of the manual and measures of adherence to the manualized treatment. This involves the following steps:

- Storage and backup of large amounts of video data.
- Continued examination of session video recordings drawn from the initial study in the US and from an ongoing study of MDMA-assisted psychotherapy in veterans conducted by the same investigators to see if they adhere to the treatment as described.
- Revision of the manual on the basis of experience drawn from ongoing studies, examining the recent literature and, when relevant, addressing specific issues that arise during MDMA-assisted psychotherapy.
- An open-label clinical study in patients that would permit refinement of the treatment approach. The study would enroll men and women, 18 years or older, with chronic PTSD, and the Clinician Administered PTSD Scale (CAPS) will serve as primary outcome measure of PTSD symptoms. The study would consist of two or three MDMA-assisted psychotherapy sessions supported by preparatory and integrative psychotherapy. Adherence to treatment criteria would be assessed for psychotherapists after undergoing a training program developed by the sponsor.
- Preparing recordings of sessions from studies taking place and planned to take place in Canada, Israel, Jordan, Switzerland and the US. This may include editing the recordings, translation of speech and insertion of English language subtitles.
- Use of adherence measures and checklists to evaluate therapist performance in recordings of experimental sessions drawn from the studies listed above. More than one rater may rate the same team of therapists after establishing inter-rater reliability for the raters.
- Development of a training program for independent raters to assess PTSD symptoms in studies of MDMA-assisted psychotherapy, including training to conduct and correctly score the CAPS.
- Using session recordings and reports from researchers to track any unforeseen issues or difficulties arising during MDMA-assisted psychotherapy and therapist response to them. The authors of the treatment manual may address any issues that appear repeatedly in recordings by revising the manual and the training program to address these issues.
- If the treatment manual is further refined, potential refinement of adherence measures and checklists to reflect contents of the manual.
- Investigating any relationships between reduction or exacerbation of PTSD symptoms over the course of MDMA-assisted psychotherapy and treatment adherence as viewed through collecting and observing these recordings.

It is expected that this program of research will take between three and ten years. If successfully completed, the investigators would produce a completed manual for use in training therapists to

perform MDMA-assisted psychotherapy as an evidence-based treatment for PTSD, and a set of measures of adherence to the standardized treatment. The sponsor plans to gain information on the degree to which investigators in other sponsor-supported studies adhered to the manualized format of the treatment through adherence measures. The sponsor could use these measures to establish whether or not the degree of treatment adherence correlated with improved psychological function or improvement in PTSD for study participants.

Personnel needed to complete this project include psychotherapists with expertise in developing treatment manuals and measures of adherence to the manualized treatment, the principal investigators for the initial study of MDMA-assisted psychotherapy in the US, at least two individuals who will observe and rate adherence to the manualized treatment, at least three Ph.D. students to analyze differences between pilot studies and bilingual individuals who will transcribe, translate and subtitle recorded materials to enable assessment of research psychotherapy sessions using the adherence measures. Though at present most analysis will involve descriptive statistics and inter-rater comparisons, the project may require access to a statistician.

At the end of the project, the sponsor and investigators hope to have a finalized, working treatment manual and evidence that adherence to the treatment can be measured. Creating a standardized treatment and a means of assessing treatment adherence will permit the conducting of larger studies that will, in turn, assist in the development of an innovative and promising treatment for PTSD.

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