A Randomized, Double-Blind, Active Placebo-Controlled Phase 2 Pilot Study of MDMA-assisted Psychotherapy in People with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)

***Study Code*: M-P9**

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Subjects: 10 people with chronic, treatment-resistant PTSD. Participants will be men and women aged 18 or older.

Study description*:* The goal of this study is to assess safety and efficacy of MDMA-assisted psychotherapy in treating chronic, treatment-resistant PTSD. The first two participants will be enrolled in an open-label lead-in. Eight subjects will then be enrolled in a randomized, double-blind active placebo-controlled study, with five subjects receiving 125 mg (high dose) and three subjects receiving 25 mg (active placebo or low dose), with an optional supplemental half-dose available 1.5 to 2.5 hours after the initial dose. Participants will have two experimental sessions of MDMA-assisted psychotherapy scheduled at a 3-5 week interval. PTSD symptoms, general psychological well-being and symptoms of depression will be assessed at baseline and two months after the second experimental session, at the end of Stage 1. Participants assigned to receive 25 mg MDMA have the opportunity to continue on to an open-label study segment, referred to as Stage 2, following similar procedures, but with participants receiving 125 mg possibly followed by 62.5 mg in two MDMA-assisted psychotherapy sessions followed by evaluation of symptoms two months after the second MDMA-assisted session, at the end of Stage 2. Participant PTSD symptoms, depression symptoms, general psychological functioning, and possible long-term benefits and harms will be assessed again 12 months after the final MDMA-assisted session.

Primary Outcome Measure: Clinician-Administered PTSD scale (CAPS)
Secondary Outcome Measures: Beck Depression Inventory-II (BDI-II), Global Assessment of Function (GAF), Posttraumatic Stress Diagnostic Scale (PDS), Pittsburg Sleep Quality Index (PSQI)
Safety Measures: Columbia Suicide Severity Rating Scale (C-SSRS), Vital signs and degree of psychological distress will be assessed periodically during each experimental session with Subjective Units of Distress (SUD)
Adverse Events and Spontaneously Reported Reactions collected and recorded during the course of the study.
Process Measures: Beliefs about condition assignment, Reactions to Research Participation Questionnaire (RRPQ)

Study Procedures*:* After giving written informed consent, prospective participants will be screened for eligibility, and all participants meeting study criteria will be enrolled. Symptoms of PTSD and depression and general psychological function will be assessed at baseline. In consultation with their prescribing physician, any individuals taking psychiatric medications will

taper off these medications, allowing for a washout period of 5 times the medication half life before the first MDMA administration. Participants using cannabis must stop using it at least 14 days prior to the first MDMA administration until the end of Stage 1 or Stage 2, as appropriate. During the study, benzodiazepines or zolpidem may be used as rescue medications if needed as approved by the investigator. Any participants who are in psychotherapy with an outside therapist at the time of enrollment may continue that therapy during the study without increasing the number or type of sessions or changing psychotherapists. All MDMA-assisted (experimental) and non-drug psychotherapy sessions will be conducted by one of three male and female co-therapist teams, with each participant working with the same team throughout their study participation. During preparatory sessions, participants will learn what to expect during experimental sessions, and during follow-up sessions they will receive support in integrating their experiences and insights from the MDMA-assisted psychotherapy sessions. The first two participants will be enrolled in an open-label lead-in that follows an identical sequence of events without randomization. Five participants will be randomized to receive a full dose of MDMA, three will be randomized to receive an active placebo dose of MDMA. The first experimental session will be preceded by three preparatory sessions and followed by three integrative psychotherapy sessions. Upon mutual agreement with the co-therapists, participants may select a companion to accompany them during part or all of the experimental session and including after the experimental session. After each experimental session, participants will spend the night at the clinic with an attendant on duty. The first integrative session will take place the day after the experimental session. Participants and therapists will report their beliefs concerning condition assignment on the day after each experimental session. There will be daily phone contact with the therapists for 7 days after each experimental session. Symptoms of PTSD, depression and general psychological function will be repeated for each participant at the end of Stage 1, and the blind will be broken. Participants who learn they were assigned to receive 25 mg MDMA will have the opportunity to enroll in Stage 2. Stage 2 consists of a similar series of procedures and visits except that participants receive two open-label MDMA sessions with full dose MDMA (125 mg possibly followed by 62.5 mg MDMA). Stage 2 will only feature one preparatory session instead of three. There will be a long-term follow up with repeated outcome measures 12 months after participants' final experimental session. The study therapists will maintain communication with the referring physician or therapist and any other health care providers requested by the participant.

Inclusion Criteria

Individuals eligible to be enrolled into this protocol are participants who:

1. Meet DSM IV criteria for chronic PTSD with a duration of at least six months. Participants may have experienced one or more traumatic event.
2. Have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.
3. Have had at least one unsuccessful attempt at treatment for PTSD.
    a. Treatment with a selective serotonin uptake inhibitor (SSRI), mirtazapine, a Serotonin Norepinephrine Reuptake Inhibitor (SNRI) or a monoamine oxidase inhibitor (MAOI)
    b. Any form of psychotherapy for the treatment of PTSD;
4. May have a concurrent affective disorder, excepting bipolar affective disorder 1;
5. Are at least 18 years old.

6. If in ongoing psychotherapy at the time of recruitment, are able to continue to see their outside therapist during the course of the study. Subjects must sign a release permitting the investigators to communicate directly with their therapist.
7. May not change therapists, increase the frequency of therapy or commence any new type of therapy until after the evaluation session at the end of Stage 1 or 2, as applicable.
8. Are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. Any psychiatric drugs will be tapered in an appropriate fashion to avoid withdrawal effects. Medications will only be discontinued after consultation with the prescribing physician.
9. Agree to, for one week preceding each experimental session:
   a. Refrain from taking any herbal supplement (except with prior approval of the research team)
   b. Refrain from taking any nonprescription medications (with the exception of non-steroidal anti-inflammatory drugs or acetaminophen unless with prior approval of the research team)
   c. Not take any prescription medications (with the exception of birth control pills, thyroid hormones or other medications approved by the research team) Note: Must have physician's approval
10. Agree to take nothing by mouth except alcohol-free liquids after 24:00 (midnight) the evening before the experimental session;
11. Agree to refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each experimental session;
12. Agree not to use caffeine or nicotine for 1 hour before and 3 hours after ingesting the drug, or until the therapists deem it safe to do so;
13. Are willing to commit to medication dosing, experimental sessions, follow-up sessions and to complete evaluation instruments;
14. Are willing to remain overnight at the study site after each experimental session until after the integrative session occurring the next morning;
15. Are willing to be driven home the morning after the experimental sessions, after the integrative therapy session either by a driver arranged by the subject or by the site personnel or taxi;
16. Are willing to be contacted via telephone on a daily basis by one of the therapists for a week after each experimental session;
17. Are willing to refrain from participating in any other clinical trial for the duration of this clinical trial, including the follow up period;
18. If female subjects of childbearing potential, must have negative pregnancy test results, be willing to have pregnancy tests and must agree to use an effective form of birth control;
19. Are proficient in speaking and reading Hebrew;
20. Agree to have all psychotherapy sessions recorded to audio/video.

Exclusion Criteria

Individuals not eligible to be enrolled into this protocol are those who:

1. Are pregnant or nursing, or of child bearing potential and not practicing an effective means of birth control;

2. Have a history of or current primary psychotic disorder or bipolar affective disorder type 1 or borderline personality disorder;
3. Are diagnosed with dissociative identity disorder or an eating disorder with active purging;
4. Have evidence or history of significant (controlled or uncontrolled) hematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, renal, gastrointestinal, immunocompromising, or neurological disease, including seizure disorder, or any other medical disorder judged by the investigator to significantly increase the risk of MDMA administration (Subjects with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded);
5. Have hypertension using the standard criteria of the American Heart Association (values of 140/90 or higher assessed on three separate occasions).
6. Have liver disease.
7. Have history of Diabetes Type I or II;
8. Have history of hyponatremia or hyperthermia;
9. Weigh less than 48 kg;
10. Would present a serious suicide risk or who are likely to require hospitalization during the course of the study;
11. Have used "Ecstasy" (material represented as containing MDMA) more than five times or at least once within 6 months of the MDMA session;
12. Require ongoing concomitant therapy with a psychiatric drug, including SSRIs, SNRIs, or MAOIs;
13. Meet DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days;
14. Have glaucoma, significant atherosclerosis or hyperthyroidism;
15. Have any current problem, which in the opinion of the investigator or medical monitor, might interfere with participation in the study;
16. Are not able to give adequate informed consent.