MAPS Protocol MP7 Synopsis * Original Protocol: December 11, 2009

***Study Title*:** An Open-Label Lead-In and Randomized, Active Placebo-Controlled Pilot Study of 3,4-methylenedioxymethamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Jordan[Protocol # MP7]

Study description: This study will enroll twelve people with treatment-resistant PTSD in a randomized, double-blind, active placebo-controlled investigation of MDMA-assisted psychotherapy. The treatment intervention will take about 3 and 1/2 to four months and consists of about twelve 60 to 90-minute non-drug preparation and integration psychotherapy sessions and three-day long MDMA-assisted psychotherapy sessions. The first two participants enroll in an open-label lead-in with full-dose MDMA. The following ten participants enroll in the randomized, double-blind study. Participants who receive active placebo may enroll in an open-label Stage 2 with full dose MDMA after their final follow-up evaluation two months after their third experimental session.

Investigators: Dr. Nasser Shuriquie, female co-investigator

Subjects: This study will enroll twelve people, men or women, aged 18 years or older, diagnosed with PTSD with a score of at least 50 on the Clinician-Administered PTSD Scale (CAPS). Participants must have undergone at least one previous psychotherapeutic or pharmacotherapeutic treatment for PTSD.

Primary Outcome Measure: Clinician-Administered PTSD Scale (CAPS)
Other Measures: Beck Depression Inventory (BDI) (efficacy), Global Assessment of Functioning (GAF) (efficacy), Columbia Suicide Severity Rating Scale (C-SSRS) (Safety)

Study Procedures: After giving written consent, participants will be screened to ensure they meet inclusion criteria without meeting any exclusion criteria. The first two participants will participate in an open-label study lead-in with full dose MDMA (125 mg MDMA followed 1.5 to 2.5 hours later by 62.5 mg) in all three day-long experimental sessions, with frequent feedback from the sponsor to the co-therapist team regarding therapeutic method. The three experimental sessions will be scheduled three to five weeks apart, with subjects spending the night in the treatment facility. Of the following ten subjects, seven will be randomly assigned to the experimental condition (125 mg MDMA followed 1.5 to 2.5 hours later by 62.5 mg), and three will be assigned to the active placebo condition (40 and 20 mg MDMA).

The therapeutic intervention will consist of baseline evaluation, three 60 to 90-minute preparatory sessions with the investigator-psychotherapists, three experimental sessions scheduled at three to five week intervals, a 90-minute integrative psychotherapy session the morning after each experimental session and two additional 60 to 90-minute integrative psychotherapy sessions between each experimental session and after the last experimental session. Additional integrative sessions may be scheduled if needed. The follow-up evaluation session will take place two months after the third experimental session. Blinding will be broken for each individual during this evaluation. Subjects receiving the active-placebo have the option of repeating the entire therapeutic intervention with open-label full-dose experimental sessions.

Inclusion Criteria

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

1. Meet DSM IV criteria for current PTSD.
2. Have a CAPS score of 50 or higher, indicating moderate to severe PTSD symptoms.
3. Have had unsuccessful treatment (defined as still meeting PTSD criteria post-treatment) with one of the following:
    a. Treatment with a selective serotonin uptake inhibitor (SSRI), mirtazapine or a monoamine oxidase inhibitor (MAOI)
    b. Any form of psychotherapy for the treatment of PTSD.
4. Are at least 18 years old
5. Are willing to commit to medication dosing, experimental sessions, and follow-up sessions and to complete evaluation instruments.
6. Are willing to refrain from taking any psychiatric medications during the study period, with the exception of gabapentin when prescribed for pain control. An exception to this may arise in the case of designated rescue medication that may be administered in the event of a crisis during or after the experimental session.
7. Agree not to change the type or frequency of current psychotherapy, nor change therapists until after the third experimental session (if they are concurrently seeing an outside therapist)
8. Agree to, for one week preceding each MDMA/placebo 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.
9. Agree to take nothing by mouth except alcohol-free liquids after 12:00 A.M. (midnight) the evening before each experimental session. Participants must also refrain from the use of any psychoactive drug, with the exception of caffeine or nicotine, within 24 hours of each active placebo dose/experimental dose MDMA session. They must agree not to use caffeine or nicotine for 2 hours before and 6 hours after each dose of drug.
10. Are willing to remain overnight at the study site after each experimental session until the non-drug session occurring the next morning**.**
11. Are willing to be driven home the morning after the experimental sessions followed by the non-drug therapy session either by a driver arranged by the subject or by the site personnel or taxi.
12. Are willing to be contacted via telephone on a daily basis by one of the investigators for a week after each experimental session.
13. (If female participants of childbearing potential), must be willing to have pregnancy tests and must agree to use an effective form of birth control
14. Are literate. They must be proficient in reading documents written in Arabic, and they must be able to effectively communicate with the therapists and other site personnel.

5.3.2 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, including sexual abstinence.
2. Have a history of or current primary psychotic disorder or bipolar affective disorder type 1 or borderline personality disorder.
3. Diagnosed with dissociative identity disorder or an eating disorder with active purging, or borderline personality disorder.
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. (Participants with hypothyroidism who are on adequate and stable thyroid replacement will not be excluded).
5. Have hypertension, peripheral vascular disease, hepatic disease (with or without abnormal liver enzymes), or history of hyponatremia or hyperthermia.
6. Weigh less than 48 kg
7. Have used "Ecstasy" (illicit drug preparations purported to contain MDMA) more than 5 times or at any time within the previous 6 months.
8. Would present a serious suicide risk or who are likely to require hospitalization during the course of the study.
9. Require ongoing concomitant therapy with a psychotropic drug.
10. Meet DSM-IV criteria for substance abuse or dependence for any substance save caffeine or nicotine in the past 60 days.
11. Are not able to give adequate informed consent.
12. Have any current problem or a history of substance abuse which, in the opinion of the investigator or medical monitor, might interfere with participation in the protocol

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Time & Events MP7 Stage 1	Screen/Baseline		Preparatory	Experimental Session 1		Experimental Session 2		Experimental Session 3		Follow-Up
Visit #	Pre-Study	V1	V 2,3,4	V5	V 6,7,8	V9	V 10,11,12	V13	V 14,15,16	V17
Type of Visit	Screening may take place over more than one day	Baseline	Preparatory Sessions	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Experimental Session 3	Integrative Sessions	Follow-Up & Outcome
Visit Timing or Study day or Window	Up to 1 month prior to Visit 1	Day 1	Approx 1 week apart	3-5 weeks post baseline	Approx. 1 week apart [A]	3-5 weeks post V5	Approx. 1 week apart [A]	3-5 weeks post V9	Approx. 1 week apart [A]	May happen over more then 1 day. 2 months post V13
Initial Phone Screen	X									
Informed Consent	X									
Medical/Psychiatric History	X									
General Physical Exam (BP, Pulse, Temp, brief systems check)	X									
Brief Neurological Exam	X									
ECG	X									
SCID	X									
Clinical LabTests, w/ HIV test	X									
Collect Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Medication Taper (if applicable)	X	X								
Study Enrollment after meeting I/E		X								
Record to Audio/Video			X	X	X	X	X	X	X	
General Well-Being		X	X	X	X	X	X	X	X	X
Drug Screen	X			X		X		X		
Pregnancy Screen (if applicable)	X			X		X		X		
Complete Randomization Procedure				X [C]						
CAPS, GAF, BDI With Independent Rater	X		X [B]							X
C-SSRS		X	X [H]	X [D, E, F]	X	X [D, E, F]	X	X [D, E, F]	X	X
Administer IP Drug+Therapy				X		X				
Monitoring of BP, Pulse and Temp.				X						
SUDS				X [E, G]		X [E, G]		X [E, G]		
Beliefs of Condition Assignment				X		X		X		
Overnight Stay				X		X		X		
Integrative Therapy Session					X		X		X	
RRPQ										X [I]
7 days Integrative Telephone Contact					X [J]		X [J]		X [J]	
Adverse Events Requiring Dr. Visit			X	X	X	X	X	X	X	X
Spontaneously Reported Side Effects				X	X	X	X	X	X	
Adverse Events of Concern			X	X	X	X	X	X	X	
Serious Adverse Events		X	X	X	X	X	X	X	X	X
Unblinding [K] Termination Stage 1										X

[A] =First Integrative session is 1 day after exp session [B] =repeat before V5 ONLY if meds are tapered [C] = Within 24 hrs prior to 1st exp. session [D] =Approximately 6 hours post MDMA [E] =at the beginning of the session [F] =as needed [G] =Approximately every 60 minutes [H] =Given on 2nd preparatory session only (V3) [I] = Only for subjects starting Long term Follow up and not going to Stage 2 [J] =For 7 days post Exp. Session, CSSRS D2 and D7 of calls only, General well being for all 7 days [K] =Determine: termination at Stage 1 or go on to Stage 2

Time & Events MP7 Stage 2	Preparatory	Experimental Session 1		Experimental Session 2			Experimental Session 3		Follow-Up
Visit #	V18*	V19	V 20,21,22	V23	V 24,25,26	V27	V28	V 29,30,31	V32
Type of Visit	Preparatory Sessions	Experimental Session 1	Integrative Sessions	Experimental Session 2	Integrative Sessions	Outcome	Experimental Session 3	Integrative Sessions	Follow-Up & Outcome
Visit Timing or Study day or Window	Within 1 month of V17*	1 week post V18	Approx. 1 week apart [A]	3-5 weeks post V19	Approx. 1 week apart [A]		3-5 weeks post V23	Approx. 1 week apart [A]	May happen over more then 1 day. 2 months post V28
Confirm Informed Consent	X								
Confirm Inclusion/Exclusion	X								
Enrollment in Stage 2	X								
Collect Concomitant Medication	X	X	X	X	X		X	X	X
Record to Audio/Video	X	X	X	X	X		X	X	
General Well-Being	X	X	X	X	X		X	X	X
Drug Screen		X		X			X		
Pregnancy Screen (if applicable)		X		X			X		
CAPS, GAF, BDI and PTGI With Independent Rater	Use V17*								X
C-SSRS	X[H]	X[D, E, F]	X	X[D, E, F]	X		X[D, E, F]	X	X
Administer IP Drug+Therapy		X		X					
Monitoring of BP, Pulse and Temp.		X							
SUDS		X[E, G]		X[E, G]			X[E, G]		
Overnight Stay		X		X			X		
Integrative Therapy Session			X		X			X	
RRPQ									X
7 days Integrative Telephone Contact			X[J]		X[J]			X[J]	
Adverse Events Requiring Dr. Visit	X	X	X	X	X		X	X	X
Spontaneously Reported Side Effects		X	X	X	X		X	X	
Adverse Events of Concern	X	X	X	X	X		X	X	
Serious Adverse Events	X	X	X	X	X		X	X	X
Complete Stage 2 go to 1yr Follow-up									X
Termination Visit									X

* If Visit 18 is more then 1 month after V17 then the measures from V17 will need to be repeated prior to starting Stage 2
[A] =first session is 1 day after exp session [D] =Approximately 6 hours post MDMA [E] =at the beginning of the session [F] =as needed [G] =Approximately every 60 minutes [H] =Given on 2nd preparatory session only (V3) [J] = For 7 days post Exp. Session, CSSRS D2 and D7 of calls only, General well being for all 7 days