**Study Title:** An Open-Label Lead-In and Randomized, Active Placebo-Controlled Pilot Study of 3,4-methylenedioxyamphetamine (MDMA)-assisted Psychotherapy in 12 Subjects with Treatment-Resistant Posttraumatic Stress Disorder (PTSD)-Jordan [Protocol # MP-7]

**Study description:** This study will enroll twelve people with treatment-resistant PTSD. Stage 1 of the study will be a randomized, double-blind, active placebo-controlled investigation of MDMA-assisted psychotherapy. The treatment intervention will take about 5.5 to 6 months and consists of about twelve 60 to 90-minute non-drug preparation and integration psychotherapy sessions and three separate day-long MDMA-assisted psychotherapy sessions. The first two participants will enroll in an open-label lead-in with full-dose MDMA. The following ten participants will 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 follow-up evaluation at the end of Stage 1. Long-term effects of the treatment will be assessed twelve months after the final experimental session.

**Principle Investigator:** Dr. Nasser Aldien Taj Aldien Shuriquie

**Subjects:** This study will enroll twelve participants, men and 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 previously undergone at least one unsuccessful psychotherapy or pharmacotherapy treatment for PTSD.

**Primary Outcome Measure:** Clinician-Administered PTSD Scale (CAPS)

**Secondary Measures:**
- **Efficacy Measures:** Beck Depression Inventory-II (BDI-II), Global Assessment of Functioning (GAF)
- **Safety Measures:** Columbia Suicide Severity Rating Scale (C-SSRS)
- **Process Measures:** Reactions to Research Participation (RRPQ)

**Study Procedures:** After giving written consent, participants will be screened to ensure they meet all 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 three day-long experimental sessions. The three experimental sessions will be scheduled three to five weeks apart, with subjects spending the night in the treatment facility. The data from these subjects will be internally reviewed for adherence to the protocol. 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 sessions will take place two months after the last experimental session. The blind 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. There will be a long-term follow up that will occur 12 months after participants’ final visit, which will depend upon whether participants completed Stage 1 or were eligible for and completed Stage 2. Participants will complete all outcome measures during the follow-up and will complete a questionnaire on the positive and negative effects of study participation.
Inclusion Criteria

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

1. Meet DSM IV criteria for current PTSD of at least six months duration.
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, a Serotonin Norepinephrine Reuptake Inhibitor (SNRI) 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 the subject is concurrently seeing an outside therapist) including any experimental therapies.
8. Agree to, for one week preceding each MDMA 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. Subjects 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. Subjects must agree not to use caffeine or nicotine for 1 hour before and 3 hours after ingesting the drug, or until the investigators deem it safe to do so.
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, after 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 subjects of childbearing potential, must be willing to have pregnancy tests and must agree to use an effective form of birth control.
14. Are literate. Subjects must be proficient in reading documents written in Arabic, and they must be able to effectively communicate with the therapists and other site personnel.
15. Must be willing not to participate in any other clinical trial for the duration of this clinical trial, including the follow up period.
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. Are 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. (Subjects 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 psychiatric drug, including SSRIs, SNRIs, or MAOIs.
10. Meet DSM-IV criteria for substance abuse or dependence for any substance other than 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.
### Table 1. Time & Events Stage 1

<table>
<thead>
<tr>
<th>Visit #</th>
<th>Screen</th>
<th>Preparatory</th>
<th>Experimental Session 1</th>
<th>Experimental Session 2</th>
<th>Experimental Session 3</th>
<th>2 Month Follow-Up</th>
<th>12 Month Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Study</td>
<td>V1</td>
<td>V 2,3,4</td>
<td>V5</td>
<td>V 6,7,8</td>
<td>V9</td>
<td>V 10,11,12</td>
</tr>
<tr>
<td>Type of Visit</td>
<td>Screening</td>
<td>Baseline</td>
<td>Preparatory Sessions</td>
<td>Experimental Session 1</td>
<td>Integrative Sessions</td>
<td>Experimental Session 2</td>
<td>Integrative Sessions</td>
</tr>
<tr>
<td>Visit Timing or Study day or Window</td>
<td>Up to 1 month before V1, can be over &gt;1 day</td>
<td>Day 1</td>
<td>Approx. 1 week apart</td>
<td>3-4 weeks past baseline</td>
<td>Approx. 1 week apart</td>
<td>3-5 weeks past V5</td>
<td>Approx. 1 week apart</td>
</tr>
</tbody>
</table>

- **A** = repeat before V5 ONLY if meds are tapered
- **B** = Within 24 hrs prior to V5
- **C** = Approximately 6 hours post MDMA
- **D** = at the beginning of the session
- **E** = as needed
- **F** = Approximately every 60 minutes
- **G** = Given on V3 only
- **H** = Only for subjects not going to Stage 2
- **I** = For 7 days post Exp. Session, CSSRS D2 and D7 of calls only. General well being for all 7 days.
- **J** = Determine: Termination at Stage 1 or go on to Stage 2
- **K** = Collected on the day of MDMA administration and for seven days after each Exp. Session
- **L** = At 1st integrative visit after each Exp. Session for subjects & investigators and at V17 for the independent rater.
### Table 2. Time & Events Stage 2

<table>
<thead>
<tr>
<th>Visit #</th>
<th>Preparatory</th>
<th>Experimental Session 1</th>
<th>Experimental Session 2</th>
<th>Experimental Session 3</th>
<th>2 Month Follow-Up</th>
<th>12 Month Follow Up</th>
</tr>
</thead>
</table>
| V18*        | V19         | V20,21,22               | V23                    | V24,25,26              | V27              | V28,29,30         | V31               
| Type of Visit| Preparatory | Experimental Session 1 | Integrative Sessions   | Experimental Session 2 | Integrative Sessions | Experimental Session 3 | Integrative Sessions | Follow-Up & Outcome | Follow up and Outcome and Termination |
| Visit Timing or Study day or Window | Within 1 month of V17* | 1 week post V18 | Approx. 1 week apart | 3-5 weeks post V19 | Approx. 1 week apart | 3-5 weeks post V23 | Approx. 1 week apart | May occur over >1 day 2 mo. post V28 | May occur over >1 day 2 mo. post V28 |

- **Confirm Informed Consent**: X
- **Confirm Inclusion/Exclusion**: X
- **Enrollment in Stage 2**: X
- **Collect Concomitant Medication**: X
- **Record to Audio/Video**: X
- **General Well-Being**: X
- **Drug Screen**: X
- **Pregnancy Screen (if applicable)**: X
- **CAPS, GAF, BDI (Ind. Rater)**: Use V17^A
- **C-SSRS**: X
- **Administer IP Drug+Therapy**: X
- **Monitoring of BP, Pulse, Temp.**: X
- **SUD**: X
- **Overnight Stay**: X
- **Integrative Therapy Session**: X
- **7 days Integrative Phone Contact**: X
- **AEs Requiring Medical attention**: X
- **Spont. Side Effects and all AEs^K**: X
- **AEs related to changes in psychiatric status or withdrawal**: X
- **Serious Adverse Events**: X
- **Complete Stage 2 go to 1yr Follow-up**: X
- **RRPQ**: X
- **Follow up Questionnaire**: X
- **Issue Memory Aid Card**: X
- **Termination Visit**: X

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**Legend**:
- A= Re-baseline if V18 is more then 1 month after V17
- C= Approximately 6 hours post MDMA
- D= at the beginning of the session
- E= as needed
- F= Approximately every 60 minutes
- H= On Day 2 and Day 7 of phone calls after experimental sessions 1 = For 7 days post Exp. Session, CSSRS D2 and D7 of calls only, General well being for all 7 days
- K= Common expected side effects will be collected on the day of MDMA administration and for seven days after each Exp. Session.