The Agony and the Ecstasy: MDMA and the Treatment of PTSD

Steven Braun
PGY-1 Resident
Central Texas Veterans Health Care System
Objectives

- State the definition, diagnostic criteria, and pharmacotherapy options for PTSD
- Identify the proposed MOA of MDMA in which it is related to the pathophysiology of PTSD
- Identify the proposed role of MDMA in the treatment of PTSD
- Evaluate primary literature and draw conclusions regarding studies involving MDMA as an adjunct to psychotherapy
- Apply critical appraisals of primary literature to a patient case
Abbreviations

- ADE: Adverse drug events
- BP: Blood pressure
- CAPS: Clinician administered PTSD Scale
- CPT: Cognitive Processing Therapy
- CRF: Corticotropin-releasing hormone
- DA: Dopamine
- DEA: Drug Enforcement Agency
- DoD: Department of Defense
- DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders-text-revision
- DSM-V: Diagnostic and Statistical Manual
- EMDR: Eye Movement Desensitization and Reprocessing
- FDA: Food and Drug Administration
- fMRI: Functional Magnetic Resonance Imaging
- HPA axis: Hypothalamic–pituitary–adrenal axis
- HR: Heart rate
- IES-R: Impact of Events Scale-Revised
- LTFU: Long-term-follow-up
- MAOi: Monoamine oxidase inhibitor
- MDMA: 3,4-Methylenedioxymethamphetamine
- MDMA-AP: MDMA-assisted psychotherapy:
- MOA: Mechanism of Action
- NE: Norepinephrine
- PFC: Prefrontal cortex
- PCL-5: PTSD checklist
- PDS: Posttraumatic Diagnostic Scale
- PE: Prolonged Exposure Therapy
- PT: Psychotherapy
- PTSD: Posttraumatic Stress Disorder
- SCL-90-R: Symptom Checklist 90-Revised
- SSRI: Selective serotonin reuptake inhibitor
- SNRI: Serotonin-norepinephrine reuptake inhibitor
- SUD: Substance abuse disorder
- TCA: Tricyclic antidepressant
- VA: Veterans Affairs
Posttraumatic Stress Disorder
PTSD: a clinically significant condition with symptoms continuing more than 1 month after exposure to a trauma that has caused significant distress or impairment in social, occupational, or other important areas of functioning.
Definition

- Trauma- and Stressor-Related Disorders in DSM-V
- Acute PTSD
  - Symptoms lasting > 1 month but < 3 months after experiencing a trauma
- Chronic PTSD
  - Symptoms lasting > 3 months after experiencing a trauma
- Appear alone or with other co-occurring conditions or psychiatric disorders

\(^1\)
Epidemiology

• Lifetime prevalence rate for PTSD\textsuperscript{3}
  • General population = 7.8%
  • Amongst veterans is 13.8%
• Women are four times more likely to develop PTSD than men\textsuperscript{4}
• Suspected underreporting of symptoms due to stigma\textsuperscript{3}
• Annual economic burden of PTSD and other anxiety disorders = $43.2 billion\textsuperscript{5}
Etiology

• “Neurocircuitry Model”
  • Seen through neuroimaging studies
  • Diminished responsivity in medial prefrontal cortex
    • Deficient inhibition of the amygdala
  • Increased activation of the amygdala
    • Deficit in extinction of fear
  • Reduced hippocampal activity and volume
    • Failure to place memories in the correct context of space and time

• Genetic component

• Exposure to a traumatic event
Pathophysiology

- **Neuroendocrine Theory**
  - Dysregulation of the HPA axis
    - Hypersecretion of CRF but low cortisol levels
    - Lack of negative feedback to diminish catecholamine levels
    - Continued stress response

- **Neurochemical Theory**
  - Hyperactive noradrenergic signaling
    - Hyperarousal symptoms
  - Decreased serotonergic transmission
    - Aggression, impulsivity, panic, obsessive thoughts
**DSM-5 Criteria for PTSD**

- **Criterion A**: The person was exposed to: death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, in the following way(s):
  - Direct exposure
  - Witnessing the trauma
  - Learning that a relative or close friend was exposed to a trauma
  - Indirect exposure to aversive details of the trauma, usually in the course of professional duties

- **Criterion B**: The traumatic event is persistently re-experienced, in the following way(s):
  - Intrusive thoughts
  - Nightmares
  - Flashbacks
  - Emotional distress after exposure to traumatic reminders
  - Physical reactivity after exposure to traumatic reminders

- **Criterion C**: Avoidance of trauma-related stimuli after the trauma, in the following way(s):
  - Trauma-related thoughts or feelings
  - Trauma-related reminders

*One required*
DSM-5 Criteria for PTSD

- **Criterion D**: Negative thoughts or feelings that began or worsened after the trauma, in the following way(s):
  - Inability to recall key features of the trauma
  - Overly negative thoughts and assumptions about oneself or the world
  - Exaggerated blame of self or others for causing the trauma
  - Negative affect
  - Decreased interest in activities
  - Feeling isolated
  - Difficulty experiencing positive affect

- **Criterion E**: Trauma-related arousal and reactivity that began or worsened after the trauma, in the following way(s):
  - Irritability or aggression
  - Risky or destructive behavior
  - Hypervigilance
  - Heightened startle reaction
  - Difficulty concentrating
  - Difficulty sleeping

**Two required**
DSM-5 Criteria for PTSD$^{17}$

- **Criterion F:** Symptoms last for more than 1 month.
- **Criterion G:** Symptoms create distress or functional impairment (e.g., social, occupational).
- **Criterion H:** Symptoms are not due to medication, substance use, or other illness
Clinical Presentation: Core Symptoms

• **Re-Experiencing of Symptoms:**
  - Recurrent, intrusive memories of the trauma
  - Recurrent, disturbing dreams
  - Flashbacks
  - Physiologic reaction to reminders

• **Hyperarousal Symptoms:**
  - Decreased concentration
  - Easily startled
  - Hypervigilance
  - Insomnia
  - Irritability or anger outbursts

• **Avoidance Symptoms:**
  - Avoidance of conversations about the trauma
  - Avoidance of thoughts or feelings about the trauma
  - Avoidance of activities that are reminders of the trauma
  - Inability to recall important aspects of the trauma
  - Anhedonia
  - Estrangement from others
  - Restricted affect
  - Sense of foreshortened future
Assessment

• **CAPS:**
  - 30-itemed structured interview
  - Used to make diagnoses of PTSD in the past week, past month, or lifetime
  - Used to assess severity of PTSD symptoms based on frequency and severity
  - Items scored on a 0-4 basis (Absent to Extreme/incapacitating)
  - Scores >50 indicate at least moderately severe PTSD
  - Scores <20 were defined as remission

• **PDS:**
  - Validated self-reporting measure to assess the presence of PTSD symptoms
  - Related to a single identified traumatic event
  - Yields a total severity score (ranging from 0 to 51)
Treatment of PTSD
## Strength of Recommendation (SR)

<table>
<thead>
<tr>
<th>Letter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A strong recommendation that clinicians provide the intervention to eligible patients. Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.</td>
</tr>
<tr>
<td>B</td>
<td>A recommendation that clinicians provide (the service) to eligible patients. At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.</td>
</tr>
<tr>
<td>C</td>
<td>No recommendation for or against the routine provision of the intervention is made. At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.</td>
</tr>
<tr>
<td>D</td>
<td>A recommendation is made against routinely providing the intervention to asymptomatic patients. At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.</td>
</tr>
<tr>
<td>I</td>
<td>The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</td>
</tr>
</tbody>
</table>
Overview of Treatment for PTSD¹

• VA- DoD Guidelines
  • Grade A recommendations
    • Trauma focused psychotherapy
    • SSRIs and SNRIs as monotherapy
  • Grade B recommendations
    • Mirtazapine, Prazosin (for nightmares), TCAs, Nefazodone, MAOIs
  • Not recommended
    • Benzodiazepines, Guanfacine, anti-convulsants

• FDA
  • Only 2 approved medications
    • Paroxetine (SSRI)
    • Sertraline (SSRI)
Treatment for PTSD Algorithm

<table>
<thead>
<tr>
<th>Initial Treatment (Reassess at 2-4 weeks)</th>
<th>Step 1 (Reassess at 4-6 weeks from initial treatment)</th>
<th>Step 2 (Reassess at 8-12 weeks from initial treatment)</th>
<th>Step 3 (Reassess at &gt; than 12 weeks from initial treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotherapy or SSRI or SNRI</td>
<td>Assess and address adherence</td>
<td>Add psychotherapy and/or switch to mirtazapine</td>
<td>Switch to alternative step 2 or to TCA or nefazodone (see page 67 for the black box warning) or phenelzine. Add psychotherapy.</td>
</tr>
<tr>
<td></td>
<td>Increase dose and/or add psychotherapy if the patient is not already in therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Switch to another SSRI or SNRI and/or add psychotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider referral to specialty care at any time during the treatment</td>
<td></td>
</tr>
</tbody>
</table>

Add prazosin at any time for sleep/nightmares
Psychotherapy

• **Aim**: reduction of symptoms severity, improvement of global functioning, and improvement in quality of life and functioning in social and occupational areas

• Trauma-focused psychotherapies (Grade A)
  • Exposure-based therapies
  • Cognitive-based therapies
  • Eye Movement Desensitization and Reprocessing

• Therapy chosen based on symptom severity, clinician expertise, and patient preference
Pharmacotherapy

**Pharmacotherapy Interventions for Treatment of PTSD: Balance of Benefit and Harm**

<table>
<thead>
<tr>
<th>SR (Strength of recommendation rating)</th>
<th>Significant Benefit</th>
<th>D (Ineffective or harmful)</th>
<th>I (Insufficient evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A (Strong recommendation)</strong></td>
<td><strong>SSRIs – paroxetine and sertraline (FDA-approved) and fluoxetine</strong>&lt;br&gt;<strong>SNRIs – venlafaxine</strong></td>
<td><strong>Benzodiazepines [Harm]</strong>&lt;br&gt;<strong>Tigabine</strong>&lt;br&gt;<strong>Guanfacine</strong>&lt;br&gt;<strong>Valproate</strong>&lt;br&gt;<strong>Topiramate</strong>&lt;br&gt;<strong>Risperidone</strong></td>
<td><strong>Atypical antipsychotics (monotherapy) - Note: Risperidone is level D</strong>&lt;br&gt;<strong>Atypical antipsychotics (as adjunct)</strong>&lt;br&gt;<strong>Conventional antipsychotics</strong>&lt;br&gt;<strong>Buspirone</strong>&lt;br&gt;<strong>Non-benzodiazepine sedative/hypnotics</strong>&lt;br&gt;<strong>Bupropion</strong>&lt;br&gt;<strong>Trazodone (as adjunct)</strong>&lt;br&gt;<strong>Gabapentin</strong>&lt;br&gt;<strong>Lamotrigine</strong>&lt;br&gt;<strong>Propranolol</strong>&lt;br&gt;<strong>Clonidine</strong></td>
</tr>
<tr>
<td><strong>B (Fair evidence)</strong></td>
<td><strong>Mirtazapine</strong>&lt;br&gt;<strong>Prazosin (Use for sleep/nightmares)</strong>&lt;br&gt;<strong>TCAs</strong>&lt;br&gt;<strong>Nefazodone [Caution</strong>&lt;br&gt;<strong>Monoamine oxidase inhibitors (phenelzine) [Caution</strong>&lt;br&gt; <strong>Caution]</strong></td>
<td><strong>Unknown</strong>&lt;br&gt;<strong>Atypical antipsychotics (monotherapy) - Note: Risperidone is level D</strong>&lt;br&gt;<strong>Atypical antipsychotics (as adjunct)</strong>&lt;br&gt;<strong>Conventional antipsychotics</strong>&lt;br&gt;<strong>Buspirone</strong>&lt;br&gt;<strong>Non-benzodiazepine sedative/hypnotics</strong>&lt;br&gt;<strong>Bupropion</strong>&lt;br&gt;<strong>Trazodone (as adjunct)</strong>&lt;br&gt;<strong>Gabapentin</strong>&lt;br&gt;<strong>Lamotrigine</strong>&lt;br&gt;<strong>Propranolol</strong>&lt;br&gt;<strong>Clonidine</strong></td>
<td></td>
</tr>
<tr>
<td><strong>C (Fair evidence but no general recommendation)</strong></td>
<td><strong>Prazosin (for global PTS symptoms)</strong></td>
<td><strong>Unknown</strong>&lt;br&gt;<strong>Atypical antipsychotics (monotherapy) - Note: Risperidone is level D</strong>&lt;br&gt;<strong>Atypical antipsychotics (as adjunct)</strong>&lt;br&gt;<strong>Conventional antipsychotics</strong>&lt;br&gt;<strong>Buspirone</strong>&lt;br&gt;<strong>Non-benzodiazepine sedative/hypnotics</strong>&lt;br&gt;<strong>Bupropion</strong>&lt;br&gt;<strong>Trazodone (as adjunct)</strong>&lt;br&gt;<strong>Gabapentin</strong>&lt;br&gt;<strong>Lamotrigine</strong>&lt;br&gt;<strong>Propranolol</strong>&lt;br&gt;<strong>Clonidine</strong></td>
<td></td>
</tr>
</tbody>
</table>

*Attention to drug-drug and dietary interactions*
Other Adjunctive Therapies

• Complementary and alternative medicine
  • Mindfulness, yoga, acupuncture, massage
• Psychosocial rehabilitation
• Spiritual support
• Social support
MDMA
History of MDMA

• Synthetic compound first developed in 1912
• Commonly known as “Ecstasy”, “Molly”, “E”, or “X”
• First considered indication was as an appetite suppressant
• In the 1970s, used as psychotherapeutic agent
• Recreational use prevalent
• Reclassified as a Schedule 1 drug in 1985\textsuperscript{15}
• Studies in the 1990’s focus on neurotoxicity
Pharmacology

- Drug class: Empathogen–entactogen; stimulant
  - Amphetamine and hallucinogenic-like properties
- MDMA is structurally related to amphetamines
  - Difference: presence of the methylenedioxy group (-O-CH₂-O-) attached to the aromatic ring
- Resembles the structure of the hallucinogen mescaline
- Racemic mixture of two enantiomers
  - S(+) MDMA has pronounced pharmacological effects
**Pharmacokinetics**

- **Absorption/Distribution:**
  - GI tract
  - Onset of action: within 30 minutes
  - Peak serum levels: 1-3 hours
  - Duration of action: 4-6 hours

- **Metabolism:**
  - Liver; P450 2D6
  - Saturable

- **Excretion:**
  - Urine
  - T1/2: ~7 hours
  - Alkaline urine can increase the T1/2 to 16-31 hours
Pharmacodynamics

Proposed mechanisms of action:

- Indirect serotonergic agonist
  - Serotonin transporter
  - Promotes release
  - Interferes with storage
  - Increased serotonin at synapse

- Enhance release of DA and NE
  - Similar mechanism with serotonin
  - Inhibition of monoamine oxidase
  - Weak agonist activity at postsynaptic serotonin receptors 5-HT$_1$ and 5-HT$_2$
  - Increased release of oxytocin
Clinical Effects

• Sought after effects:
  • Euphoria
  • Sense of well being
  • Greater sociability
  • A feeling of closeness to others
  • Extraversion
  • Tolerance of others

• Sharpened sensory perception
• Greater capability of communication
• Increased lucidity
• Increased sensitivity of emotions
• “An expanded mental perspective”
• “Improved self-examination”
Adverse Effects

• Immediate effects:
  • Increase in BP, HR, and body temperature
  • Bruxism
  • Dehydration
  • Nausea, vomiting, diarrhea
  • Increased wakefulness

• Delayed effects:
  • Insomnia
  • Loss of appetite
  • Depression
  • Irritability
  • Anxiety
  • Memory impairment

• Toxicity
  • Life-threatening increases in BP and HR
  • Hyperthermia
  • Hyponatremia
  • Hepatotoxicity
  • Serotonin Syndrome
Prior Medication Trials with MDMA\textsuperscript{7,14}

- Nichols and Shulgin performed first clinical study (1978)
  - Produced “an easily controlled altered state of consciousness with emotional and sensual overtones”
- Leo Zeff was the first to use MDMA in clinical practice
- In the 1980’s, over 150 therapists used MDMA in treatment settings
- Clinical Trials did not appear until post-2000
- fMRI imaging studies
  - Decreased amygdala activation
  - Increase prefrontal cortex activation
Proposed Role in PTSD$^{7,14}$

- Proposed as a therapeutic catalyst or adjunct to exposure therapy
- Noted complications of psychotherapy in PTSD:
  - Trauma affects patient’s ability to trust therapist
  - High therapy dropout rates due to small window of “optimal arousal”
    - Prone to anxiety and numbing
  - Therapy can cause distress and dissociation
  - Lack of sociability makes connecting with therapist difficult
  - High fear of revisiting negative memories
Proposed role of MDMA in treatment of PTSD

<table>
<thead>
<tr>
<th>MDMA Effects</th>
<th>Role of MDMA in treatment of PTSD</th>
<th>Correlated Receptors/Neuroanatomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improves fear extinction learning</td>
<td>Patient can reflect on memories without feeling overwhelmed</td>
<td>Release of noradrenaline and cortisol</td>
</tr>
<tr>
<td>Increases emotional attachment and feelings</td>
<td>Improved relationship between patient and therapist.</td>
<td>Multiple factors, including release of oxytocin.</td>
</tr>
<tr>
<td>of trust and empathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved detection of happy faces and reduced</td>
<td>Enhances levels of shared empathy and pro-social functioning</td>
<td>Increased PFC activation and decreased amygdala activation</td>
</tr>
<tr>
<td>detection of negative facial expressions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduces subjective fear response on recall of</td>
<td>Opportunity to reflect upon painful memories of trauma during psychotherapy</td>
<td>Decreased cerebral blood flow in the right amygdala and hippocampus.</td>
</tr>
<tr>
<td>negative memories</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduces depression and anxiety</td>
<td>Provides patient with an experience of positive mood and reduced anxiety in which</td>
<td>Release of pre-synaptic serotonin</td>
</tr>
<tr>
<td></td>
<td>to engage in therapy</td>
<td></td>
</tr>
<tr>
<td>Stimulates alterations in the perceptions of</td>
<td>Provides patient with an opportunity to see old problems in a new light</td>
<td>Increased activity at serotonin receptors</td>
</tr>
<tr>
<td>meaning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raises levels of arousal</td>
<td>Stimulating effect increases motivation to engage in therapy</td>
<td>Release of NE and DA</td>
</tr>
</tbody>
</table>
Case Question

JH is a 34 year-old Caucasian male who is a veteran that was previously deployed in Iraq and Afghanistan. He was diagnosed with PTSD 6 years ago. He has had previous trials of venlafaxine, fluoxetine, sertraline, prazosin, paroxetine, and mirtazapine. He also received 6 months of exposure therapy but continues to experience symptoms of flashbacks, hypervigilance, and aggression. He is treatment refractory and is hesitant to trial anymore prescription medications. Given his treatment hx, would you be comfortable recommending MDMA in combination with therapy for this patient?

1. Yes
2. Yes, with reservations
3. No
4. Need more information
Literature Review
First Randomized Clinical Trial: Mithoefer et al. 2011

Title

The safety and efficacy of \{+/-\}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study.

Hypothesis

MDMA could be administered without harm to people with chronic, treatment-resistant PTSD and, in conjunction with psychotherapy, would lead to a significant decrease in PTSD symptoms compared with the same psychotherapy in conjunction with inactive placebo.
First Randomized Clinical Trial: Mithoefer et al. 2011

**Inclusion Criteria**

- Subjects aged 21–70 years
- DSM-IV-TR criteria for the diagnosis of crime or war-related chronic PTSD
- Treatment-resistant symptoms
  - CAPS score of ≥ 50
  - 3 months of SSRI or SNRI
  - 6 months of psychotherapy

**Exclusion Criteria**

- Freedom from any major medical conditions
- Borderline Personality Disorder
- Axis I disorder except:
  - Anxiety disorders
  - Affective d/o other than bipolar d/o type I
  - SUD; remission ≥ 60 days
- Negative drug screening
First Randomized Clinical Trial: Mithoefer et al. 2011

**Study Design**
- Randomized, placebo-controlled, double-blind, and crossover design study

**Detailed Methods**
- **Phase I**
  - Two 90 minute introductory sessions with therapists
  - Two All day MDMA or placebo experimental session
    - Therapy + MDMA 125mg (n=12) or PT + Placebo (n=8)
    - MDMA 62.5mg or Placebo given 2.5hr after initiation of therapy
- **Phase II**
  - 2 months after second experimental session
  - Open-label MDMA treatment for placebo subjects

**Outcomes**
- Primary Outcome Difference in CAPS score:
  - Baseline, 4 days after each of 2 psychotherapy sessions, and 2 months after second psychotherapy session
- Secondary Outcomes: IES-R
- Safety Outcomes: Neurocognitive testing, BP, and temperature, ADEs
Baseline Characteristics
- Average duration of PTSD was 19+ years
- No significant differences except duration of previous therapy
- Female: 85%; Caucasian: 100%

Results
- **Primary Outcome:**
  - Phase I: Mean overall difference of CAPS score at 2 months post-therapy sessions was significantly greater in MDMA group
    - Mean $\Delta$ CAPS of MDMA arm: -51; n = 12
    - Mean $\Delta$ CAPS of Placebo arm: -20.5; n = 8
  - Phase II:
    - Mean $\Delta$ CAPS: -31.7; n = 7
- **Secondary Outcome:**
  - IES-R
    - Mean $\Delta$ IES-R MDMA: -29.9
    - Mean $\Delta$ IES-R Placebo: -12.5
    - Statistically significant difference; p = 0.027
First Randomized Clinical Trial: Mithoefer et al. 2011

Results

• Safety Outcomes:
  • No differences in neurocognitive measures; no serious ADEs
  • Side effects:
    • MDMA arm day of sessions: jaw tightness, nausea, feeling cold, dizziness, loss of appetite, and impaired balance
    • Placebo and MDMA arms: anxiety, insomnia, headache and fatigue.
    • MDMA (One week after): irritability and loss of appetite
    • Placebo (One week after): insomnia

• Elevations in BP, HR, Temp in MDMA group; transient
• Clinical response (>30% reduction from baseline in CAPS total severity score)
  • Phase 1: 83.3% (10/12) in the MDMA arm; 25% (2/8) in the placebo arm
  • Phase 2: clinical response rate was 100% in the seven subjects
## First Randomized Clinical Trial: Mithoefer et al. 2011

### Primary Outcome for Phase 1

<table>
<thead>
<tr>
<th></th>
<th>Mean CAPS of Placebo</th>
<th>Mean CAPS of MDMA</th>
<th>Total Δ CAPS of Placebo</th>
<th>Total Δ CAPS of MDMA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>79.6</td>
<td>79.2</td>
<td>NA</td>
<td>NA</td>
<td>0.966</td>
</tr>
<tr>
<td>B</td>
<td>74.1</td>
<td>37.8</td>
<td>-5.5</td>
<td>-41.4</td>
<td>0.013*</td>
</tr>
<tr>
<td>C</td>
<td>66.8</td>
<td>29.3</td>
<td>-12.8</td>
<td>-49.9</td>
<td>0.002*</td>
</tr>
<tr>
<td>D</td>
<td>59.1</td>
<td>25.5</td>
<td>-20.5</td>
<td>-51</td>
<td>0.013*</td>
</tr>
</tbody>
</table>

* Denotes statistical significance

### Primary Outcome for Phase 2

<table>
<thead>
<tr>
<th></th>
<th>Baseline** CAPS</th>
<th>End*** CAPS</th>
<th>Δ CAPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=7</td>
<td>65.6</td>
<td>33.9</td>
<td>-31.7</td>
</tr>
</tbody>
</table>

** 2 months post-placebo  
*** 4-6 weeks after 2nd MDMA session

** A: Baseline  
** B: 4 days after 1st session  
** C: 4 days after 2nd session  
** D: 2 months after 2nd session
First Randomized Clinical Trial: Mithoefer et al. 2011

A: Baseline  
B: 4 days after 1st session  
C: 4 days after 2nd session  
D: 2 months after 2nd session
First Randomized Clinical Trial: Mithoefer et al. 2011

Discussion
- Clinical significance shown by high percentage of >30% decrease in CAPS
- Lack of clinically significant adverse effects between treatment arms
- If approved in practice, MDMA would require specialty clinics

Limitations
- Small sample size; mostly female; all Caucasian
- Transparency of blinding
- Additional follow-up sessions more frequent in MDMA arm
- Durability of results limited to 2 month follow-up

Author’s Conclusion
- MDMA-assisted psychotherapy can be administered to posttraumatic stress disorder patients without evidence of harm
- It may be useful in patients refractory to other treatments
Critically Appraised

**Strengths:**
- Randomized, placebo based trial
- Strong exclusion criteria: eliminating other diagnoses and other psychotropic medications
- Use of CAPS for primary outcome
- Robustness of results at 2 months post-therapy

**Weaknesses:**
- Small sample size
- Lack of long-term follow-up
- Differences among therapists
- Baseline characteristics
- More therapy session given post-treatment to MDMA arm
- Lack of blinding

**Presenter’s Conclusion**
Well performed study; however, the small sample size, higher prevalence of follow-up sessions in MDMA group, and lack of remission rates post 2 months after therapy limits knowledge regarding long-term success with MDMA as an adjunctive treatment.
Follow-up to First Clinical Trial: Mithoefer et al. 2013

Title
Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study

Objective
To evaluate the symptoms of PTSD in subjects who underwent MDMA + psychotherapy in the initial Mithoefer trial as a long-term follow-up and to assess if continued improvement occurred with these subjects
Follow-up to First Clinical Trial: Mithoefer et al. 2013

Methods

• 20 original subjects were contacted
• LTFU ranged from 17-74 months (mean = 45.4)
• Primary Outcome: CAPS
• Secondary Outcome: IES-R
• Post-treatment outcomes at 2-month follow-up compared to LTFU

Results

• 16 subjects completed CAPS and IES-R
• No statistical significant differences between end of study and LTFU
• Subjects mostly maintained statistical and clinical symptom relief
• 2 of the subjects did relapse (CAPS > 50)
Follow-up to First Clinical Trial: Mithoefer et al. 2013

Table 1. Early final study CAPS and IES-R Scores, 2 months after two MDMA-assisted sessions, versus the LTFU scores obtained in this study, for the same subjects.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-month</td>
<td>16</td>
<td>24.6</td>
<td>18.6</td>
<td>0.1</td>
<td>15</td>
<td>.91</td>
</tr>
<tr>
<td>LTFU</td>
<td>16</td>
<td>23.7</td>
<td>22.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES-R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-month</td>
<td>16</td>
<td>19.8</td>
<td>19.5</td>
<td>0.4</td>
<td>15</td>
<td>.72</td>
</tr>
<tr>
<td>LTFU</td>
<td>16</td>
<td>22.1</td>
<td>21.8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Follow-up to First Clinical Trial: Mithoefer et al. 2013

**Discussion**
- Important to take into account 3 subjects did not complete LTFU
- Relapse rates comparable to other modes of treatment
- No subject developed SUD
- Favorable reports of cognitive function and memory

**Limitations**
- Only 16/19 MDMA patients responded
- The longer the f/u, more time for other confounding variables
- Other confounders: 8/19 in psychotherapy; 12/19 on psychotropic medications

**Author’s Conclusion**
- There was an enduring, clinically meaningful benefit from MDMA-assisted psychotherapy to PTSD patients

**Presenter’s Conclusion**
- There tends to be a long-term, durable benefit of PTSD symptom improvement with those treated with MDMA + psychotherapy; however, the many potential confounding variables make it difficult to determine the true impact of the experimental treatment.
Second Randomized Clinical Trial: Oehen et al. 2013

Title
A randomized, controlled pilot study of MDMA(±3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD)

Hypothesis
Intended to serve as a proof of concept and to secondarily confirm the initial findings of the Mithoefer et al. to address the question of if an “active placebo” could help optimize blinding and if three MDMA sessions were more effective than only two in the reduction of symptoms of PTSD that would remain stable at a 1 year follow-up.
Inclusion Criteria

- DSM-IV-R criteria for chronic PTSD
- Treatment-resistant symptoms
  - CAPS score of $\geq 50$
  - 3 months of SSRI or SNRI
  - 6 months of psychotherapy
- Required to taper psychotropic medications

Exclusion Criteria

- Freedom from any major medical conditions except hypothyroidism
- Hx of psychotic illness, Borderline Personality Disorder, Dissociative identity d/o, Bipolar d/o type I
- Not excluded:
  - Anxiety d/o; depression
  - Eating d/o w/o purging
  - SUD; remission $\geq 60$ days
- Positive drug screening
- MDMA $>5$ occasions or last 6 months
## Second Randomized Clinical Trial: Oehen et al. 2013

### Study Design
- Randomized, placebo-controlled, double-blind, and crossover design study

### Detailed Methods

#### Stage I:
- Three MDMA-dosed sessions + PT
- Randomized 2:1 to full-dose group (n = 8) or “active placebo” (n=4)
- Full dose: 125mg MDMA + PT, **AND** 62.5mg 2.5hr after initial dose
- “active placebo”: 25mg MDMA + PT AND 12.5mg 2.5hr after initial dose
- Assessments at baseline, 3 weeks after 2nd session, 3 weeks after 3rd session; 2, 6, 12 months after 3rd MDMA session

#### Stage II
- “active placebo” w/o a clinical response; 3 sessions of full-dose tx
- Assessments at 2, 6, and 12 months after third MDMA session

#### Stage III
- Full-dosed participants without a clinical response; allocated to 2 additional high dose (150mg/75mg MDMA) sessions + PT

### Outcomes
- **Primary Outcome:** Change in CAPS score
- **Other Outcomes:** Clinical response; PDS
- **Safety Outcomes:** HR, BP, and temperature, ADEs
Second Randomized Clinical Trial: Oehen et al. 2013

- Clinical Insufficient Response

  - The investigator’s and patients’ subjective impression of a lack of improvement
  - CAPS score changes from baseline to 2 months after the third experimental session ≤ 15 points
  - Overall CAPS score still ≥ 50 points at the outcome measurement 2-months after the third MDMA-session
Second Randomized Clinical Trial: Oehen et al. 2013

Baseline Characteristics
- Average duration of PTSD was 18.3 years
- Previous therapy, mean number of months: 123 (placebo) vs 39.9 (full-dose)
- Female: 83%; no other significant differences between groups

Results
- Primary Outcome:
  - Stage I: Mean overall difference of CAPS score at 3 weeks post-therapy sessions was greater in MDMA group
    - Mean $\Delta$ CAPS of full-dose MDMA arm: -15.6 (23.5%); n = 8
    - Mean $\Delta$ CAPS of “active placebo arm”: -3.2 (5%); n = 4
    - p = 0.066; not significant
    - Significant difference in CAPS scores between 3 weeks after the 3rd session compared to the 2nd session; p = 0.016
- Secondary Outcome:
  - PDS
    - Decreased in full dose group: -8.6
    - Increased in “active placebo” group: +7.3
    - Statistically significant; p = 0.014
CAPS Scores by Group over Time

**CAPS mean total scores by group for time T0-T2 (SD)**

**T0**: Baseline < 4 weeks before MDMA and after discontinuation of psychotropic medication
- Active Placebo: 63.4 (7.9) Full Dose: 66.4 (13.6)
- T1: 3 weeks post MDMA-session 2
  - Active Placebo: 60.0 (6.8) Full Dose: 63.0 (17.8)
- T2: 3 weeks post MDMA-session 3 (end of treatment)
  - Active Placebo: 66.5 (7.6) Full Dose: 50.8 (19.7)

**CAPS Change scores (SD):**
- T0-T1: Active Placebo: -3.3 (9.9) Full dose: -3.4 (12.0)
- T1-T2: Active Placebo: 6.5 (10.3) Full dose: -12.2 (8.1)
- T0-T2: **Active Placebo**: 3.2 (15.3) Full dose: -15.6 (18.1)
Second Randomized Clinical Trial: Oehen et al. 2013

Results

- **Safety Outcomes**:
  - No serious ADEs; 2 drop outs due to ADEs
  - Day of sessions in both full-dosed and “active placebo”:
    - Headache, **insomnia, loss of appetite**, restlessness
    - Full-dosed: tight jaw, thirst, and feeling cold
    - Elevations in BP, HR, Temp in MDMA group; transient
  - Clinical response:
    - Full-dose: 4/8; all still meet PTSD criteria; reduction in severity
      - 3 of these non-responders -> Stage III; no further improvements
    - “Active placebo”: 0/4
      - All 4 -> Stage II; 2 no longer met PTSD criteria; 2 improved to moderate symptoms
  - 1 year follow-up
    - Mean Δ CAPS of full-dose MDMA arm: -24 (35%)
    - Mean Δ CAPS of Stage II arm: -35 (52%)
    - 5/12 subjects no longer met PTSD criteria
Second Randomized Clinical Trial: Oehen et al. 2013

Discussion

• Safety profile showed no difference between 25mg and 125mg of MDMA
• Three experimental sessions more effective than two
• Further improvement over 1-year follow-up
• Placebo response was not found
• MDMA a catalyst as opposed to an adjunct to therapy

Limitations

• Study was underpowered for primary outcome
• Low dose was not tolerated psychologically
• Adherence to the therapy manual at time lacking
• Inter-rater variability
• Not powered for differences in gender and countries of origin

Author’s Conclusion

• MDMA + PT can effectively be performed in an outpatient setting without severe ADEs
• Significance was not shown with symptom reduction
• Future studies should include three instead of only two preparatory sessions
Second Randomized Clinical Trial: Oehen et al. 2013

Critical Appraisal

**Strengths:**
- Randomized placebo control study
- Use of an “active placebo”
- Blinding technique
- Longer follow-up (1 year)
- Use of CAPS

**Weaknesses:**
- Additional non-MDMA based therapy sessions with full-dosed arm
- Statistical analysis may be flawed
- Small sample size
- Did not include drop-outs in analysis
- Primary outcome not significant

**Presenter’s Conclusion**
This trial’s use of an “active placebo” and a 1-year follow-up improved upon the previous study; however, possible flawed statistics with a small sample size and a primary outcome that was not significant make it difficult to determine if the high response rate at 1 year was due to MDMA + PT.

Title
Treating posttraumatic stress disorder with MDMA-assisted psychotherapy: A preliminary meta-analysis and comparison to prolonged exposure therapy

Objective
Aims to provide a comparison of the cumulative effect size of the MDMA-assisted psychotherapy studies with those of prolonged exposure therapy

Hypotheses

- MDMA-AP will have a larger cumulative effect size than PE will for primary outcome measures
- MDMA-AP will have a larger cumulative effect size than PE will for secondary outcome measures
- MDMA-AP will have lower cumulative dropout rates than PE will

Rationale

- Effect size: quantitative measure of the strength of a phenomenon
  - Larger absolute value indicates a stronger effect
  - Not based on what is statistically significant
- Large sample sizes can produce significant p-values with minimal clinical effects
- Small sample sizes can produce large effect sizes w/o significance
  - MDMA-AP studies

- The two placebo controlled clinical trials involving MDMA-AP
  - Mithoefer et al. 2011 and Oehen et al. 2013; N = 37
- Meta-analysis published on prolonged exposure therapy
  - Powers et al. 2010
    - Objective: estimate the overall efficacy of PE for PTSD relative to adequate controls
    - N = 675
    - 13 studies
    - All published randomized controlled trials of PE vs. control
    - Measures: effect sizes for primary and secondary outcomes
      - Primary: Hedges' g = 1.08
      - Secondary Hedges' g = 0.77
- Conclusion:
  - No significant difference between PE and other active treatments
  - PE is a highly effective treatment for PTSD

#### Methods
- Effects sizes and dropout rates are compared
- Effect size calculations:
  - Powers et al (2010): Hedges’ g
  - MDMA-AP: Cohen’s d
  - Corrected with Hedges and Olkin formula
- Effect sizes calculated for both primary and secondary outcomes
- Evaluated publication bias

#### Results
- **Primary Outcome Measures**
  - Overall effect size large for both PE and MDMA-AP
  - Effect size higher in MDMA-AP
- **Secondary Outcome Measures**
  - Overall effect size large for both PE and MDMA-AP
  - Effect size higher in MDMA-AP
- **Drop Out Rates**
  - PE meta-analysis: 27.0%
  - MDMA-AP: 12.7%

Results

Table 1. Summary of effect sizes by treatment type.

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges’ g primary outcome$^a$</th>
<th>Hedges’ g secondary outcome$^b$</th>
<th>Dropout rate % (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>1.08</td>
<td>0.77</td>
<td>27.0 (10.8)</td>
</tr>
<tr>
<td>MDMA-AP</td>
<td>1.17</td>
<td>0.87</td>
<td>12.7 (5.6)</td>
</tr>
</tbody>
</table>
### Discussion

- One difference to take note of: PE trials used psychological placebo conditions (psychological and waitlist controls).
- Patients undergoing PE have a heightened sense of arousal without much time to process; potential reason for high drop outs.

### Limitations

- Meta-analysis trials had much larger sample sizes (N = 675 vs N = 37).
- Differences in patient demographics.
- PE trials: patients could remain on psychotropic medications.

### Author’s Conclusion

- MDMA-AP had larger effect sizes in both primary and secondary outcomes.
- MDMA-AP had lower drop out rates.
- Results suggest that MDMA-AP offers a promising treatment for PTSD.

Critical Appraisal

**Strengths:**
- Effect sizes can be more effective tool with small sample sizes
- Converted to Hedges’ G for comparison
- Evaluated publication bias

**Weaknesses:**
- Primary and secondary outcomes were not all consistent with assessments selected
- Meta-analysis: diagnosis of PTSD; MDMA-AP: treatment refractory, severe
- Therapies not comparable
- Bias

**Presenter’s Conclusion**
The large effect sizes in both primary and secondary outcomes of the MDMA-AP trials illustrate the treatment’s effectiveness; however, the difference in patient demographics and inconsistency of assessments selected make comparisons difficult.
Case

- JH is a 34 year-old Caucasian male who is a veteran that was previously deployed in Iraq and Afghanistan. He was diagnosed with PTSD 6 years ago. He has had previous trials of venlafaxine, fluoxetine, sertraline, prazosin, paroxetine, and mirtazapine. He also received 6 months of exposure therapy but continues to experience symptoms of flashbacks, hypervigilance, and aggression. He is treatment refractory and is hesitant to trial anymore prescription medications. Given his treatment hx, would you be comfortable recommending MDMA in combination with therapy for this patient?

1. Yes
2. No
Summary and Conclusions

• Randomized controlled trials of MDMA in combination with psychotherapy to treat PTSD illustrate a high clinical response and decrease in CAPS score even at longer follow-up periods
• MDMA appears to not have severe ADEs and can be given in an outpatient setting
• Effect sizes of clinical trials are large and comparable to PE
• Given the exclusion criteria of the studies, data is not available concerning MDMA + psychotherapy for patients with comorbid psychiatric illnesses including substance abuse.
• Given sample sizes are small, larger phase 3 trials needed to further show long-term efficacy and safety of MDMA + psychotherapy for the treatment of PTSD
• Would not currently recommend without more data but remains a viable option in the future
Based on promising results like Mr. Hardin’s, the Food and Drug Administration gave permission Tuesday for large-scale, Phase 3 clinical trials of the drug — a final step before the possible approval of Ecstasy as a prescription drug.

If successful, the trials could turn an illicit street substance into a potent treatment for PTSD.
Acknowledgements

- Dr Richard Wilcox, PHD
- Dr. Brendon Hogan, PharmD
- Dr. Katerine Getchell, PharmD, BCACP
- CTVHCS Co-residents


References


The Agony and the Ecstasy: MDMA and the Treatment of PTSD

Steven Braun
PGY-1 Resident
Central Texas Veterans Health Care System