MDMA Assisted Psychotherapy for Treatment Resistant PTSD

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MDMA ASSISTED PSYCHOTHERAPY FOR TREATMENT RESISTANT PTSD

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OBJECTIVES
Recall pathophysiology, diagnostic criteria, and current treatment options for PTSD
Understand the pharmacological effects of MDMA and potential benefit in treating PTSD
Recognize strengths and limitations for the use of MDMA based on current literature

BACKGROUND
POST TRAUMATIC STRESS DISORDER

INTRODUCTION
Psychiatric condition following exposure to trauma
Lifetime prevalence: 8%
Veterans: 17%

PATHOPHYSIOLOGY
- Increased noradrenergic activity – amygdala, hypothalamus, PFC
- Decreased serotonergic activity – ACC, amygdala, hippocampus
- HPA axis dysregulation of CRF and cortisol
- Increased extra-synaptic glutamate – hippocampus and PFC

DIAGNOSTIC CRITERIA PER DSM-V
- Direct or indirect exposure to actual or threatened:
  - Death, serious injury, sexual violence
  - Witnessing trauma, indirect exposure to aversive detail, learning of a friend/relative’s exposure to trauma
- Symptoms:
  - Duration > 1 month
  - Cause significant distress and/or functional impairment
  - Not due to another cause

MDMA: Recall pathophysiology, diagnostic criteria, and current treatment options for PTSD
MDMA: Understand pharmacological effects of MDMA and potential benefit in treating PTSD
MDMA: Recognize strengths and limitations for the use of MDMA based on current literature
**Diagnostic Criteria, Cont’d**

1. **Re-experiencing**
   - Intrusive thoughts
   - Nightmares
   - Flashbacks
   - Emotional distress, physical reactivity in response to reminders

2. **Avoidance**
   - Trauma-related thoughts/feelings
   - Trauma-related reminders

2. **Negative thoughts/mood**
   - Negative affect
   - Loss of interest
   - Isolation
   - Negative thoughts of self or world
   - Extreme blame
   - Inability to recall key features

2. **Hyperarousal**
   - Irritability
   - Risky behavior
   - Hypervigilance
   - Heightened startle response
   - Decreased concentration
   - Impaired sleep

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**Assessment Tools**

- **Primary Care PTSD Screen-5**
  - 5-item scale
  - Positive screen: score >3

- **Clinician-Administered PTSD Scale for DSM-5 (CAPS)**
  - 30-item scale
  - Assess symptom frequency & severity
  - Used for weekly changes or for a one-time diagnosis

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**Clinician-Administered PTSD Scale for DSM-5 (CAPS)**

<table>
<thead>
<tr>
<th>Total Severity Score</th>
<th>Symptom Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 19</td>
<td>Asymptomatic/few symptoms</td>
</tr>
<tr>
<td>20 to 39</td>
<td>Mild PTSD/threshold</td>
</tr>
<tr>
<td>40 to 59</td>
<td>Moderate PTSD/threshold</td>
</tr>
<tr>
<td>60 to 79</td>
<td>Severe PTSD symptomatology</td>
</tr>
<tr>
<td>&gt;80</td>
<td>Extreme PTSD symptomatology</td>
</tr>
</tbody>
</table>

- 15-point change in CAPS total severity score is a clinically significant change

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**Treatment Algorithm**

**Psychotherapy**

- First line = trauma-focused therapy
  - Exposure and/or cognitive restructuring
    - Memory reconsolidation
- Second line = non-trauma-focused therapy
  - Interpersonal psychotherapy
  - Stress inoculation training
  - Present-centered therapy
PHARMACOTHERAPY

First Line Agents
- Sertraline*
- Paroxetine*
- Fluoxetine
- Venlafaxine

Second Line Agents
- Mirtazapine
- Nefazodone
- TCAs (imipramine)
- Phenelzine

MEDICATION CONSIDERATIONS

First Line Pharmacotherapy Agents
- Sertraline
- Paroxetine
- Fluoxetine
- Venlafaxine

- Re-experiencing
- Avoidance
- Negative thoughts/mood
- Hyperarousal

RECOMMENDATIONS WITH INSUFFICIENT EVIDENCE

Prazosin
- Not recommended as monotherapy or augmentation
- Insufficient evidence for nightmares

BENZODIAZEPINES AND FEAR EXTINCTION

- Benzodiazepines in conjunction with exposure therapy can undermine the long-term fear reduction
- GABA-A agonism decreases activation of the hippocampus and prefrontal cortex and can impair extinction learning

KNOWLEDGE CHECK

What are the 4 core symptoms of PTSD?

CURRENT ISSUES IN THE VETERAN POPULATION

- Higher prevalence than general populations (17% versus 8%)
- High drop-out rates with trauma-focused psychotherapies (27-40%)
- Chronic PTSD is associated with increased medical morbidity, occupational and relationship problems, decreased quality of life, overall decreased life satisfaction and happiness, and increased risk of suicide
MDMA AND ITS ROLE IN PTSD

BACKGROUND

DIFFICULTIES OF USE

Schedule I: Drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse.

Commonly abused medication with typical effects euphoria, wakefulness, intimacy, sexual arousal, and disinhibition

MDMA MECHANISM OF ACTION

Increase serotonin
Increase dopamine release
Increase noradrenaline release

HYPOTHESIS:

MDMA, via prosocial effects, increases the ability of patients to address the underlying psychopathology of PTSD through the reprocessing of traumatic memories.

PSYCHOLOGICAL EFFECTS OF MDMA IN THE CONTEXT OF PSYCHOTHERAPY

<table>
<thead>
<tr>
<th>Category</th>
<th>MDMA Induced State</th>
<th>Psychotherapeutic Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood/affect</td>
<td>Euphoria</td>
<td>Positive and fearless emotional state</td>
</tr>
<tr>
<td></td>
<td>Decreased fear/anxiety</td>
<td>Less emotional avoidance</td>
</tr>
<tr>
<td>Interpersonal behavior</td>
<td>Decreased social fearful</td>
<td>Decreased defensiveness</td>
</tr>
<tr>
<td></td>
<td>Decreased defense</td>
<td>Decreased isolation</td>
</tr>
<tr>
<td></td>
<td>Increased social behavior</td>
<td>Increased sense of trust</td>
</tr>
<tr>
<td></td>
<td>Increased sense of trust</td>
<td>Increased openness</td>
</tr>
<tr>
<td></td>
<td>Increased openness</td>
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</tbody>
</table>

MDMA BEHAVIORAL EFFECTS

Positive effects
- Euphoria and wellbeing
- Sense of closeness to others
- Greater sociability
- Sharpened sensory perception
- Greater tolerance of others views and feelings

Negative effects
- Hallucination
- Insomnia
- Anxiety
- Agitations
- Panic attacks
- Brief psychotic episodes
**MDMA PHYSIOLOGICAL EFFECTS**

<table>
<thead>
<tr>
<th>Common adverse effects</th>
<th>Cardiovascular effects</th>
<th>Increase muscle tension</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dry mouth</td>
<td>• ↑ heart rate</td>
<td>• Clenching jaw</td>
</tr>
<tr>
<td>• Ataxia</td>
<td>• ↑ blood pressure</td>
<td>• Tooth grinding</td>
</tr>
<tr>
<td>• Headache</td>
<td>• ↓ cardiac output</td>
<td>• Restless leg movement</td>
</tr>
<tr>
<td>• Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Increased muscle tension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Blurred vision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Loss of appetite</td>
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</tr>
</tbody>
</table>

**Cardiovascular effects**

- ↑ heart rate
- ↑ blood pressure
- ↓ cardiac output

**Common adverse effects**

- Dry mouth
- Ataxia
- Headache
- Nausea
- Increased muscle tension
- Blurred vision
- Loss of appetite

**MDMA PHARMACOKINETICS**

**Metabolism:**
- N-demethylation to 3,4-methylenedioxymethamphetamine (MDA)
- Demethylation occurs primarily with CYP2D6

**Excretion:**
- Metabolites are excreted by the urine
- Elimination half life is about 8 hours

Nonlinear pharmacokinetics resulting in saturation and risk of toxicity

**MDMA RELATED TOXICITY**

- Serotonin neurotoxicity
- Hepatic toxicity
- Cardiovascular toxicity
- Cerebral toxicity

**MDMA ENHANCES MOLECULES INVOLVED IN MEMORY, LEARNING, AND FEAR EXTINCTION**

**MDMA-Mediated**

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Memory, learning, and fear extinction mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>Induces affective states to alter fear memories with safe information</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Increases attention</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>Positive behavioral reinforcement</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Deactivation of memory traces</td>
</tr>
<tr>
<td>N-acetylglutamate</td>
<td>Enhances extinction learning</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Mediates socially reinforced learning</td>
</tr>
<tr>
<td>Glutamate</td>
<td>Enhances learning and memory</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Suppresses amygdala activity</td>
</tr>
<tr>
<td>Cortisol</td>
<td>Modulates learning and memory</td>
</tr>
</tbody>
</table>

**MEMORY RECONSOLIDATION AND FEAR EXTINCTION**

- MDMA-mediated enhanced serotonin release can induce positive affective and prosocial effects to signal safe and supportive setting
- Could lead to less drop out rates of trauma-focused therapy

**MDMA MEDIATES EMOTIONAL PROCESSING**

- Reduced amygdala activity
- Decreased cerebral blood flow to medial prefrontal cortex
- Increased cerebral blood flow to ventromedial prefrontal cortex
- Decreased activation of temporal lobe

**REFERENCES**

MDMA AS AN ADJUNCT TO TRADITIONAL PSYCHOTHERAPY IN THE TREATMENT OF PTSD

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 (2011)

Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Dobli R.

MITHOEFER ET AL (2011)

Inclusion/Exclusion Criteria
- Inclusion: 21-70 yr old, treatment resistant PTSD
- Exclusion: Borderline Personality Disorder or any current Axis I disorder (except for anxiety disorder, effective disorders other than bipolar disorder type I, substance abuse or dependence in remission for >60 days, and eating disorder without active purging)

Study Design
- Double-blind randomization to 125mg MDMA or Placebo
- Two 8 hours psychotherapy sessions
- Overnight stay in clinic after treatment sessions
- 90 min non-drug therapy sessions
- Daily phone contact for 1 week
- 2 month follow up

Outcomes
- Mean change in CAPS score

Patient Characteristics
- Average age 40 years
- 85% female
- PTSD for an avg of 19 + years relating to a crime

Results 125 mg MDMA (n=12)
- 53.7-point reduction in CAPS at 2 month follow up (p=0.015)

Inactive Placebo (n=8)
- 20.5-point reduction in CAPS at 2 month follow up

Overall Conclusion: There was a greater reduction in CAPS scores at the 2-month follow-up in patients who underwent MDMA assisted psychotherapy

MITHOEFER ET AL (2011) LIMITATIONS
- N=20 patients
- Long psychotherapy sessions
- 90 min next day therapy session and daily phone contact for 1 week
- MDMA group received additional psychotherapy sessions
- Inactive placebo used causing blinding difficulty

The 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 (2013)

Mithoefer MC, Wagner MT, Mithoefer A., Jerome L, Martin S, Yazar-Klonsinski B, Michel Y, Brewerton TD, and Dobli R.
**MITHOEFER ET AL (2013)**

**Inclusion/Exclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
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</thead>
<tbody>
<tr>
<td>12 patients in original MDMA group from previous study</td>
<td>Significant medical conditions (except treated hypothyroidism)</td>
</tr>
<tr>
<td>7 out of 8 patients originally in the placebo group who crossed over the MDMA group in stage 2</td>
<td>Psychiatric conditions: history of psychotic illness, bipolar disorder type I, borderline personality disorder, dissociative identity disorder, and substance abuse within 60 days of enrollment</td>
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</tbody>
</table>

**Study Procedures**

Long term follow-up of the previous study was assessed between 17 to 74 months using mailed CAPS and IES questionnaires.

**Outcomes**

Mean change in CAPS score

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**OEHEN ET AL (2013)**

**Inclusion/Exclusion Criteria**

<table>
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<tr>
<td>18 yrs or older, similar definition of treatment resistant PTSD from previous trials</td>
<td>Significant medical conditions (except treated hypothyroidism)</td>
</tr>
<tr>
<td>Medically well controlled psychiatric conditions: symptomatic chronic pain, personality disorder, substance abuse within 60 days of enrollment</td>
<td>Psychiatric conditions: history of psychotic illness, bipolar disorder type I, borderline personality disorder, dissociative identity disorder, and substance abuse within 60 days of enrollment</td>
</tr>
</tbody>
</table>

**Study Design**

<table>
<thead>
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<tbody>
<tr>
<td>MDMA Group (n=8)</td>
</tr>
<tr>
<td>2) Active placebo (n=4)</td>
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<tr>
<td></td>
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<tr>
<td>Placebo Group (n=4)</td>
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**Outcomes**

CAPS scores changes from baseline to 2 months after the 3rd MDMA session, and at 1 year.

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**OEHEN ET AL (2013)**

**Patient Characteristics**

<table>
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<td>Age 40 years</td>
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**Study Design**

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**Outcomes**

CAPS scores changes from baseline to 2 months after the 3rd MDMA session, and at 1 year.

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**Overall Conclusion**

Efficacy of MDMA assisted psychotherapy sessions failed to reach statistical significance, but it was noted that 3 sessions was more effective than 2 sessions.
OEHEN ET AL (2013)

N=12 patients
12 month follow-up could not be assessed
Active placebo less tolerable
Did not reach significance even after an increase in dose to 150mg
Lorazepam administered to 6 MDMA patients for anxiety and distress
There is no data as to what dose is effective

MITHOEFER ET AL (2018)

Inclusion/Exclusion Criteria
Inclusion: 18 yrs or older, PTSD for 6 months or more, CAPS score of 50 or more with failure to respond to or resistance to previous psychotherapy or pharmacotherapy
Exclusion: Major medical conditions (except substance abuse in remission for 60 days or more, anxiety, eating disorders, alcoholics, methadone maintained patients,heart disease,history of suicide attempts,prolonged QT interval)

Study Design
Double blind randomization:
1) Active placebo
2) 30mg MDMA
3) 75mg MDMA
4) 125mg MDMA

Stage 1:
Two 8 hour MDMA assisted sessions (1 month apart)*

Stage 2:
1) 30mg and 75mg MDMA groups crossed over to 3 additional sessions with (100-125mg)
2) 125mg MDMA group had an additional open label session

Every MDMA assisted session was followed by 3 non-drug therapy sessions, overnight stay in clinic, daily phone contact for 1 week

Outcomes
Mean change in CAPS total score from baseline to 1 month after the second experimental session

* Every active drug session required three 90 min non-drug therapy sessions to establish therapeutic alliance

MITHOEFER ET AL. (2018) LIMITATIONS
75 mg showed to be more effective, could be due to chance (n=26)
After the 30mg group crossed over to a higher dose, there was a 27 pt reduction in CAPS, could be this partial activation caused more harm to the patient
Increases in suicidal ideation
12 month follow-up cannot be assessed
45% of patients in the 125mg MDMA group still met CAPS diagnostic criteria at the end

ADVERSE EFFECTS
During the session
- Fatigue
- Anxiety
- Headache
- Muscle tension
- Premature ventricular contractions
- Suicide ideation (in 30mg and 125mg groups)

During 7 phone contact days
- Fatigue
- Anxiety
- Insomnia

3,4-Methylenedioxymethamphetamine-Assisted Psychotherapy for Post-traumatic Stress Disorder in Military, Veterans, Firefighters, and Police Officers: A Randomized, Double-Blind, Dose-Response, Phase 2 Clinical Trial (2018)


Mean age 37 years old
White males
Mean duration PTSD of 85 months

Results MDMA Results
1) 75mg (n=7): 58.3 point change in CAPS score (p=0.0005)
2) 125mg (n=12): 44.3 change in CAPS score (p=0.004)

Placebo Results
30mg MDMA (n=7): 11.4 point change in CAPS score

Overall Conclusion: 75mg doses of MDMA assisted psychotherapy led to larger decrease in CAPS scores than the active placebo and the higher 125mg treatment dose
SUMMARY

- Treatment resistance PTSD definition that limits generalizability
- Neurocognitive effects in these studies were not assessed
- Time intensive therapy and not practical
- The trials considered a significant change in CAPS score to be 15 points
- Blinding has been in issue in all studies
- Long-term follow-up cannot be accurately assessed

CONCLUSION

There is not strong enough evidence to support the use of MDAMA adjunct to psychotherapy for treatment resistant PTSD.

REFERENCES

Abbreviations

- MDMA: 3,4—Methylenedioxyamphetamine
- PTSD: Post Traumatic Stress Disorder
- NE: Norepinephrine
- PFC: Prefrontal cortex
- ACC: Anterior cingulate cortex
- HPA: Hypothalamic-pituitary-adrenal axis
- CRF: Corticotropin releasing factor
- CRH: Corticotropin releasing hormone
- TCA: Tricyclic antidepressants
- ADR: Adverse drug reaction