MDMA-Assisted Psychotherapy for PTSD

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VA Portland Health Care System
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Disclaimer

- MDMA is currently a Schedule I substance
  - The use of MDMA is restricted to clinical trial and expanded access settings
Course Learning Objectives

• Summarize MDMA-assisted psychotherapy for PTSD clinical trial outcomes

• Describe access and the pathway to FDA approval for MDMA-assisted psychotherapy

• Discuss current and upcoming VA studies of MDMA-assisted psychotherapy
PTSD

• 11-20% OIF/OEF Veterans have PTSD
• Third most prevalent service-connected disability
• >$3 billion for PTSD care/year
• $17 billion on service-connection for PTSD

www.ptsd.va.gov; Committee on the Assessment of Ongoing Efforts in the Treatment of Posttraumatic Stress Disorder; Treatment for Posttraumatic Stress Disorder in Military and Veteran Populations: Final Assessment. National Academies Press (US); 2014 Jun 17. 5
PTSD: 2017 VA/DoD Clinical Practice Guidelines

PSYCHOTHERAPY

Cognitive Processing Therapy (CPT)
CPT teaches you how to change the upsetting thoughts and feelings you have had since your trauma.

Prolonged Exposure (PE)
PE teaches you to gradually approach trauma-related memories, feelings, and situations you have been avoiding since your trauma.

Eye Movement Desensitization and Reprocessing (EMDR)
EMDR helps you process and make sense of your trauma while paying attention to a back-and-forth movement or sound (such as a light or tone).

PTSD: 2017 VA/DoD Clinical Practice Guidelines

**MEDICATIONS**

- Paroxetine
- Sertraline
- Fluoxetine
- Venlafaxine

MDMA: Timeline in Medicine

• 1912: Merck first synthesizes MDMA
• 1970’s: Psychoactive properties discovered, first legal use as adjunct to psychotherapy
• 1980’s: Recreational use increases
• 1985: DEA designates MDMA as Schedule I substance
MDMA: Timeline in Medicine

- **1986**: Multidisciplinary Association of Psychedelic Studies (MAPS) is founded
- **1992**: First Phase 1 human safety study
- **2004**: First Phase 2 clinical trial of MDMA-Assisted Psychotherapy for PTSD begins enrollment
- **2017**: FDA designates Breakthrough Therapy status
- **2018**: First Phase 3 clinical trial begins enrollment
- **2022**: Expanded Access begins enrollment at select sites
MDMA (±3,4-methylenedioxymethamphetamine)

- Ring substituted phenethylamine
- Chemically related to amphetamines
- Unique pharmacologic properties
  - ↑ social engagement (Kirkpatrick & de Wit 2015)
  - ↑ openness (Wagner et al. 2017)
  - ↑ receptiveness to positive affect (Hysek et al. 2012)
  - ↑ empathy (Hysek et al. 2014)
  - ↑ disclosure of emotional content (Baggott et al. 2015)
  - “empathogen-entactogen”

Sarparast, et al. Psychopharmacology. 2022
Ecstasy: Morbidity & Mortality

<table>
<thead>
<tr>
<th>Adulterant detected</th>
<th>Number of samples containing adulterant (n=211)</th>
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<tr>
<td>Unknown</td>
<td>90 (43%)</td>
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<tr>
<td>Methylene</td>
<td>35 (7%)</td>
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<tr>
<td>Other Cathinones</td>
<td>21 (4%)</td>
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<tr>
<td>Methamphetamine</td>
<td>13 (3%)</td>
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<tr>
<td>Benzylpiperazine</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (2%)</td>
</tr>
<tr>
<td>Mephedrone</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>2C compound</td>
<td>5 (1%)</td>
</tr>
<tr>
<td>Butylone</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>4 (0.8%)</td>
</tr>
<tr>
<td>para-Methoxyamphetamine</td>
<td>3 (0.6%)</td>
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<tr>
<td>Lysergic acid diethylamide</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Other Piperazine</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1 (0.2%)</td>
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</tbody>
</table>
Ecstasy: Morbidity & Mortality

MDMA: Pharmacodynamics/Pharmacokinetics

- Dose 80-120mg + ½ dose @ 1.5-2hrs
- Onset 30-60 mins
- Peak 75-120 mins
- Duration 3-6 hours
- Metabolism:
  - 80% CYP2D6/CYP3A4
  - 20% renally excreted unchanged
MDMA: Pharmacodynamics/Pharmacokinetics

- Receptor agonism
  - 5-HT1A/2A/2B/2C
  - α1/α2A/β-adrenergic
  - D1/D2 (dopamine)
  - M1/M2 (muscarinic)
  - H1 (histamine)
- ↑ intrasynaptic monoamines
  - 5HT>>>>>>NE>>DA
- Downstream release
  - Oxytocin/Vasopressin
  - Prolactin
  - ACTH/cortisol

5-HT1A/2A
- Elevated mood
- Decreased anxiety & fear
- Increased self-confidence
- Altered perceptions

NE/DA/Cortisol
- Hypersalience
- Activation
- Emotional Learning

Release of Oxytocin/prolactin
- Increased empathy
- Increased trust
- Decreased defensiveness
- Improved stress regulation

**MDMA/PTSD**

**PTSD is associated with:**
- Increased amygdalar activity
- Decreased hippocampal activity
- Decreased vmPFC activity
- Heightened fear response limits ability to explore trauma in therapy
- Avoidance/emotional numbing
- Lack of trust, hypervigilance

**MDMA is associated with:**
- Reduction in amygdalar activity
- Increased hippocampal activity
- Activation in vmPFC activity
- Reduction in fear and defensiveness
- Increased access to traumatic memories without flooding
- Increased sense of safety and trust

MDMA/PTSD: Therapeutic Elements

• Result of interaction between:
  • the effects of the medicine (drug)
  • the mindsets of the participant and the therapists (set)
  • the therapeutic environment (setting)
  • social support

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https://maps.org/2014/01/27/a-manual-for-mdma-assisted-therapy-in-the-treatment-of-ptsd/
MDMA/PTSD: Clinical Trial Protocol

MDMA/Placebo + Psychotherapy (~8 hours)

Experimental Session

3 Preparatory Sessions

3 Integration Sessions

3 Integration Sessions

Non-Drug Psychotherapy (90 mins)
MDMA/PTSD: Potential Adverse Effects

• Physiological
  • Muscle tightness (63% v 11%)
  • Decreased appetite (52% v 11%)
  • Nausea (30% v 11%)
  • Increase in blood pressure and heart rate

• Psychological
  • Increased anxiety (70% v 55%)

• Interpersonal
MDMA/PTSD: Contraindications

- Pre-existing cardiac or cerebrovascular disease
  - Exception is controlled hypertension with normal cardiac tests
- Primary psychotic disorder
- Bipolar I disorder
- Pregnancy
- Concomitant psychiatric medications
MDMA/PTSD: Phase 2 Trial
Chronic, Severe, Tx-Refractory PTSD (n=20)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>40.4yrs (7.2)</td>
</tr>
<tr>
<td>Male</td>
<td>15%</td>
</tr>
<tr>
<td>Married</td>
<td>50%</td>
</tr>
<tr>
<td>PTSD, # years</td>
<td>20.67 (14.42)</td>
</tr>
<tr>
<td>Disability for PTSD</td>
<td>15%</td>
</tr>
<tr>
<td>Childhood Sexual Abuse</td>
<td>40%</td>
</tr>
<tr>
<td>Hx substance use d/o</td>
<td>15%</td>
</tr>
<tr>
<td>Comorbid MDD</td>
<td>80%</td>
</tr>
<tr>
<td>Comorbid anxiety d/o</td>
<td>15%</td>
</tr>
<tr>
<td>Therapy, # years</td>
<td>4.88 (4.13)</td>
</tr>
<tr>
<td>Med Trial</td>
<td>4.2</td>
</tr>
<tr>
<td>Baseline CAPS-IV</td>
<td>79.4 (22.4)</td>
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</tbody>
</table>

Mean CAPS-IV Score

- Baseline
- 3-5 days Post Session 1
- 3-5 days Post Session 2
- 2 months Post Session 2

Effect size = 1.9

125 mg + 62.5 mg

**MDMA/PTSD: Phase 2 Trial**

**Veterans/First Responders (n=26)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>37.2yrs (10.3)</td>
</tr>
<tr>
<td>Male</td>
<td>73%</td>
</tr>
<tr>
<td>Military Trauma (vs firefighters/police)</td>
<td>85%</td>
</tr>
<tr>
<td>PTSD, # years</td>
<td>7.12 (5.33)</td>
</tr>
<tr>
<td>Pre-Study Therapy</td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>92%</td>
</tr>
<tr>
<td>Prolonged Exposure</td>
<td>19%</td>
</tr>
<tr>
<td>Group Therapy</td>
<td>27%</td>
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<tr>
<td>Pre-Study Psychiatric Meds</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>96%</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>88%</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>38%</td>
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<tr>
<td>Sleep Aids</td>
<td>50%</td>
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<tr>
<td>Comorbid MDD</td>
<td>77%</td>
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<tr>
<td>Suicidal Ideation, history</td>
<td>85%</td>
</tr>
<tr>
<td>Suicidal Behavior, history</td>
<td>42%</td>
</tr>
<tr>
<td>Baseline CAPS-IV</td>
<td>86.5 (16.2)</td>
</tr>
</tbody>
</table>

Effect Sizes:
- 75mg (v 30mg)     2.8
- 125mg (v 30mg)    1.1
- 75mg (v 125mg)    1.7
MDMA/PTSD: Phase 2 Trials (n=103)

Control Group (0-40 mg, n=31)
- Subjects with 15 point drop in CAPS-IV:
  - No: 58%
  - Yes: 42%
- Subjects with 15 point drop & did not meet PTSD criteria:
  - No: 81%
  - Yes: 19%

Active MDMA Group (75-125 mg, n=72)
- Subjects with 15 point drop in CAPS-IV:
  - No: 78%
  - Yes: 22%
- Subjects with 15 point drop & did not meet PTSD criteria:
  - No: 47%
  - Yes: 53%

Subjects did not meet PTSD criteria at 12-month follow-up (n=90)
- No: 68%
- Yes: 32%
MDMA/PTSD: Phase 3 Trial (n=90)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(n = 90)</th>
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<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>41 yrs (11.9)</td>
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<tr>
<td>Female</td>
<td>65.6%</td>
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<tr>
<td>PTSD, # years</td>
<td>14.1 yrs (11.5)</td>
</tr>
<tr>
<td>Dissociative subtype PTSD</td>
<td>21.1%</td>
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<tr>
<td>Veteran</td>
<td>17.8%</td>
</tr>
<tr>
<td>Comorbid MDD</td>
<td>91.1%</td>
</tr>
<tr>
<td>Previous Therapy</td>
<td>97.8%</td>
</tr>
<tr>
<td>Sertraline trial</td>
<td>18.9%</td>
</tr>
<tr>
<td>Paroxetine trial</td>
<td>6.7%</td>
</tr>
<tr>
<td>Baseline CAPS-V</td>
<td>44.1 (6.0)</td>
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</table>

Phase 3 Trial Results Published

67% of participants in the MDMA-assisted therapy group no longer had PTSD after 3 sessions, compared to 32% in the placebo with therapy group.

MDMA/PTSD: Phase 3 Trial
(n=90)

Effect size = 0.91
MDMA/PTSD: What is required for FDA-Approval?

- Complete second **Phase 3** study October 2022
- Present **New Drug Application** to FDA
- **FDA-approval** by 2023?
- If so, first FDA-approved **medication-psychotherapy combination**
  - REMS Program
  - Prescriber training
  - Therapist training and supervision

**Diagram:**
- **PART A**
  - Online Course (14 hours)
- **PART B**
  - Training Retreat (7 days)
- **PART C**
  - Experiential Learning (3+ days)
- **PART D**
  - Practice Session (1 day)
- **PART E**
  - Supervision and Evaluation
MDMA/PTSD: Cost Effectiveness

**Phase 2:** 2-3 prep + 2 MDMA + 6-8 integration
- $7,543 per patient (91.2% therapists’ compensation)
- For each 1,000 patients treated:
  - 30-yr saving to medical system = $103 million, 5,553 QALYs, averts 42.9 deaths
- Breaks even at 3.1 years

**Phase 3:** 3 prep + 3 MDMA + 9 integration
- $11,537 per patient
- For each 1,000 patients treated:
  - 30-yr saving to medical system = $132.9 million, 4,856 QALYs, and averts 61.4 deaths
- Breaks even at 3.8 years

MDMA/PTSD: Cognitive-Behavioral Conjoint Couples Therapy (n=6 couples)

Marine Veteran

2 tours in Iraq
turret gunner on a humvee

First MDMA-assisted session
MDMA/PTSD: VHA Research

- Loma Linda VA (PI: Shannon Remick)
- VA Portland Health Care System (PI: Chris Stauffer)
  - MDMA-Assisted Group Therapy for PTSD
- Bronx VA/Icahn School of Medicine (PI: Rachel Yehuda)
  - 2 vs 3 MDMA sessions
  - Training program for VA providers
  - Email Junhong.chen@va.gov
- San Diego VAMC (PI: Leslie A. Moreland)
  - MDMA-assisted couples therapy
- VA Greater Los Angeles Healthcare System (PI: Stephanie L. Taylor & Stephen Marder)

[Link: https://icahn.mssm.edu/research/center-psychedelic-psychotherapy-trauma-research]
Questions?