MDMA-Assisted Psychotherapy for Post-Traumatic Stress Disorder: Effectiveness and Value

Public Meeting — May 30, 2024

Diana Chao, Executive Director, Letters to Strangers

• Diana serves as an advisor on the Mental Health America Youth Council, who has received funding from healthcare companies. Letters to Strangers has received a $5000 donation from an executive member at Pfizer as a private individual donation.

Naomi M. Mathis, Assistant National Legislative Director, Disabled American Veterans

• No conflicts to disclose.
Clinical Experts

Jessica Maples-Keller, PhD, Assistant Professor, Emory University School of Medicine

• Dr. Maples-Keller has received funding from healthcare companies, such as COMPASS Pathways and Multidisciplinary Association of Psychedelic Studies (MAPS) for research trials on MDMA-assisted exposure therapy for PTSD.

Joar Øveraas Halvorsen, cand.psychol., PhD, Associate Professor and Consultant Clinical Psychologist, Norwegian University of Science and Technology, St. Olav's University Hospital

• No conflicts to disclose.
ICER Speakers

Sarah K. Emond, MPP
President & CEO

David Rind, MD, MSc
Senior Management Lead

Reem A. Mustafa, MD, MPH, PhD
Evidence Author

Steven D. Pearson, MD, MSc
Special Advisor

Brett McQueen, PhD
Lead Modeler
Why are we here today?

I have a lot of nightmares. They have to do with what happened to me. There are places that remind me of my trauma and there are people that remind me of my trauma, and I would avoid those at all costs. So basically, I just wanted to be alone. I don’t want to try to explain it to people. I didn’t want to have to go over my experiences every single time. I trusted no one, even my own family. I started believing that I didn’t deserve help, that I didn’t deserve to be happy.

Person with PTSD
(https://www ptsd.va.gov/apps/AboutFace/)
Why Are We Here Today?

• What happens the day these treatments receive FDA approval?

• Questions about:
  • What are the risks and benefits?
  • How do new treatments fit into the evolving landscape?
  • What are reasonable prices and costs to patients, the health system, and the government?
  • What lessons are being learned to guide our actions in the future?
The Impact on Rising Health Care Costs for Everyone

100 Million People in America Are Saddled With Health Care Debt

By Noam N. Levey
June 16, 2022

Why Delaware is eyeing a 27% premium hike on state employees' health insurance

Amanda Fries
Delaware News Journal
Published 4:35 a.m. ET Feb. 1, 2024 | Updated 9:29 p.m. ET Feb. 6, 2024
Organizational Overview

• New England CEPAC

• Institute for Clinical and Economic Review (ICER)
Funding 2024

- Nonprofit Foundations: 68%
- Manufacturer Contributions: 14%
- Health Plans and Provider Group Contributions: 8%
- ICER Analytics Subscribers: 9%
- Philanthropy/Other: 1%

ICER Policy Summit and non-report activities only
How Was the ICER Report Developed?

- Scoping with guidance from patients, clinical experts, manufacturers, and other stakeholders
- ICER evidence analysis in collaboration with University of Kansas Medical Center and cost-effectiveness modeling in collaboration with University of Colorado Anschutz Medical Campus
- Public comment and revision
- Expert reviewers
  - Diana Chao, BA, Letters to Strangers
  - Arash Javanbakht, MD, Wayne State University School of Medicine
  - Dominic Trépel, PhD, Trinity College Dublin
- How is the evidence report structured to support NE CEPAC voting and policy discussion?
Value Assessment Framework: Long-Term Value for Money

- Special Social/Ethical Priorities
- Benefits Beyond “Health”
- Total Cost Overall
  Including Cost Offsets
- Health Benefits:
  Return of Function, Fewer Side Effects
- Health Benefits:
  Longer Life
# Agenda (ET)

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>10:00 AM</td>
<td>Meeting Convened and Opening Remarks</td>
</tr>
<tr>
<td>10:20 AM</td>
<td>Presentation of the Clinical Evidence</td>
</tr>
<tr>
<td>11:00 AM</td>
<td>Presentation of the Economic Model</td>
</tr>
<tr>
<td>11:40 AM</td>
<td>Public Comments and Discussion</td>
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<tr>
<td>12:15 PM</td>
<td>Lunch Break</td>
</tr>
<tr>
<td>12:50 PM</td>
<td>NE CEPAC Deliberation and Vote</td>
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<tr>
<td>1:50 PM</td>
<td>Break</td>
</tr>
<tr>
<td>2:00 PM</td>
<td>Policy Roundtable Discussion</td>
</tr>
<tr>
<td>3:30 PM</td>
<td>Reflections from New England CEPAC</td>
</tr>
<tr>
<td>4:00 PM</td>
<td>Meeting Adjourned</td>
</tr>
</tbody>
</table>
Presentation of the Clinical Evidence

Reem A. Mustafa, MD, MPH, PhD
Professor of Medicine, Division of Nephrology and Hypertension
Director, Outcomes and Implementation Research, University of Kansas Medical Center
Key Collaborators

<table>
<thead>
<tr>
<th>Team Role</th>
<th>Assigned Team Member</th>
</tr>
</thead>
<tbody>
<tr>
<td>Research Lead</td>
<td>Dmitriy Nikitin, MSPH</td>
</tr>
<tr>
<td>Research Assistant</td>
<td>Emily Nhan, BA</td>
</tr>
</tbody>
</table>

Disclosures

Financial support provided to Dr. Mustafa from the Institute for Clinical and Economic Review (ICER)

Dr. Mustafa and other members of ICER (Nikitin, Nhan) have no conflicts to disclose defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.
Post-Traumatic Stress Disorder (PTSD)

- PTSD is a complex psychiatric disorder associated with substantial disability and poor quality of life. It can involve nightmares, flashbacks, intrusive thoughts, and avoidance of trauma reminders

- In the US, about 13 million adults (5%) experience PTSD symptoms annually

- In 2018, the total economic burden beyond normal healthcare costs for PTSD in the US was $232.2 billion ($19,630 per individual)

- PTSD is more prevalent in certain subgroups: women, veterans, racial/ethnic groups
Insights from Discussions with Patients

• ICER reached out to over 20 clinicians, 15 patient advocacy organizations, and hosted a focus group and interviews with individual patients

• PTSD makes daily activities extremely difficult for some patients, burdening patients and caregivers

• Accessing trauma-focused psychotherapies is challenging, with high dropout rates

• Despite trying various treatments, many still report persistent PTSD symptoms
Insights from Discussions with Patients

• Patients express concerns over lack of new FDA-approved PTSD treatments in 20 years

• Some patients self-medicate or experiment with illegal/unproven compounds out of desperation

• Patients perceive that successful therapy reduces symptom severity, builds coping skills, alleviates suicidality, and fosters autonomy without medication reliance
Standard of Care and Management

Trauma-focused Psychotherapy

• Prolonged Exposure Therapy
• Cognitive Behavioral Processing Therapy
• Cognitive Processing Therapy
• Eye Movement Desensitization and Reprocessing

Pharmacotherapy

• Paroxetine
• Sertraline
• Venlafaxine
• Fluoxetine
New Therapy: MDMA-Assisted Psychotherapy

- Midomafetamine (3,4-Methylenedioxymethamphetamine) capsules to be used in combination with psychological interventions, including psychotherapy and other supportive services from a health care provider

- The MDMA-AP protocol in the trials requires approximately 42 hours of therapy with two therapists per patient (84 therapist hours) and doses range from 80 to 180 mg of MDMA per session
  - Three 90-minute preparation sessions
  - Three 8-hour MDMA-AP assisted sessions
  - Nine 90-minute integration sessions

- FDA: Advisory Committee Meeting June 4, and expected decision by August 14, 2024
Scope of Review

• Population
  • Adults diagnosed with moderate-to-severe PTSD

• Intervention
  • MDMA-AP (Lykos Therapeutics, Inc.)

• Comparator
  1. Lykos-specific non-assisted psychotherapy (LSNAP). LSNAP served as control arm in pivotal trials but is not an established form of standalone psychotherapy
  2. Short-term trauma-focused psychotherapies for PTSD (e.g., Prolonged Exposure, Cognitive Behavioral Therapy)
Clinical Evidence
## Key Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Age, mean years</th>
<th>PTSD duration, mean years</th>
<th>PTSD severity, %</th>
<th>CAPS-5, mean score</th>
<th>Prior lifetime MDMA use, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAPP1</td>
<td>90</td>
<td>41</td>
<td>14.1</td>
<td>Severe: 100%</td>
<td>44.1</td>
<td>32.2%</td>
</tr>
<tr>
<td>MAPP2</td>
<td>104</td>
<td>39.1</td>
<td>16.2</td>
<td>Moderate: 27% Severe: 73%</td>
<td>39.1</td>
<td>46.2%</td>
</tr>
</tbody>
</table>

CAPS-5: Clinician-Administered PTSD Scale for DSM-5, MDMA: Midomafetamine, n: number, N: total number, PTSD: posttraumatic stress disorder
Maintenance of Blinding

• The psychoactive and physiological effects of MDMA make it difficult to maintain blinding of participants and therapists

• In MAPP2 trial:
  • 94% of participants in the MDMA-AP arm correctly guessed their assigned treatment
  • 75% of participants in the LSNAP arm did so

• An informal evaluation of the MAPP1 trial indicated comparable findings

• Maintenance of blinding among trial therapists was not assessed in either the MAPP1 or MAPP2 trials

LSNAP: Lykos-specific non-assisted psychotherapy, MDMA: Midomafetamine
Primary Treatment Goals: Reduction in PTSD Symptoms

• Clinician-Administered PTSD Scale for DSM–5 (CAPS-5)
  • 30-item questionnaire (0-80 total score) corresponding to the DSM-5 diagnosis for PTSD. Requires the identification of a single index trauma to serve as the basis of symptom inquiry
  • Primary outcome: Change from baseline through 18 weeks
    • Responder (≥10-point decrease on CAPS-5),
    • Loss of Diagnosis (no longer meeting symptom criteria),
    • Remission (loss of diagnosis and a total CAPS-5 score of ≤11)
Question 1: Reduction in PTSD Symptoms

- The CAPS-5 score changed [Mean difference (MD) -10.18 (95% CI -13.80, -6.56)] in the MDMA-AP versus LSNAP study arm
  - No established clinically meaningful threshold on CAPS-5, collaborator agreement with FDA established 10 points as clinically meaningful
- The standardized effect size (Cohen's d) between the two groups was 0.8, suggesting a large treatment effect size
- Patients treated with MDMA-AP may be more likely than LSNAP to:
  - Be treatment responders RR 1.32
  - Achieve loss of diagnosis RR 1.7
  - Meet criteria for remission RR 2.86
Durability of Treatment Effect

- Phase III trial participants showed reduction in PTSD symptoms two months after the final experimental session, demonstrating short-term health benefit
- Long-term follow-up data from MAPP1 and MAPP2 trials are not yet available
Harms

- Common adverse events with MDMA-AP included muscle tightness, decreased appetite, bruxism, hyperhidrosis, fatigue, restlessness, and insomnia.

- Transient increases in blood pressure, body temperature, and heart rate were observed with MDMA-AP.

- Limited evidence on risk of MDMA abuse or cardiac events due to short-term (18 weeks) follow-up.

Harms: Risk of Suicide Ideation

• High baseline risk of suicidal ideation (~90% of trial participants with positive lifetime suicidal ideation) - Risk of suicide ideation (RR: 0.89; 95% CI 0.64 to 1.24) with MDMA-AP vs LSNAP

• MDMA-AP lowered the risk of treatment withdrawals (RR: 0.32)
  • Higher rates of discontinuation occurred in the LSNAP arms of the MAPP1 and 2 trials (16% in both MAPP1 and 2) compared to the MDMA-AP arms (1.9 and 8.7%)

• At least one known instance, a participant who suspected they were receiving LSNAP treatment withdrew from the study

CI: confidence interval, MDMA-AP: MDMA-assisted psychotherapy, RR: relative risk
Harms: Therapist Misconduct

• There have been concerns that MDMA heightens suggestibility and lowers judgement and for this reason in the phase II and III trials there were pairs of therapists (male and female) to reduce this risk

• Despite these measures, in the phase II trial there was a widely-reported serious event where a therapist sexually assaulted a patient

• Led to suspension of Phase II study to review safety and compliance
Other Outcomes of Interest

- Due to the considerable uncertainties about these seemingly positive trials, we will not discuss the results of secondary and exploratory outcomes (e.g., functional disability, depression symptoms, alcohol abuse...etc.)
Question 2: MDMA-AP vs TFPs

Differences in study design, baseline medication use, patient criteria, and therapies themselves make direct comparisons of effectiveness between MDMA-AP and other TFP challenging:

• MDMA-AP has demonstrated a moderate to large treatment effect size for reducing PTSD symptoms, similar to some TFPs vs usual care
• Around 40% of MDMA-AP participants achieved PTSD remission, compared to ~53-63% remission rates reported for CBT in a meta-analysis
• Treatment discontinuation rates were lower for MDMA-AP (5%) compared to some TFPs (13-30% dropout)
• MDMA-AP protocol is more resource-intensive (42 hrs, 2 therapists) compared to typical TFP delivery (8-20 hrs, 1 therapist)

CBT: cognitive behavioral therapy, LSNAP: Lykos-specific non-assisted psychotherapy, MDMA-AP: MDMA-assisted psychotherapy, PTSD: posttraumatic stress disorder, TFP: trauma-focused psychotherapy
Concerns About Conduct of MDMA-AP Trials

• ICER spoke to a therapist and a small number of patients involved in the MAPP trials, and experts familiar with the research space. We heard concerns about the conduct of the trials by Lykos Therapeutics including design choices affecting result interpretation and potential misconduct.

• Strong prior beliefs about psychedelics' value among trial participants and therapists.
  • Pressures to report favorable outcomes.
  • Severe negative outcomes being downplayed/underreported.

• Instances of patients prevented from participating in long-term follow-up.
Controversies and Uncertainties

- Trials likely unblinded, making control comparison difficult
- Potential biases in reporting benefits/harms – see Section 2.1
- CAPS-5, while commonly used, may not fully capture PTSD changes for certain populations
- Small samples/short follow-up may underestimate harms
- Implementing MDMA-AP could be very challenging for healthcare systems

CAPS-5: Clinician-Administered PTSD Scale for DSM-5, MDMA-AP: MDMA-assisted psychotherapy, PTSD: posttraumatic stress disorder
Benefits Beyond Health and Special Ethical Priorities

• Substantial unmet need despite currently available treatments

• Women, veterans and racial/ethnic minority groups in the US have a higher burden of PTSD. If efficacious, MDMA-AP may have potential to reduce health disparities

• The extent to which MDMA-AP may impact caregivers' quality of life and functioning is unclear, due to uncertainty around the therapy's effectiveness in reducing patients' PTSD symptoms
Summary

• The MAPP trials showed improvements in many patients treated with MDMA-AP, with few short-term harms

• While this suggests MDMA-AP could be an important addition to PTSD treatment options, there are concerns about the validity and generalizability of the results

• Multiple experts believe additional trials are needed to prove the benefits outweigh potential harms, despite being hopeful about using psychedelics for PTSD

• ICER cannot assess the frequency of misreporting benefits and/or harms, and thus the overall net benefit of MDMA-AP. We continue to believe that it is vital that regulatory bodies investigate these issues since ICER is unable to assess them

• Comparative studies of MDMA-AP against gold-standard TFP are necessary to evaluate its efficacy and guide clinical implementation
# ICER Evidence Ratings for MDMA-AP

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comparator</th>
<th>Population</th>
<th>Evidence Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMA-AP</td>
<td>Lykos Specific Non-Assisted Psychotherapy</td>
<td>Adults with moderate to severe PTSD</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Short-term Trauma Focused Psychotherapy</td>
<td>Adults with moderate to severe PTSD</td>
<td>I</td>
</tr>
</tbody>
</table>

I: Insufficient – Any situation in which the level of certainty in the evidence is low
“One hundred and nine therapists and principal/co-investigators contributed to the Phase 3 trials of MDMA-AP for PTSD. To our knowledge, none of them were consulted before the preliminary report was issued. However, this group is in the strongest position to describe the studies and address accusations related to inappropriate study design and conduct. In the absence of such input, a number of assertions in the ICER report represent hearsay, and should be weighted accordingly.”
Comments

• ICER Report: “Some patients were prevented from entering the long-term follow-up study and felt this was done to keep these negative outcomes out of the data set”

• Principal Investigator: “This is untrue. No participants were prevented from entering the phase 3 long-term follow-up study (MPLong).”

• ICER Response: “We had first-hand reports of such events. We cannot be certain that these reports were accurate, but we do wonder whether [the PI] is certain that this could not have occurred.”
Questions?
Presentation of the Economic Evidence

Brett McQueen, PhD
Associate Professor
University of Colorado Anschutz Medical Campus
## Key Review Team Members

<table>
<thead>
<tr>
<th>Team Role</th>
<th>Assigned Team Member</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modeler(s) and Economics Lead</td>
<td>R. Brett McQueen</td>
</tr>
<tr>
<td>Modeling team member</td>
<td>Antal Zemplenyi</td>
</tr>
<tr>
<td>Modeling team member</td>
<td>Mike DiStefano</td>
</tr>
</tbody>
</table>

## Disclosures

Financial support provided to the University of Colorado from the Institute for Clinical and Economic Review (ICER)

R. Brett McQueen has no conflicts to disclose defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.
Objective

This exploratory analysis compared the cost-effectiveness of MDMA-AP to no short-term intervention for PTSD as estimated by the effectiveness of the control arm of the randomized trial (LSNAP).

PTSD

MDMA: 3,4-methylenedioxyamphetamine, MDMA-assisted psychotherapy, PTSD: Post-traumatic stress disorder; LSNAP: Lykos-specific non-assisted psychotherapy
## Unmet Need

<table>
<thead>
<tr>
<th>Condition</th>
<th>Absolute evLY Shortfall</th>
<th>Proportional evLY Shortfall</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD</td>
<td>7.4</td>
<td>21%</td>
</tr>
<tr>
<td><strong>Other Example Conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Depressive Disorder</td>
<td>9.7</td>
<td>32%</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>18.9</td>
<td>52%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>2.6</td>
<td>19%</td>
</tr>
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</table>
Methods in Brief
## Methods Overview

<table>
<thead>
<tr>
<th>Methods</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>Decision tree and Markov cohort model</td>
</tr>
<tr>
<td>Setting</td>
<td>United States</td>
</tr>
<tr>
<td>Perspective</td>
<td>Health Care Sector Perspective and Modified Societal Perspective</td>
</tr>
<tr>
<td>Time Horizon</td>
<td>Lifetime</td>
</tr>
<tr>
<td>Discount Rate</td>
<td>3% per year (costs and outcomes)</td>
</tr>
<tr>
<td>Cycle Length</td>
<td>1 year</td>
</tr>
<tr>
<td>Primary Outcome</td>
<td>Cost per quality-adjusted life year (QALY) gained; equal value of life years gained</td>
</tr>
</tbody>
</table>

evLY: equal value of life years gained, QALY: quality-adjusted life years
Model Schematic

Decision tree: 0-12 months – assessment of response

- Asymptomatic (M1)
- Mild (M2)
- Moderate (M3)
- Severe (M4)
- Death (M5)

MDMA-AP

- No short-term intervention as estimated by control arm

Markov Model: 12 months to lifetime

- M1: Asymptomatic (M1)
- M2: Mild (M2)
- M3: Moderate (M3)
- M4: Severe (M4)
- M5: Death (M5)

Need for one-time re-treatment from M1, M2, and M3

MDMA: 3,4-methylenedioxymethamphetamine, MDMA-assisted psychotherapy, M: Markov state, asymp = asymptomatic
Key Assumptions

• The cost of standard of care reflected real-world treatment scenarios instead of protocol driven assumptions on treatment without MDMA

• Simulated CAPS-5 scores from recent phase III trial evidence to generate post-intervention effectiveness for health state distributions in model

• Utilities across PTSD severity distributions from the first phase III trial were used to estimate treatment effects on quality of life outcomes at follow-up for both arms of the model
## Key Model Inputs: Initial and post-trial state distributions (PTSD severity)

<table>
<thead>
<tr>
<th>PTSD Health State</th>
<th>Baseline Distribution</th>
<th>Post-Trial Distribution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MDMA-AP</td>
<td>Placebo</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>0%</td>
<td>46.2%</td>
<td>21.4%</td>
</tr>
<tr>
<td>Mild</td>
<td>0%</td>
<td>23.9%</td>
<td>27.3%</td>
</tr>
<tr>
<td>Moderate</td>
<td>26.92%</td>
<td>20.0%</td>
<td>25.7%</td>
</tr>
<tr>
<td>Severe</td>
<td>73.08%</td>
<td>9.9%</td>
<td>25.7%</td>
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</table>

PTSD: Post-traumatic stress disorder, MDMA: 3,4-methylenedioxymethamphetamine, MDMA-assisted psychotherapy.
### Key Model Inputs: Costs

<table>
<thead>
<tr>
<th>Direct Costs</th>
<th>Input†</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of intervention (MDMA + Lykos-specific manualized therapy)*</td>
<td>$23,117</td>
<td>Marseille et al. 2020; Mitchell et al. 2023; CPT codes</td>
</tr>
<tr>
<td>Asymptomatic health state</td>
<td>$4,830</td>
<td>Davis et al. 2022; Walker et al. 2003; National Institute of Mental Health: PTSD statistics 2007; authors’ calculation</td>
</tr>
<tr>
<td>Mild health state</td>
<td>$9,670</td>
<td></td>
</tr>
<tr>
<td>Moderate health state</td>
<td>$13,340</td>
<td></td>
</tr>
<tr>
<td>Severe health state</td>
<td>$19,720</td>
<td></td>
</tr>
</tbody>
</table>

MDMA: 3,4-methylenedioxymethamphetamine, MDMA-assisted psychotherapy

*Using a placeholder price of $10,000 per treatment course for MDMA drug costs. Intervention costs also include the costs of Lykos-specific non-assisted psychotherapy.

†Inputs varied in sensitivity analyses
### Key Model Inputs: Utilities

<table>
<thead>
<tr>
<th>PTSD Health State</th>
<th>Input†</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0.83</td>
<td>Marseille et al. 2022</td>
</tr>
<tr>
<td>Moderate</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0.61</td>
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</tr>
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</table>

PTSD: Post-traumatic stress disorder

† Inputs varied in sensitivity analyses
## Key Model Inputs: Retreatment and Mortality

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Input†</th>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td>Annualized retreatment rate (one time within the first 5 years)</td>
<td>6%</td>
<td>Benitez et al. 2012</td>
</tr>
<tr>
<td>PTSD all-cause mortality risk</td>
<td>RR: 1.47 (95% CI: 1.06-2.04)</td>
<td>Nilaweera et al. 2023</td>
</tr>
<tr>
<td>PTSD suicide mortality risk</td>
<td>RR: 2.09 (95% CI: 1.11-3.94)</td>
<td>Akbar et al. 2022; calibration to Centers for Disease Control data on deaths by suicide</td>
</tr>
</tbody>
</table>

PTSD: Post-traumatic stress disorder
† Inputs varied in sensitivity analyses
Results
## Exploratory Results

<table>
<thead>
<tr>
<th>Drug</th>
<th>Intervention Costs</th>
<th>Non-Intervention Costs</th>
<th>Total Cost</th>
<th>PTSD-Related Deaths by Suicide per 100,000 people</th>
<th>QALYs</th>
<th>Life Years</th>
<th>evLYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMA-AP*</td>
<td>$28,000</td>
<td>$207,000</td>
<td>$235,000</td>
<td>478</td>
<td>17.5</td>
<td>21.50</td>
<td>17.5</td>
</tr>
<tr>
<td>Placebo</td>
<td>$0</td>
<td>$267,000</td>
<td>$267,000</td>
<td>697</td>
<td>16.2</td>
<td>21.48</td>
<td>16.2</td>
</tr>
</tbody>
</table>

PTSD: Post-traumatic stress disorder  evLYs: equal value of life years, QALYs: quality-adjusted life years, MDMA: 3,4-methylenedioxymethamphetamine, MDMA-assisted psychotherapy

*Using a placeholder price of $10,000 per treatment course for MDMA drug costs. Intervention costs also include the costs of Lykos-specific non-assisted psychotherapy.
## Exploratory Incremental Results

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost per QALY Gained</th>
<th>Cost per Life Year Gained</th>
<th>Cost per evLY Gained</th>
<th>Cost per death by suicide averted</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMA-AP* vs. placebo</td>
<td>Less costly, more effective</td>
<td>Less costly, more effective</td>
<td>Less costly, more effective</td>
<td>Less costly, more effective</td>
</tr>
</tbody>
</table>

MDMA: 3,4-methylenedioxymethamphetamine, MDMA-assisted psychotherapy, evLYs: equal value of life years, QALYs: quality-adjusted life years

*Using a placeholder price of $10,000 per treatment course for MDMA drug costs. Intervention costs also include the costs of Lykos-specific non-assisted psychotherapy.
One Way Sensitivity Analyses

Proportion of Mild PTSD MDMA-AP Post-Intervention
Health utility for Severe PTSD
Proportion of Moderate PTSD MDMA-AP Post-Intervention
Proportion of Severe PTSD MDMA-AP Post-Intervention
Health utility for Asymptomatic PTSD
Mortality Multiplier for PTSD
Health utility for Moderate PTSD
Health utility for Mild PTSD

Incremental QALYs Per Person (MDMA-AP vs. Placebo)

MDMA: 3,4-methylenedioxymethamphetamine, MDMA-assisted psychotherapy, PTSD: Post-traumatic stress disorder
# Probabilistic Sensitivity Analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost-Effective at $50,000 per QALY and evLY</th>
<th>Cost-Effective at $100,000 per QALY and evLY</th>
<th>Cost-Effective at $150,000 per QALY and evLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMA-AP*</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

MDMA: 3,4-methylenedioxymethamphetamine, MDMA-assisted psychotherapy, QALY: quality-adjusted life years

*Using a placeholder price of $10,000 per treatment course for MDMA drug costs. Intervention costs also include the costs of Lykos-specific non-assisted psychotherapy.
## Scenario Analyses

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Exploratory Result</th>
<th>Scenario Analysis 1: Modified Societal Perspective</th>
<th>Scenario Analysis 2: Time Horizon of 3 Years</th>
<th>Scenario Analysis 3: Time Horizon of 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMA-AP*</td>
<td>Less costly, more effective</td>
<td>Less costly, more effective</td>
<td>$157,000 per QALY and evLY</td>
<td>$81,000 per QALY and evLY</td>
</tr>
</tbody>
</table>

MDMA: 3,4-methylenedioxymethamphetamine, MDMA-assisted psychotherapy, QALY: quality-adjusted life years

*Using a placeholder price of $10,000 per treatment course for MDMA drug costs. Intervention costs also include the costs of Lykos-specific non-assisted psychotherapy.
Limitations

• Data regarding the impact of MDMA-AP in terms of a change in the distribution of PTSD across stages of severity was requested from Lykos Therapeutics and not provided

• No observed treatment effect estimates on health-related quality of life utility scores available from the MAPPS trials

• No evidence on MDMA-AP versus other short-term trauma focused therapies
Comments Received

• Inclusion of costs and benefits of spillover effects of PTSD, e.g., substance abuse disorders

• Real-world mortality and other inputs across PTSD severity states

• Caregiver burden in modified societal perspective
Conclusions

- Exploratory analysis of MDMA-AP provides clinical benefit in terms of gains in QALYs, evLYs, and deaths by suicide as compared to no short-term intervention.

- Key drivers were short-term improvements in PTSD-related symptoms and quality of life by severity of PTSD-related symptoms.
Questions?
Public Comment and Discussion
Conflicts of Interest:

- Sarah works as a research assistant at McGill university, where professors/labs may receive funding from health care companies.
Lily Ross, MDiv, PhD
Independent Researcher, Journalist

Conflicts of Interest:

• No conflicts to disclose.
Molly Richardson
Patient Expert

Conflicts of Interest:

- No conflicts to disclose.
Conflicts of Interest:

- No conflicts to disclose.
Conflicts of Interest:

- No conflicts to disclose.
Meaghan Buisson, BSc
Independent Researcher

Conflicts of Interest:

• No conflicts to disclose.
Lunch

Meeting will resume at 12:50 PM ET
Voting Questions
Clinical Evidence
Patient Population for all questions:
Adults with a diagnosis of moderate-to-severe PTSD; patients may be receiving ongoing therapy and/or medications such as SSRI antidepressants.
1. Is current evidence adequate to demonstrate that the net health benefit of MDMA-AP is superior to that of not treating with MDMA-AP?
2. Is the current evidence adequate to demonstrate that the net health benefit of MDMA-AP is superior to that of short-term trauma-focused psychotherapies (TFP)?
Benefits Beyond Health and Special Ethical Priorities
To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements:
3. There is substantial unmet need despite currently available treatments.
4. This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.
To help inform judgments of overall long-term value for money, please indicate your level of agreement with the following statements based on the relative effects of MDMA-AP versus not treating with MDMA-AP:
5. The treatment is likely to produce substantial improvement in caregivers’ quality of life and/or ability to pursue their own education, work, and family life.
6. The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.

Start presenting to display the poll results on this slide.
Long-Term Value for Money
Given the available evidence on comparative clinical effectiveness and incremental cost effectiveness, and considering benefits beyond health and special ethical priorities, what is the long-term value for money of MDMA-AP versus not treating with MDMA-AP?
Break

Meeting will resume at 2:00PM ET
Policy Roundtable
# Policy Roundtable

<table>
<thead>
<tr>
<th>Participant</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diana Chao</strong>, Executive Director, Letters to Strangers</td>
<td>Diana serves as an advisor on the Mental Health America Youth Council, who has received funding from healthcare companies. Letters to Strangers has received a $5000 donation from an executive member at Pfizer as a private individual donation.</td>
</tr>
<tr>
<td><strong>Peter Glassman, MBBS, MSc</strong>, Chair, Medical Advisory Panel, VA Pharmacy Benefits Management Services</td>
<td>Peter Glassman is a full-time employee at the U.S. Department of Veterans Affairs.</td>
</tr>
<tr>
<td><strong>Jessica Maples-Keller, PhD</strong>, Assistant Professor, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine</td>
<td>Dr. Maples-Keller has received funding from healthcare companies, such as COMPASS Pathways and Multidisciplinary Association of Psychedelic Studies (MAPS) for research trials on MDMA-assisted exposure therapy for PTSD.</td>
</tr>
<tr>
<td><strong>Naomi M. Mathis</strong>, Assistant National Legislative Director, Disabled American Veterans</td>
<td>No conflicts to disclose.</td>
</tr>
<tr>
<td><strong>Joar Øveraas Halvorsen, cand.psychol., PhD</strong>, Associate Professor and Consultant Clinical Psychologist, Norwegian University of Science and Technology, and St. Olav's University Hospital</td>
<td>No conflicts to disclose.</td>
</tr>
<tr>
<td><strong>Marina Sehman, PharmD, CSP</strong>, Clinical Director, IPD Analytics</td>
<td>Marina Sehman is a full-time employee at IPD Analytics.</td>
</tr>
</tbody>
</table>
New England CEPAC Council Reflections
Next Steps

• Meeting recording posted to ICER website next week

• Final Report published on or around June 27th, 2024
  • Includes description of New England CEPAC votes, deliberation, policy roundtable discussion

• Materials available at: https://icer.org/assessment/ptsd-2024
Adjourn