MDMA-Assisted Therapy for Posttraumatic Stress Disorder

Darrick May, MD
Psychiatrist / Medical Director
Boulder Integrated Health

June 17, 2022
Disclosures

- Dr. May receives wages as an independent contractor from MAPS Public Benefit Corporation (MPBC)—whose only shareholder is the Multidisciplinary Association for Psychedelic Studies (MAPS), a 501(c)(3) non-profit research and educational organization—for his work on MDMA studies.

- Multiple Roles in MDMA-Assisted Therapy Studies:
  - Co-Principal Investigator at the Fort Collins, CO site
  - Study Therapists and Physician at the Boulder, CO site
  - Associate Supervisor for Therapist Training Program
  - Therapist Adherence Rater (previously)

- Many slides herein were created by MPBC staff
Learning Objectives

1) Gain familiarity with the process of how MDMA-assisted therapy is provided in the context of FDA-approved studies

2) Describe the results of the first phase 3 study of MDMA-assisted therapy for PTSD
Public Benefit Model of Drug Development

MAPS funds MPBC, covering research, clinical trials, programs, and operations

Non-profit Drug Development

Proceeds furthers MAPS mission

501c3 non-profit, founded 1986

Sponsors psychedelic-assisted therapy trials

Educates people to benefit from the careful uses of psychedelics and marijuana

Advocates for healing and justice in evidence-based, equitable, and compassionate frameworks

Founded in 2014

Catalyzes healing through psychedelic drug development

Trains therapists in psychedelic-assisted therapies

Pioneers equitable access, prioritizing public benefit above profit
## MAPS Core Values

1. **Integrity**
   - **Information is shared transparently.** Communications are respectful, honest, and forthright, and our decisions are informed by compassion and research.

2. **Perseverance**
   - We mindfully persist in the face of challenges, and we build with a balanced, long term vision.

3. **Curiosity**
   - We are always open to new possibilities: we try new things, take risks, and learn from our mistakes.

4. **Equity**
   - We work for ethical and equitable access for all.
Why MDMA?

MDMA is capable of inducing unique psychopharmacological effects, such as:

- Decreased feelings of fear and defensiveness
- Increased feelings of wellbeing
- Increased sociability and extroversion
- Increased interpersonal trust
- An alert state of consciousness

MDMA was used as an adjunct to psychotherapy by a considerable number of psychiatrists and therapists before it was placed in Schedule I in 1985 in contradiction of available evidence.
## History of MDMA

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1912</td>
<td>1st synthesized by Merck in Germany</td>
</tr>
<tr>
<td>1950s</td>
<td>U.S. Army studied at U of M as a toxin/stimulant for chemical warfare</td>
</tr>
<tr>
<td>1970s</td>
<td>Shulgin synthesizes MDMA and introduces to Leo Zeff. 1st paper published.</td>
</tr>
<tr>
<td>1980s</td>
<td>Used by therapists to enhance psychotherapy</td>
</tr>
<tr>
<td>1980s</td>
<td>Becomes popular street drug</td>
</tr>
<tr>
<td>1985</td>
<td>Temporarily placed on Schedule 1</td>
</tr>
<tr>
<td>1986</td>
<td>MAPS is founded, 28-Day General Tox studies completed</td>
</tr>
<tr>
<td>1988</td>
<td>Permanently placed on Schedule 1</td>
</tr>
<tr>
<td>1992</td>
<td>FDA approves MAPS-funded Phase 1 study</td>
</tr>
<tr>
<td>2001</td>
<td>FDA approves IND for PTSD</td>
</tr>
<tr>
<td>2003</td>
<td>First PTSD trial begins</td>
</tr>
<tr>
<td>2016</td>
<td>End of Phase 2 Meeting with FDA</td>
</tr>
<tr>
<td>2017</td>
<td>FDA grants breakthrough designation to treatment</td>
</tr>
<tr>
<td>2018</td>
<td>Phase 3 trials begin</td>
</tr>
<tr>
<td>2020</td>
<td>Phase 3 pivotal trial completed</td>
</tr>
</tbody>
</table>
Progression of MDMA clinical research

- **November 2001**: First Phase 2 protocol approved by FDA. MDMA-assisted psychotherapy for PTSD.
- **February 2004**: DEA approval granted.
- **April 2004**: First participant enrolled.
- **As of 2016**: Six Phase 2 MDMA/PTSD clinical trials completed.
- **August 2017**: FDA grants Breakthrough Therapy Designation. Agreement on Special Protocol Assessment reached for Phase 3 trials.
MDMA Pharmacodynamics

- Triple reuptake inhibitor:
  - Serotonin > Norepinephrine > Dopamine

- MAO-A Inhibitor

- VMAT-2 Inhibitor

- Postsynaptic activation of monoamine receptors triggers release of oxytocin, cortisol, arginine vasopressin, prolactin, ACTH

References available in MDMA Investigator’s Brochure www.maps.org
PTSD: Difficulty in Extinction of Fear

- Re-experiencing traumatic event (e.g., flashbacks, nightmares)
- Avoidance of trauma-related thoughts/situations
- Negative changes in beliefs & feelings (e.g., exaggerated self-blame, isolation)
- Hyperarousal & reactivity (e.g., irritability, hypervigilance)
- At least 1-month duration of symptoms
- Symptoms cause distress or functional impairment

Rauch et al. 2006, dsm-5
MDMA Facilitates Learning to Overcome Fear Memories

In rodents:
- Promotes fear extinction in mice
- Modifies fear memories during reconsolidation in rats
- Triggers neuroplasticity in context of learning paradigm in mice via BDNF, mediated by SERT
- Reopens critical period in social reward learning in adult mice, which closes after adolescence

In humans without PTSD:
- ↓ amygdala & insula activation (fear/anxiety-related behavior)
- ↑ connectivity between amygdala & hippocampus

In humans with PTSD:
- Reprocessing of traumatic memories and less internalization of fear memories
- Reduction in activation of middle/posterior cingulate cortex & medial prefrontal cortex correlates with PTSD treatment outcomes
- May attenuate activity in Default Mode Network in PTSD*

Young et al. 2015; young et al. 2017; hake et al. 2019; ly et al. 2018; nardou et al. 2019; * publication in preparation
# Need for Further PTSD Treatments

<table>
<thead>
<tr>
<th></th>
<th><strong>Sertraline</strong></th>
<th><strong>Paroxetine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Effect Size</strong></td>
<td><strong>Dropout</strong></td>
</tr>
<tr>
<td>Study 1</td>
<td>0.31</td>
<td>29.3%</td>
</tr>
<tr>
<td>Study 2</td>
<td>0.37</td>
<td>28.4%</td>
</tr>
<tr>
<td>Study 3</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- 7-8% of the population will have PTSD at some point in their lives (10% of women, 4% of men)
- About 8 million adults have PTSD during a given year
- 41% of children and youth (aged 1-17) experienced a physical assault in the last year
- Insufficiently treated PTSD is serious
  - All-cause mortality hazard: 2.41 (95%CI 2.11-2.73)
  - Type 2 diabetes: OR=3.56 (95%CI 1.43-8.85)
  - 53% increase risk of cardiac events or cardiac mortality, 27% remains after adjusting for depression

Manualized MDMA-Assisted Therapy


Michael C. Mithoefer, M.D.

Other contributors:
Annie Mithoefer, B.S.N.,
Lisa Jerome, Ph.D.,
June Ruse, Psy.D
Rick Doblin, Ph.D.,
Elizabeth Gibson, M.S.,
Marcela Ot’alora G.,L.P.C.,
Evan Sola, Psy.D candidate

Available without charge at maps.org

Our adaptation of the foundation laid by Stanislav Grof, MD and many others
MDMA-Assisted Therapy Set & Setting

Divided dose of MDMA, administered 2 or 3 times, 1 month apart as an adjunct to therapy

- Controlled clinical setting in supportive environment
- Inner-directed approach, with occasional guidance/redirection offered as choice
- Follow the “Inner healing intelligence”
- Empathetic rapport & presence supports participant's own unfolding experience and body's own healing process
- Periods of going inward
- Music to support experience
- Elements of mindfulness, often somatic focused
- Importance of preparation and integration

Mithoefer et al., 2016
Inner Healing Intelligence

“In some schools it is called the Higher Self or the Soul. In others, it is simply referred to as a healing mechanism. No matter what it is called, all systems are referring to that mysterious and ultimately nameless force within us that is in charge of our transformation.”

Tav Sparks
Therapeutic Features

Hyperarousal
- Increased sensation
- Emotional reactivity
- Intrusive imagery
- Disorganized cognitive processing

Arousal

Hypoarousal
- Numbing of emotions
- Disabled cognitive processing
- Fragmented personality

Window of Tolerance/
Optimal Arousal Zone

Psychoeducation
- Distress management
- Cognitive restructuring
- Emotion regulation
- Interpersonal regulation

Adapted from Ogden P et al. Psychiatr clin north am. 2006;29(1):263-279, xi-xii
Phase 2 Study Design

Stage 1
- Prep Sessions
- Integrative Sessions
- Integrative Sessions
- Experimental Session
- Integrative Sessions
- Integrative Sessions
- Experimental Session

Stage 2
- Open-label crossover for Low/Medium/Placebo Group
- Unblind
- Assessment Primary Endpoint
- Assessment Two Month Follow up
- Assessment Long-term Follow-up
5 Sites (US, Switzerland, Canada & Israel)  
N = 103  
Chronic PTSD, had prior treatment

Control-subtracted Effect Size:
- Post 2 Sessions = 0.8
- Post 3 Sessions = 0.9

Pre-post Effect Size:
- Post 2 Sessions = 1.4
- Post 3 Sessions = 1.9

More than 2/3 no longer met criteria for PTSD at the end of treatment

Pooled Result
6 Phase 2 Studies
Phase 2 Remission of PTSD Diagnosis After 2 sessions

Pooled data from Phase 2 studies:

- Mean: 18 years of PTSD before study enrollment
- 82% Treatment Response at Study Exit

Control + Therapy Group

- 23%

MDMA + Therapy Group

- 54%

2-Month Follow Up

(0-40 mg MDMA, n=31)

(75-125 mg MDMA, n=72)

Meets PTSD diagnosis requirements

No longer meet requirements for a PTSD diagnosis

Mithoefer et al. 2011; Oehen et al. 2013; Mithoefer et al. 2018; Ot’alora et al. 2018; Mithoefer et al. 2019; Feduccia et al. 2019
Durability in Remission After 2 or 3 Active Dose Sessions in Phase 2 Studies

In pooled Long-term Follow-up:

- No significant change in PTSD severity from Study Exit, 12+ months later (1-6 years)
- Clinically significant gains in symptom relief sustained
- 11 of 91 (12%) relapsed, 9 due to additional stressors

67% of Subjects (n=91) Did Not Meet PTSD Criteria 12+ Months after Active Dose MDMA*

* Includes blinded and open-label MDMA in crossover

Mithoefer et al. 2011; Mithoefer et al. 2013; Oehen et al. 2013; Mithoefer et al. 2018; Ot’alora et al. 2018; Mithoefer et al. 2019; Feduccia et al. 2019; Jerome et al. 2020
Secondary Benefits Found in Phase 2 Studies

- Improvement in Sleep

- Posttraumatic Growth Index:
  - positive changes in self-perception and interpersonal relationships
  - correlates with improvement in PTSD
  - durable at 12+ months follow-up
Course of Treatment includes
9 Integration Sessions

3 Preparatory Sessions (90 min each)

MDMA Therapy Session (8 hrs)

3 Integration Sessions (90 min each)

3 Integration Sessions (90 min each)

3 Integration Sessions (90 min each)

Follow Up
Integration Sessions

- Open-ended and client directed
- Invite participant to discuss material that emerged during the session
- Exploration of insights
- Processing emotional distress or cognitive dilemmas
- Inquire about somatic experience
- Discuss relational issues if and when they arise
- Encouragement of supportive behaviors, and activities (e.g. journaling, art, time in nature, listening to music from sessions, movement, meditation)
Unique Integration Considerations - MDMA-AT

- Co-therapist model
- Experiential sessions are long (much material to cover)
- Details and recall of experience heightened and/or more vivid
- Set number of integration sessions per current protocol
- Set treatment length per protocol (4 months)
- Relational element of MDMA-AT including termination process
Elements of other therapies that arise in MDMA-assisted sessions

- Safe, supportive setting
- Imaginal exposure
- Cognitive restructuring
- Transference
- Psychodynamic
- Attention to the body
- Multiplicity of the psyche
- Transpersonal/Spiritual
- Corrective attachment
- Active imagination
MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study

Jennifer M. Mitchell, Michael Bogenschutz, [...] Rick Doblin
FDA Phase 3 Site Locations
- First Phase 3 Study Completed, second one underway -

- San Francisco, CA | research institution
- New York, NY | research institution
- Madison, WI | research institution
- Vancouver, Canada | research institution
- Israel | research institution
- San Francisco, CA | private practice
- Los Angeles, CA | private practice
- Boulder, CO | private practice
- Fort Collins, CO | private practice
- New Orleans, LA | private practice
- New York, NY | private practice
- Charleston, SC | private practice
- Boston, MA | private practice
- Montreal, Canada | private practice

15 Sites – US, Canada Israel

Expanded Access / compassionate use
Approved in US and Israel
Phase 3 PTSD Trial Design

- Pivotal Phase 3 study completed (N=90)
- 15 site-study with 80+ therapists
- 80 mg + 40 mg or 120mg + 60 mg MDMA vs. Placebo
- Divided dose administered 1.5-2 hours post first dose

- Both groups receive identical therapy
- Blinded Independent Rater Pool for Outcome Assessments with bias minimization
- Open label crossover for control group
- 12-month Long-term Follow-up
## Demographics of Pivotal Phase 3 Trial

<table>
<thead>
<tr>
<th>Demographic</th>
<th>MDMA-assisted therapy (N=46)</th>
<th>Placebo with therapy (N=44)</th>
<th>Total (N=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong>, mean (SD)</td>
<td>43 (13)</td>
<td>38 (10)</td>
<td>41 (12)</td>
</tr>
<tr>
<td><strong>Female</strong>, biological, n(%)</td>
<td>59%</td>
<td>73%</td>
<td>66%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>6%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>Asian</td>
<td>4%</td>
<td>11%</td>
<td>8%</td>
</tr>
<tr>
<td>Black/African American</td>
<td>0%</td>
<td>4%</td>
<td>2%</td>
</tr>
<tr>
<td>Native Hawaiian/Pacific Islander</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>White</td>
<td>85%</td>
<td>68%</td>
<td>77%</td>
</tr>
<tr>
<td>Multiple</td>
<td>4%</td>
<td>14%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latinx, n(%)</td>
<td>11%</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Trauma History</strong>, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developmental</td>
<td>87%</td>
<td>82%</td>
<td>84%</td>
</tr>
<tr>
<td>Combat exposure</td>
<td>13%</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Multiple</td>
<td>89%</td>
<td>86%</td>
<td>88%</td>
</tr>
<tr>
<td>Dissociative subtype, n(%)</td>
<td>13%</td>
<td>30%</td>
<td>21%</td>
</tr>
</tbody>
</table>
## Trauma History from Phase 3 Trial

### Apparent Principal Cause of PTSD Amongst Study Participants

For 30 of 90 subjects, principal trauma occurred during childhood.

<table>
<thead>
<tr>
<th>Cause</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual assault or sexual trauma</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Armed or unarmed assault</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Combat or exposure to a war zone</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Sudden violent or accidental death</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Witnessing actual or threats of suffering or death of others</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>School or mass shooting</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Source: MAPPI Data on file
Suicidality History Prior to Phase 3 Trial

- Positive ideation: MDMA (91.3%) vs Placebo (93.2%)
- Serious ideation: MDMA (43.5%) vs Placebo (38.6%)
- Positive behavior: MDMA (34.8%) vs Placebo (29.5%)
MDMA is Superior to Therapy with Placebo in Phase 3 Trial

- Key Secondary Endpoint: Functional Impairment significantly improved (p=0.0116)
- 4 dropouts in MDMA group: 2 COVID-related, 1 AE (depressed mood), 1 early efficacy
- 7 dropouts in Placebo group: 2 COVID-related, 2 SAEs, 2 AEs (insomnia, anxiety), 1 choice

### Mean CAPS-5 PTSD Scores by Treatment Group

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Baseline</th>
<th>Post Session 1</th>
<th>Post Session 2</th>
<th>Post Session 3</th>
<th>N</th>
<th>p &lt; 0.0001, d = 0.91</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo with therapy</td>
<td>[Graph]</td>
<td>[Graph]</td>
<td>[Graph]</td>
<td>[Graph]</td>
<td>46 MDMA</td>
<td></td>
</tr>
<tr>
<td>MDMA-assisted therapy</td>
<td>[Graph]</td>
<td>[Graph]</td>
<td>[Graph]</td>
<td>[Graph]</td>
<td>46 MDMA</td>
<td></td>
</tr>
</tbody>
</table>

![Graph showing Mean CAPS-5 PTSD Scores by Treatment Group](image_url)
Response & Remission
Post 3 Sessions in Phase 3 Trial

● 88% Treatment Response (10-point drop in CAPS-5)

● 5 non-responders to MDMA

● 14 in remission after MDMA (33%)
  vs. 2 Placebo (5%)
Treating PTSD with MDMA-Assisted Therapy

Phase 3 Trial Results Published in *Nature Medicine*, May 2021
Results of 1st Phase 3 trial for MDMA-assisted psychotherapy

Mean CAPS-5 Scores by Treatment Group

Drop out rates:
- Placebo – 10.0%
- MDMA – 6.5%
- PE – 54.6%
- CPT – 44.8%
MDMA Has Large Effect Size in Phase 3 Trial

Zoloft Study #640: 0.31
Zoloft Study #671: 0.37

Paxil Study #627: 0.09 (failed)
Paxil Study #648: 0.45
Paxil Study #651: 0.56

MDMA Therapy Phase 3

0.91: Placebo-corrected MDMA effect size
2.1: Between-subjects effect size of MDMA plus Therapy
Dissociative Subtype of PTSD Responds to MDMA in Phase 3 Trial

Drops in CAPS-5 [PTSD scale]

- Dissociative Subtype: N=6, p< 0.0001 (MDMA: -36.1, Placebo: -22.1)
- Other Study Participants: N=46, p= 0.0027 (MDMA: -11.9, Placebo: -13.3)
## Treatment-Related Adverse Events in Phase 3

<table>
<thead>
<tr>
<th>Adverse Drug Reaction (&gt;7%)</th>
<th>MDMA (N=46)</th>
<th>Placebo (N=44)</th>
<th>Adverse Drug Reaction (&gt;7%)</th>
<th>MDMA (N=46)</th>
<th>Placebo (N=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle tightness</td>
<td>63%</td>
<td>11%</td>
<td>BP increased</td>
<td>11%</td>
<td>-</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>52%</td>
<td>11%</td>
<td>Feeling jittery</td>
<td>11%</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>30%</td>
<td>11%</td>
<td>Chest pain (non-cardiac)</td>
<td>11%</td>
<td>2%</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>20%</td>
<td>2%</td>
<td>Dry Mouth</td>
<td>11%</td>
<td>4%</td>
</tr>
<tr>
<td>Feeling cold</td>
<td>20%</td>
<td>7%</td>
<td>Vision Blurred</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Restlessness</td>
<td>15%</td>
<td>-</td>
<td>Pollakiuria</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>15%</td>
<td>-</td>
<td>Intrusive Thoughts</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness (postural)</td>
<td>13%</td>
<td>4%</td>
<td>Vomiting</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>Bruxism</td>
<td>13%</td>
<td>2%</td>
<td>Stress</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>13%</td>
<td>-</td>
<td>Musculoskeletal Pain</td>
<td>9%</td>
<td>-</td>
</tr>
</tbody>
</table>

- Adverse reactions resolve within few days post-dosing
- MDMA is sympathomimetic
- Most frequent non-serious adverse events for the MDMA group:
  - Muscle tightness
  - Decreased appetite
Adverse Events of Special Interest in Phase 3

- **Suicidality**
  (Suicidal thoughts, behavior, self-harm)
  - 3 participants in MDMA group (3 events)
  - 5 participants in placebo group (10 events)

- **Cardiovascular**
  (Irregular heartbeats, palpitations)
  - 0 participants in MDMA group
  - 1 participant in placebo group

- **Abuse potential**
  (Dependence, substance use disorder)
  - 0 participants in MDMA group
  - 0 participants in placebo group

---

**Serious Adverse Events of Suicidal ideation and/or attempt**

- 0 participants in MDMA group
- 2 participants in placebo group:
  - 1 attempted suicide twice
  - 1 self-hospitalized with severe suicidal ideation, but no attempt
Phase 3 and Program Summary

- Small p-value in 2 Phase 2 studies (0.001 & 0.002) and Phase 3 (0.0001)
- Large effect size in Phase 2 (0.8) and Phase 3 (0.91)
- Confirmed efficacy and reproducibility with an adequate well controlled study
- No site-to-site variability in 15-site Phase 3 study
- Positive Risk/Benefit Ratio confirmed
  - No high level risks
  - Medium level risks: Cardiovascular (sympathomimetic), Psychological Distress
  - Low level risks: Thermoregulatory, osmoregulatory, reproductive/developmental
Expanded Access – Accelerating Access to Treatment

- Access to treatment prior to FDA approval for 50 treatment-resistant PTSD patients
- Move forward our goal of inclusion & diversity
- Establish centers of excellence
- Prepare Therapist workforce and Network of Clinics to deliver once FDA-approved
- Test risk mitigation procedures in clinical treatment setting
- Collect safety-related Health Outcome Data
- Develop Real World Evidence to support Commercialization/implementation planning
- Build business case for payers
Next Steps: FDA Approval & Projected Rollout

Model Parameters

State Timing
- States tiered across Wave 1, 2, and 3 based on market prioritization analysis determining start years
- Controlled substance rescheduling requirements determine quarter of state coming online

Patient volume
- Based on estimate of state PTSD population, subset of population seeking treatment, and subset well-indicated for MDMA-AT; conservatively assumes 2 MDMA sessions per patient

S-shaped adoption curve
- Each state categorized across 2 key dimensions: Maximum penetration (high, medium, low) and Ramp-up speed (fast, medium, slow)

Therapist Capacity
- Projected capacity for the U.S. aggregated based on MDMA Training Program pipeline targets Used as volume constraint if capacity insufficient to meet projected demand

Therapist capacity acts as limiting factor in first year post-launch

Practicing therapists (Thousands, EOY)

- 2023 Q4 launch
- 2023: <1
- 2024: 51
- 2025: 116
- 2026: 140
- 2027: 172
- 2028: 256
- 2029: 376
- 2029 Q3 loss of data exclusivity

Annual Therapist Capacity (k sessions)
MDMA Sessions Delivered (k)
Health Equity

- **Patient Assistance Programs**
  - Ensure that the cost of drug is not a barrier to patient

- **Favorable reimbursement**
  - From a variety of commercial insurance and public payers
  - Primary mandate of MPBC market access team
Third-party payers are likely to save money within 3 years by covering this form of therapy.
Next Steps: New Indications & Protocols

PTSD: Cognitive Behavioral Conjoint Therapy & Group Therapy

Major Depressive Disorder

Social Anxiety Disorder

Substance Use Disorder and Alcohol Use Disorder

Anxiety Associated with Life-Threatening Illness

Obsessive Compulsive Disorder

Eating Disorders
Thank You!