MDMA-Assisted Therapy for Posttraumatic Stress Disorder

Darrick May, MD
Psychiatrist / Medical Director
Boulder Integrated Health

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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

MAPS
MULTIDISCIPLINARY ASSOCIATION FOR PSYCHEDELIC STUDIES

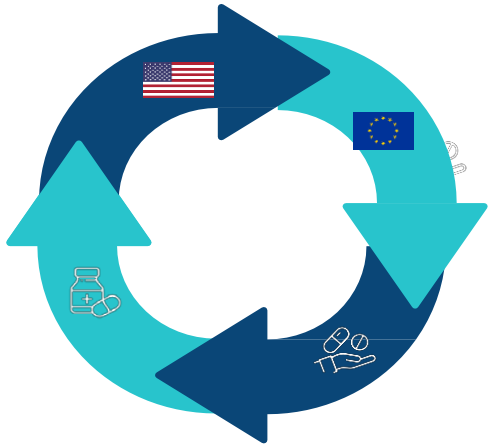
501c3 non-profit, founded 1986

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

Non-profit Drug Development



MAPS Public Benefit Corporation

Founded in 2014

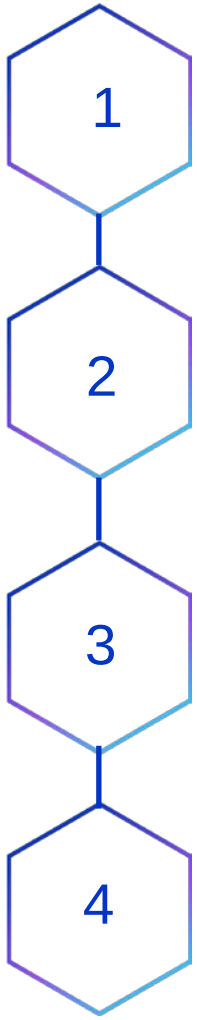
Catalyzes healing through psychedelic drug development

Trains therapists in psychedelic-assisted therapies

Pioneers equitable access, prioritizing public benefit above profit

Proceeds furthers MAPS mission

MAPS Core Values



Integrity

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

Perseverance

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

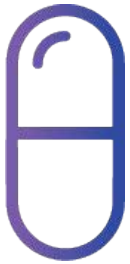
Curiosity

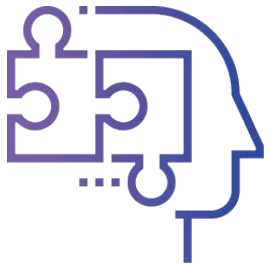
We are always open to new possibilities: we try new things, take risks, and learn from our mistakes.

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.

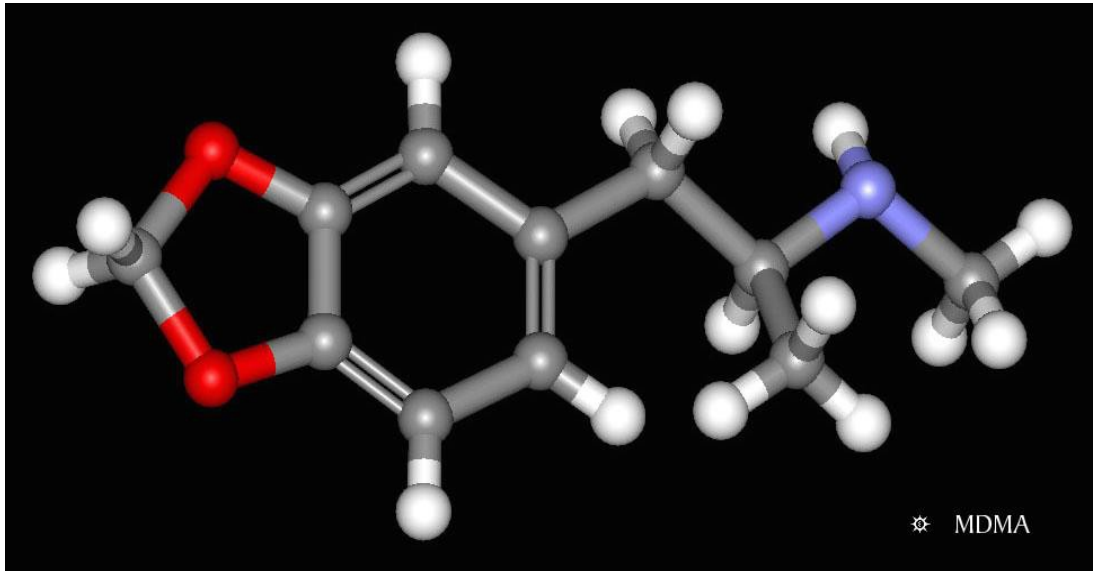
History of MDMA

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

Progression of MDMA clinical research

MDMA Pharmacodynamics

- Triple reuptake inhibitor:
  - Serotonin > Norepinephrine > Dopamine
- MAO-A Inhibitor
- VMAT-2 Inhibitor



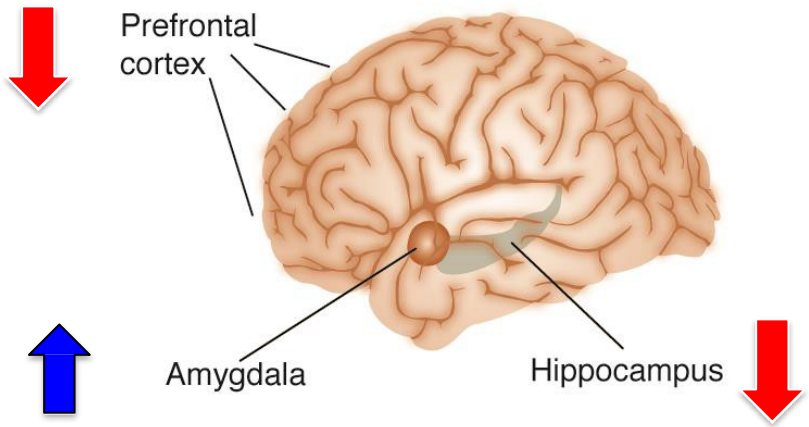
3,4- methylenedioxymethamphetamine (MDMA)

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

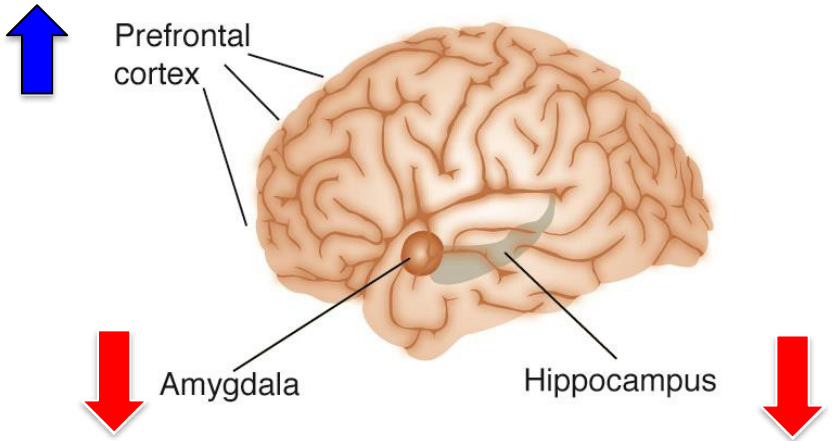
References available in MDMA Investigator's Brochure www.maps.org

PTSD: Difficulty in Extinction of Fear

Non-Dissociative Sub-type



Dissociative Sub-type



- 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

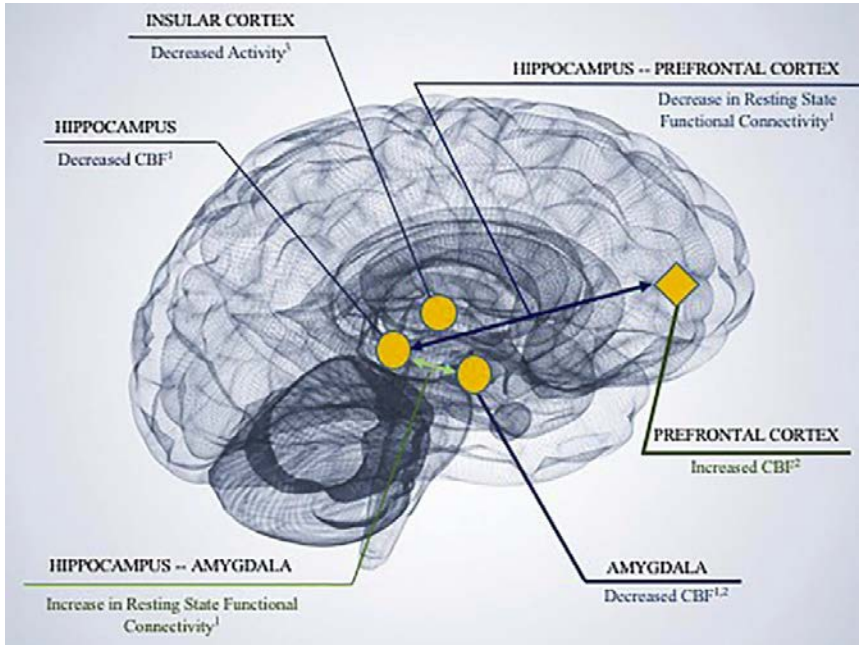
MDMA Facilitates Learning to Overcome Fear Memories

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



MDMA Effects in Healthy Brains

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

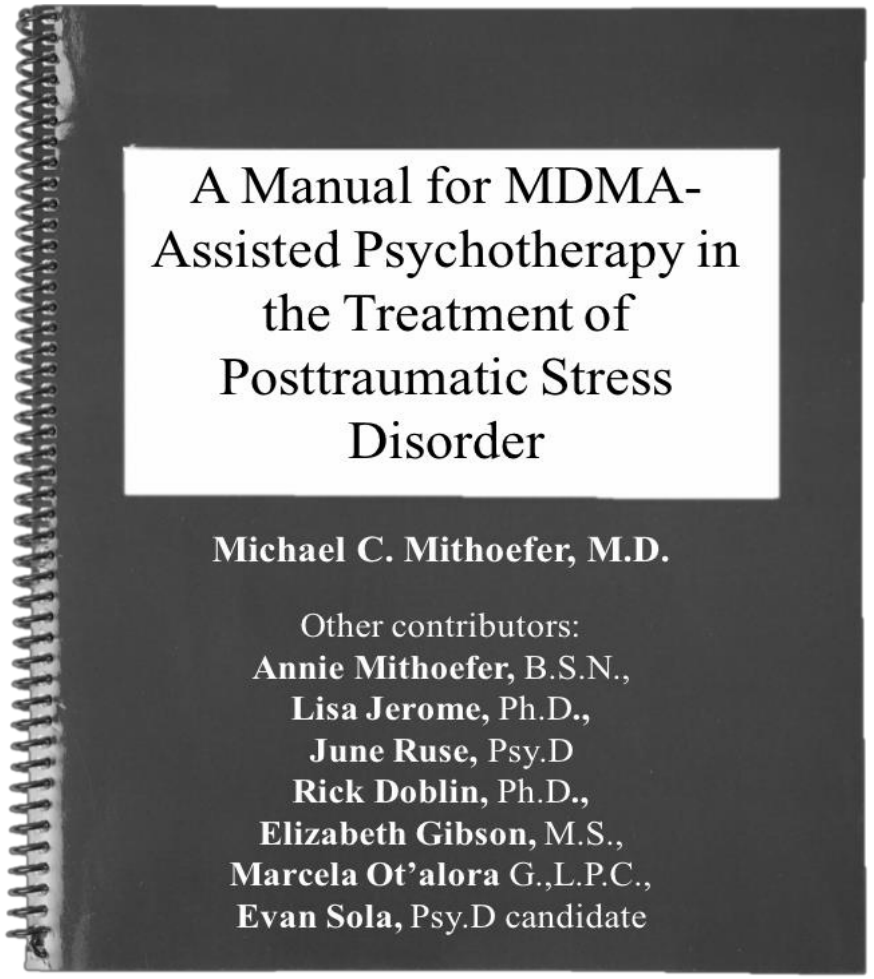
Need for Further PTSD Treatments

	Sertraline		Paroxetine	
	Effect Size	Dropout	Effect Size	Dropout
Study 1	0.31	29.3%	0.56	35.5%
Study 2	0.37	28.4%	0.45	39.0%
Study 3	-	-	0.09	33.0%

- 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

Ahmadi, 2011; Lukaschek 2013; Edmond & Rubin, 2004; Kessler et al. 2005; Marshall et al. 2000; Kibler et al. 2009; Dorrington et al. 2014; Tarrier & Gregg 2004

Manualized MDMA-Assisted Therapy



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

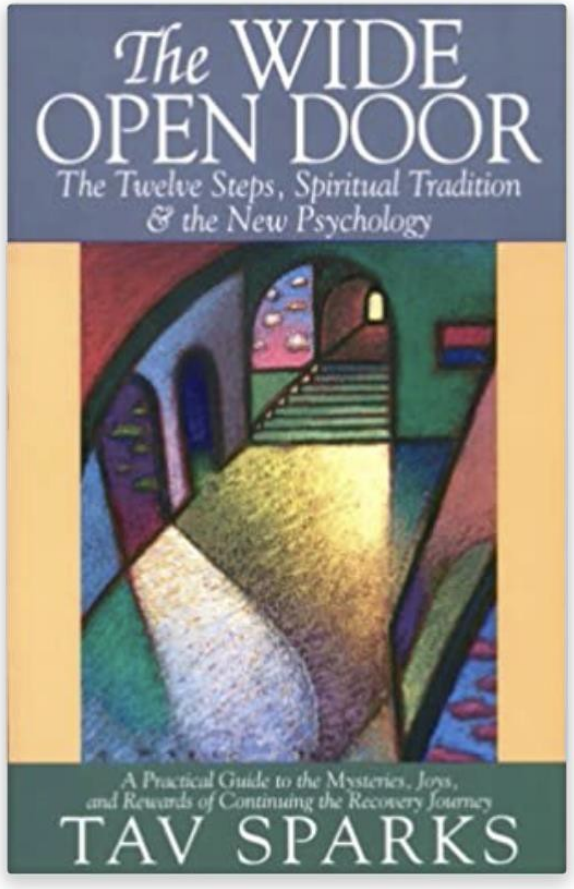
Phase 3 Clinical Trial Site

Mithoefer et al., 2016

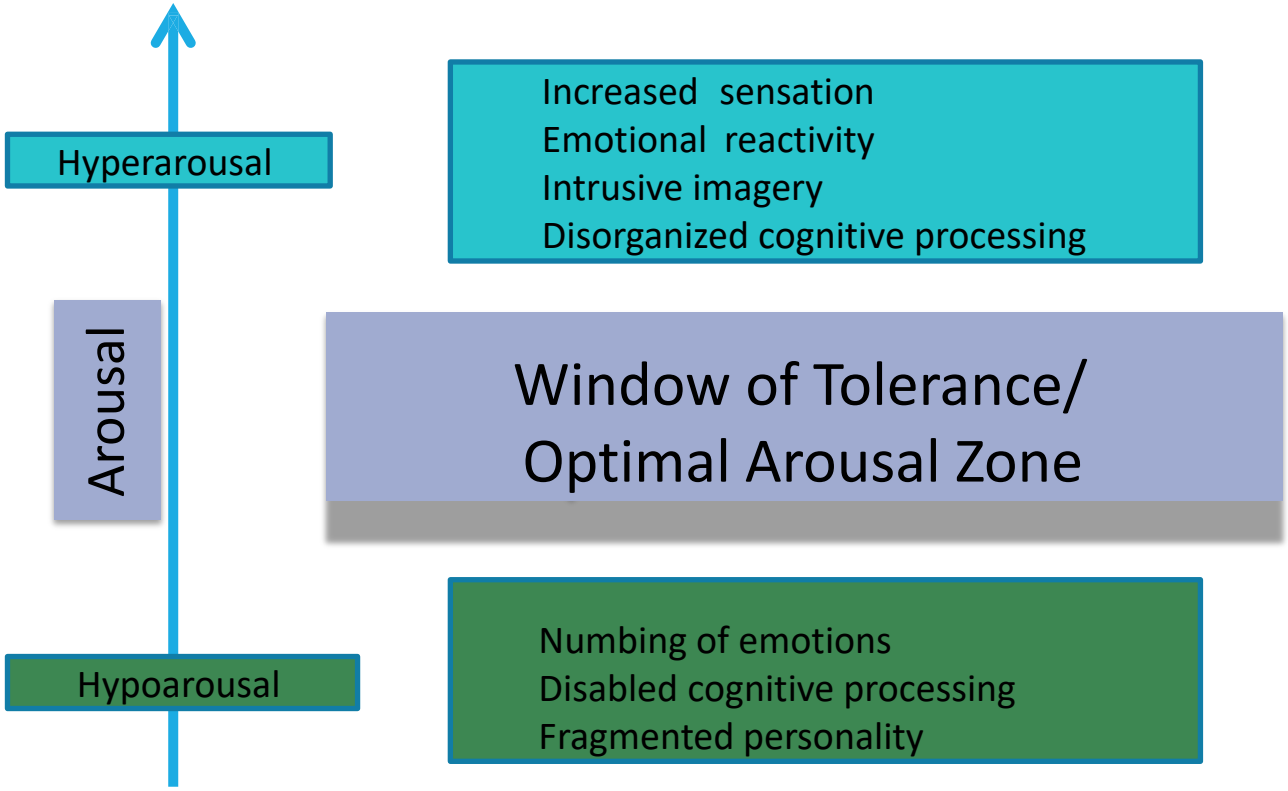
Inner Healing Intelligence

"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



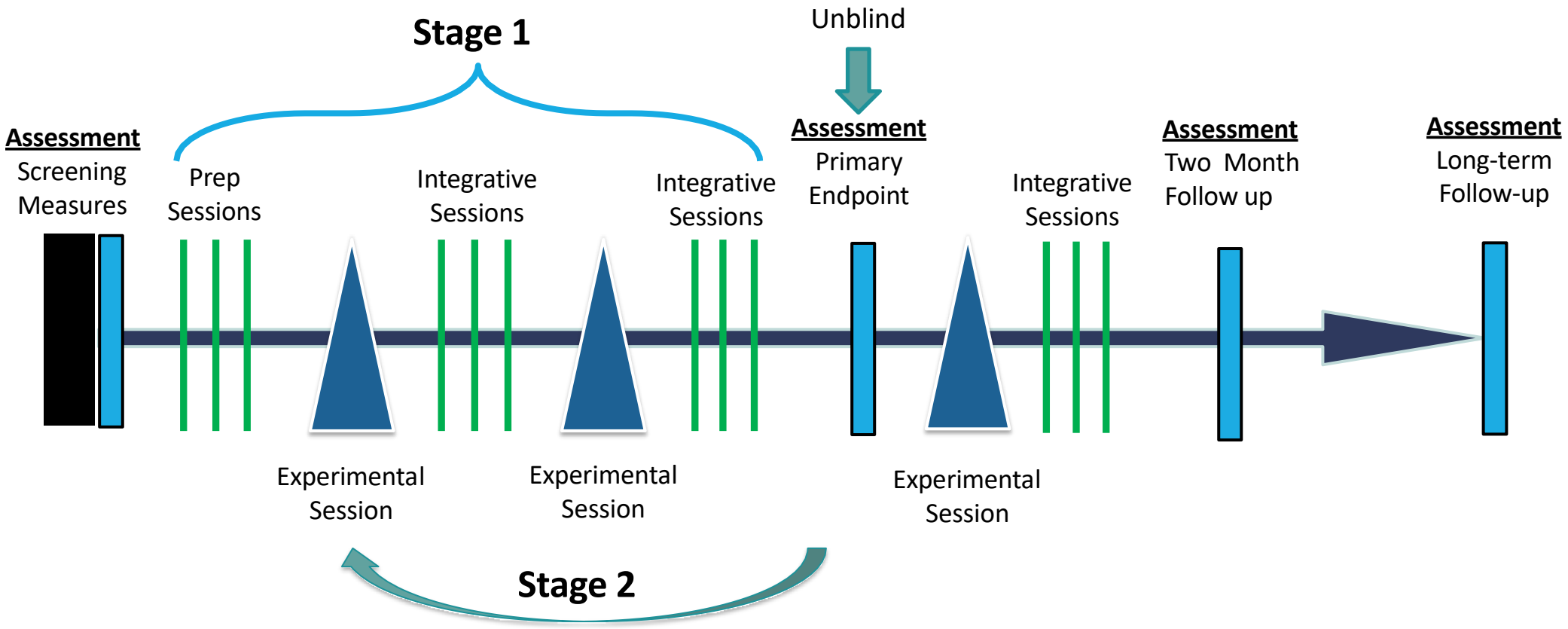
Therapeutic Features



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



Open-label crossover for Low/Medium/Placebo Group

Pooled Result
6 Phase 2 Studies

Psychopharmacology
https://doi.org/10.1007/s00213-019-05249-5

ORIGINAL INVESTIGATION

MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials

Michael C. Mithoefer[1] · Allison A. Feduccia[2] · Lisa Jerome[2] · Anne Mithoefer[3] · Mark Wagner[1] · Zach Walsh[4] · Scott Hamilton[5] · Berra Yazar-Klosinski[6] · Amy Emerson[2] · Rick Doblin[6]

Received: 26 November 2018 / Accepted: 12 April 2019

Abstract

Background Posttraumatic stress disorder is a prevalent mental health condition with substantial impact on daily functioning that lacks sufficient treatment options. Here we evaluate six phase 2 trials in a pooled analysis to determine the study design for phase 3 trials of MDMA-assisted psychotherapy for PTSD.

Methods Six randomized, double-blind, controlled clinical trials at five study sites were conducted from April 2004 to February 2017. Active doses of MDMA (75–125 mg, $n = 72$) or placebo/control doses (0–40 mg, $n = 31$) were administered to individuals with PTSD during manualized psychotherapy sessions in two or three 8-h sessions spaced a month apart. Three non-drug 90-min therapy sessions preceded the first MDMA exposure, and three to four followed each experimental session.

Results After two blinded experimental sessions, the active group had significantly greater reductions in CAPS-IV total scores from baseline than the control group [MMRM estimated mean difference (SE) between groups − 22.0 (5.17), $P < 0.001$]. The between-group Cohen's d effect size was 0.8, indicating a large treatment effect. After two experimental sessions, more participants in the active group (54.2%) did not meet CAPS-IV PTSD diagnostic criteria than the control group (22.6%). Depression symptom improvement on the BDI-II was greatest for the active group compared to the control group, although only trended towards significant group differences [MMRM, estimated mean difference (SE) between groups −6.0 (3.03), $P = 0.053$]. All doses of MDMA were well tolerated, with some expected reactions occurring at greater frequency for the active MDMA group during experimental sessions and the 7 days following.

Conclusions MDMA-assisted psychotherapy was efficacious and well tolerated in a large sample of adults with PTSD. These studies supported expansion into phase 3 trials and led to FDA granting Breakthrough Therapy designation for this promising treatment.

Trial registration ClinicalTrials.gov Identifier: NCT00090064, NCT00353938, NCT01958593, NCT01211405, NCT01689740, NCT01793610.

Keywords MDMA · MDMA-assisted psychotherapy · Posttraumatic stress disorder · Anxiety · Psychedelic

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00213-019-05249-5) contains supplementary material, which is available to authorized users.

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

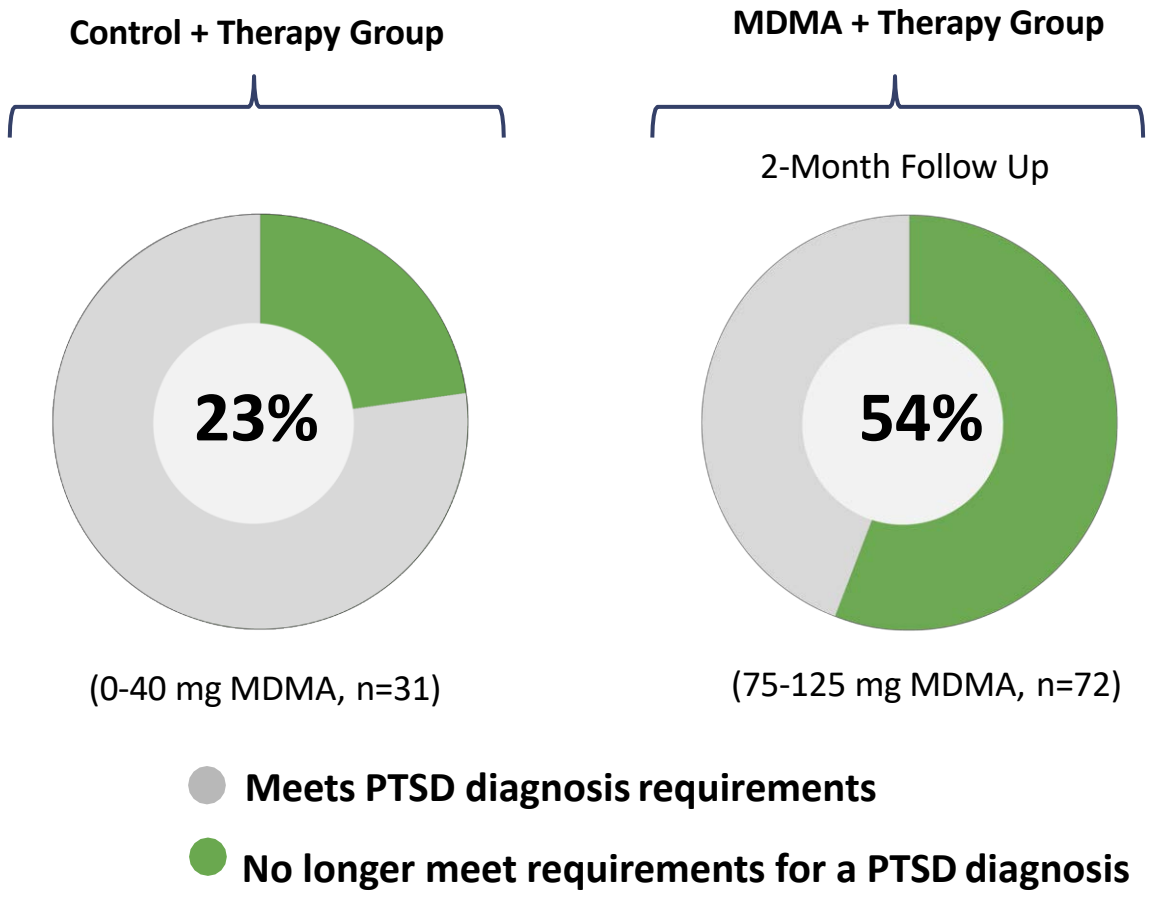
Post 3 Sessions = 1.9

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

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



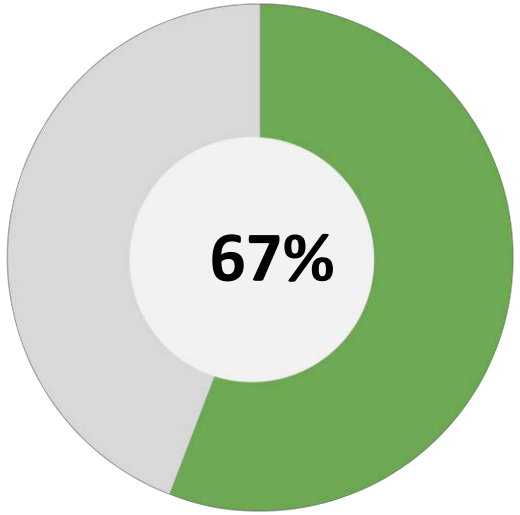
Mithoefer et al. 2011; Oehen et al. 2013; Mithoefer et al. 2018; Ot'alora et al. 2018; Mithoefer et al. 2019; Feduccia et al. 2019

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

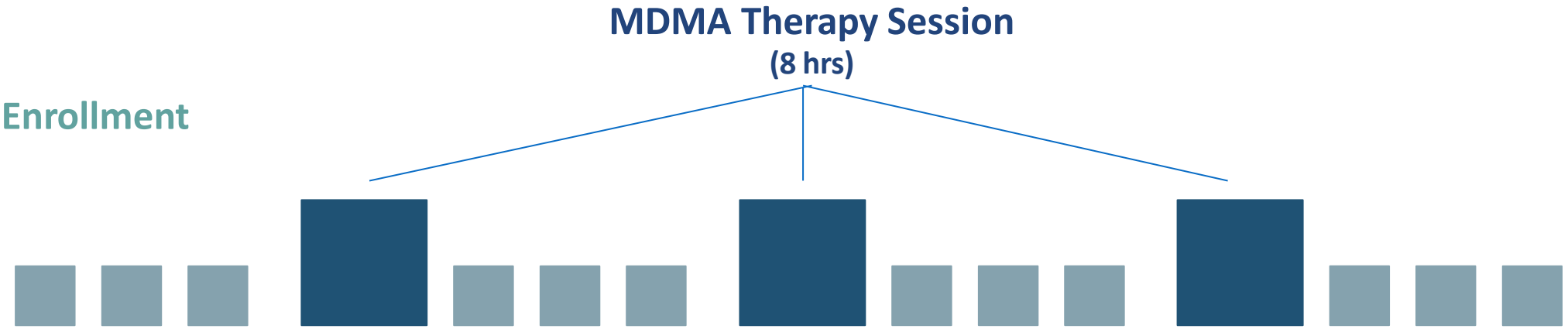
- Posttraumatic Growth Index:
  - positive changes in self-perception and interpersonal relationships
  - correlates with improvement in PTSD
  - durable at 12+ months follow-up

Ponte et al. in press; Gorman et al. 2020; Wagner et al. 2013; Jerome et al. 2020

Course of Treatment includes 9 Integration Sessions

Screening

Enrollment



3 Preparatory Sessions
(90 min each)

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

Article | Open Access | Published: 10 May 2021

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 -

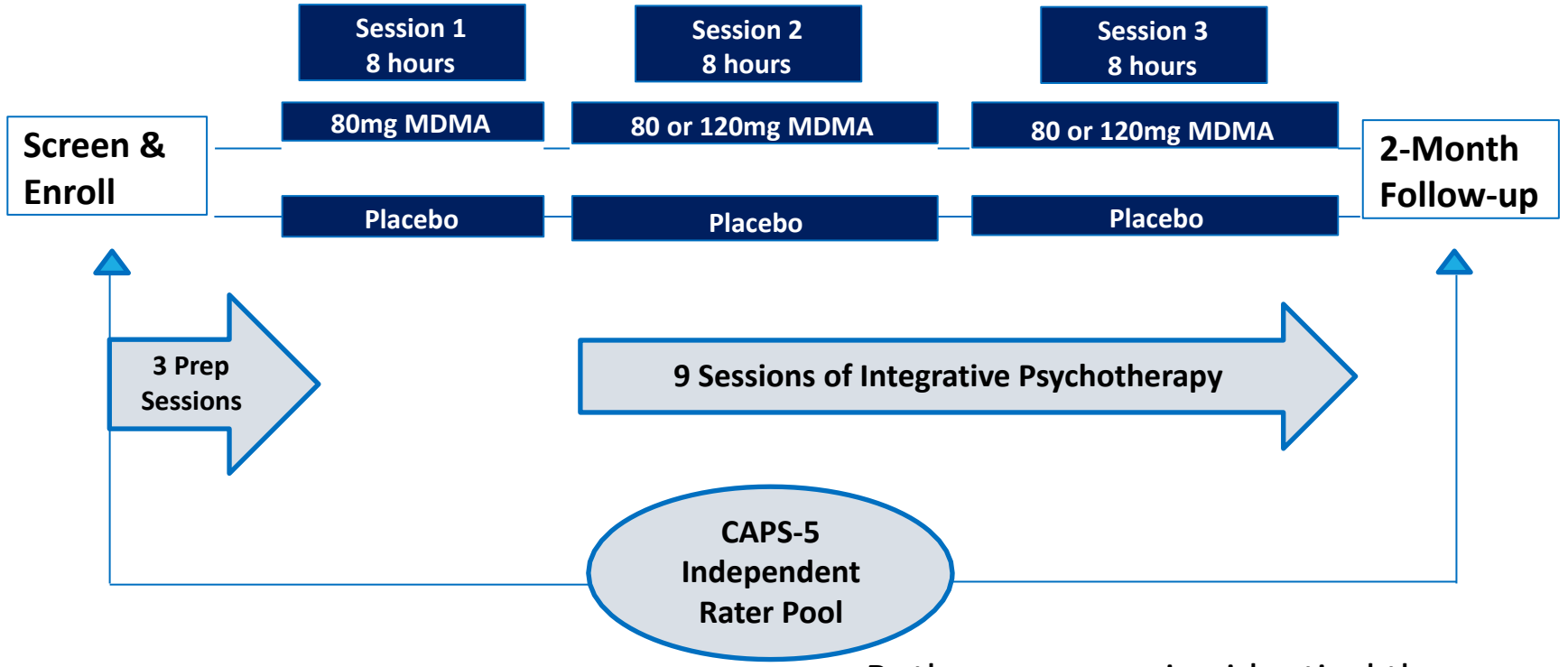
- **San Francisco, CA** | research institution
- **New York, NY** | research institution
- **Madison, WI** | research institution
- **Vancouver, Canada** | research institution
- **Israel** | research institution
- **San Francisco, CA** | private practice
- **Los Angeles, CA** | private practice
- **Boulder, 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

Expanded Access / compassionate use

Approved in US and Israel

15 Sites – US, Canada Israel

Phase 3 PTSD Trial Design

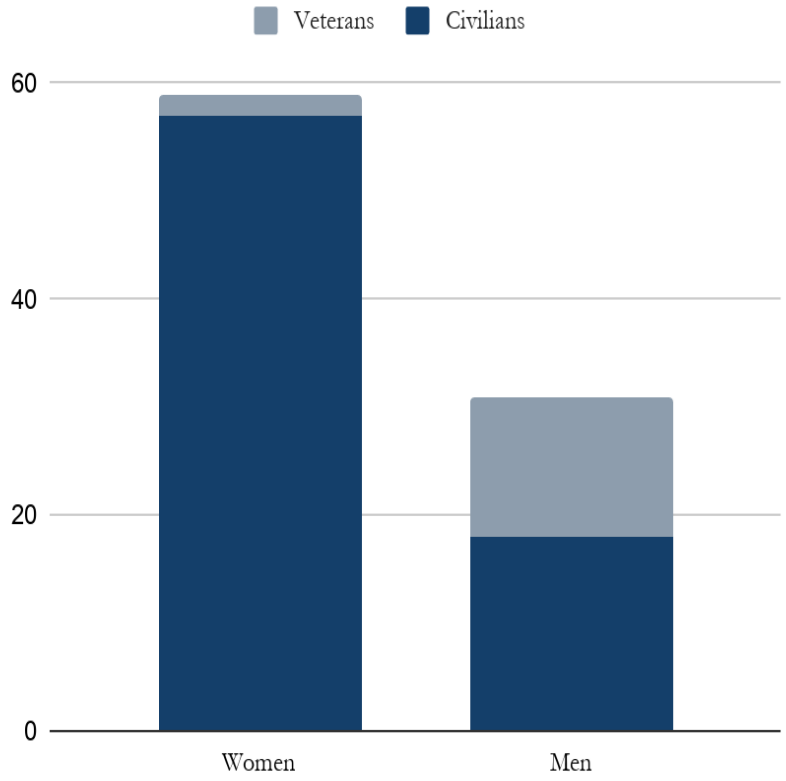


- Pivotal Phase 3 study completed (N=90)
- 15 site-study with 80+ therapists
- 80 mg + 40 mg or 120mg + 60 mg MDMA vs. Placebo
- Divided dose administered 1.5-2 hours post first dose

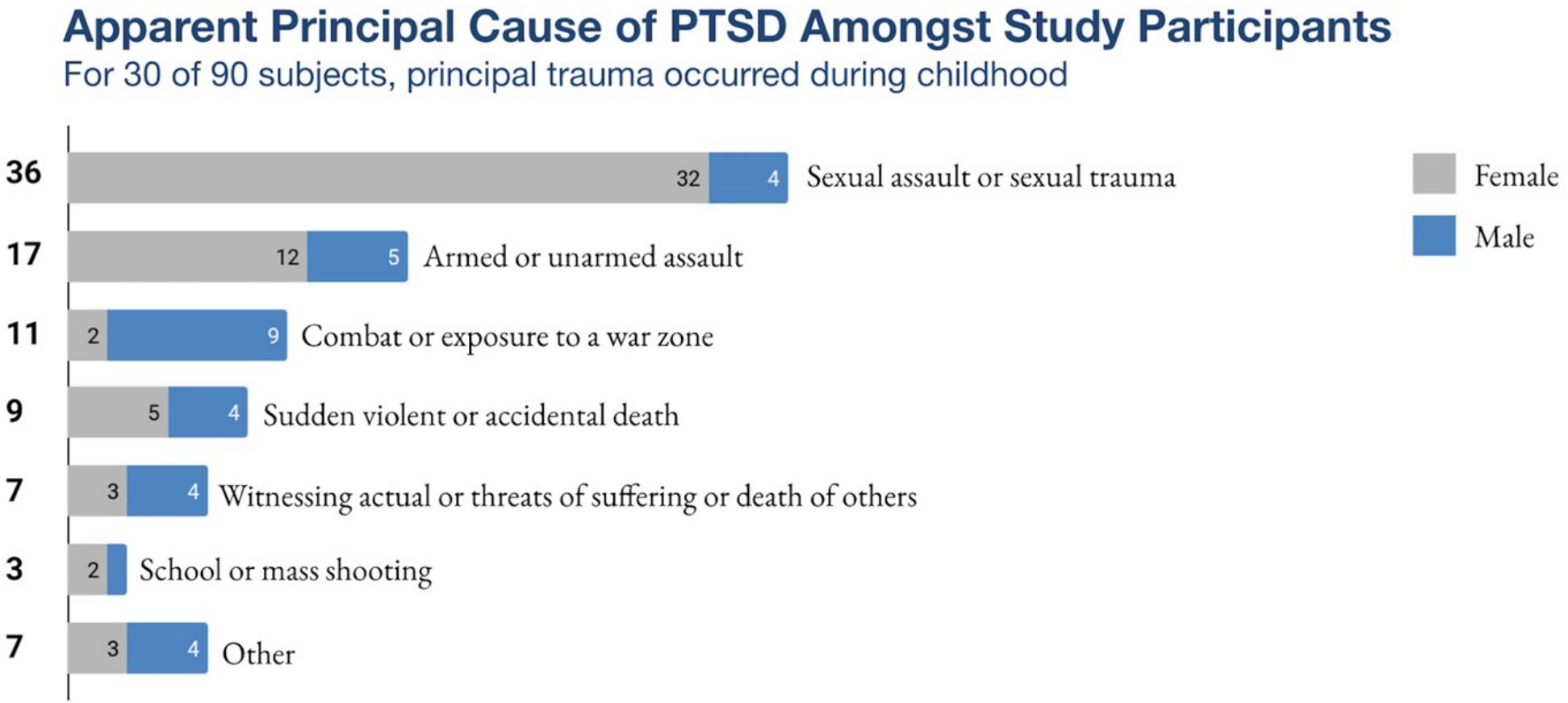
- Both groups receive identical therapy
- Blinded Independent Rater Pool for Outcome Assessments with bias minimization
- Open label crossover for control group
- 12-month Long-term Follow-up

Demographics of Pivotal Phase 3 Trial

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

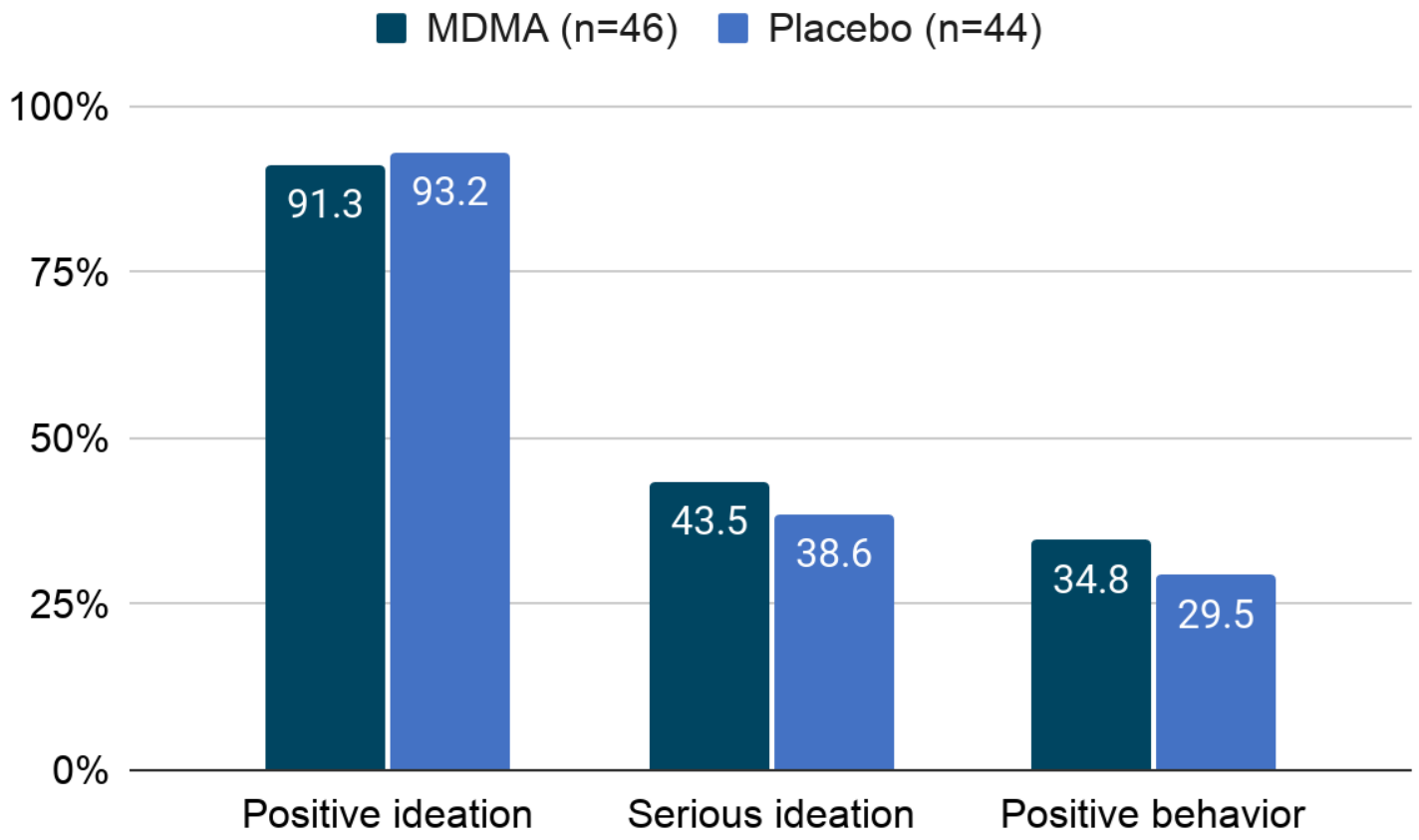


Trauma History from Phase 3 Trial



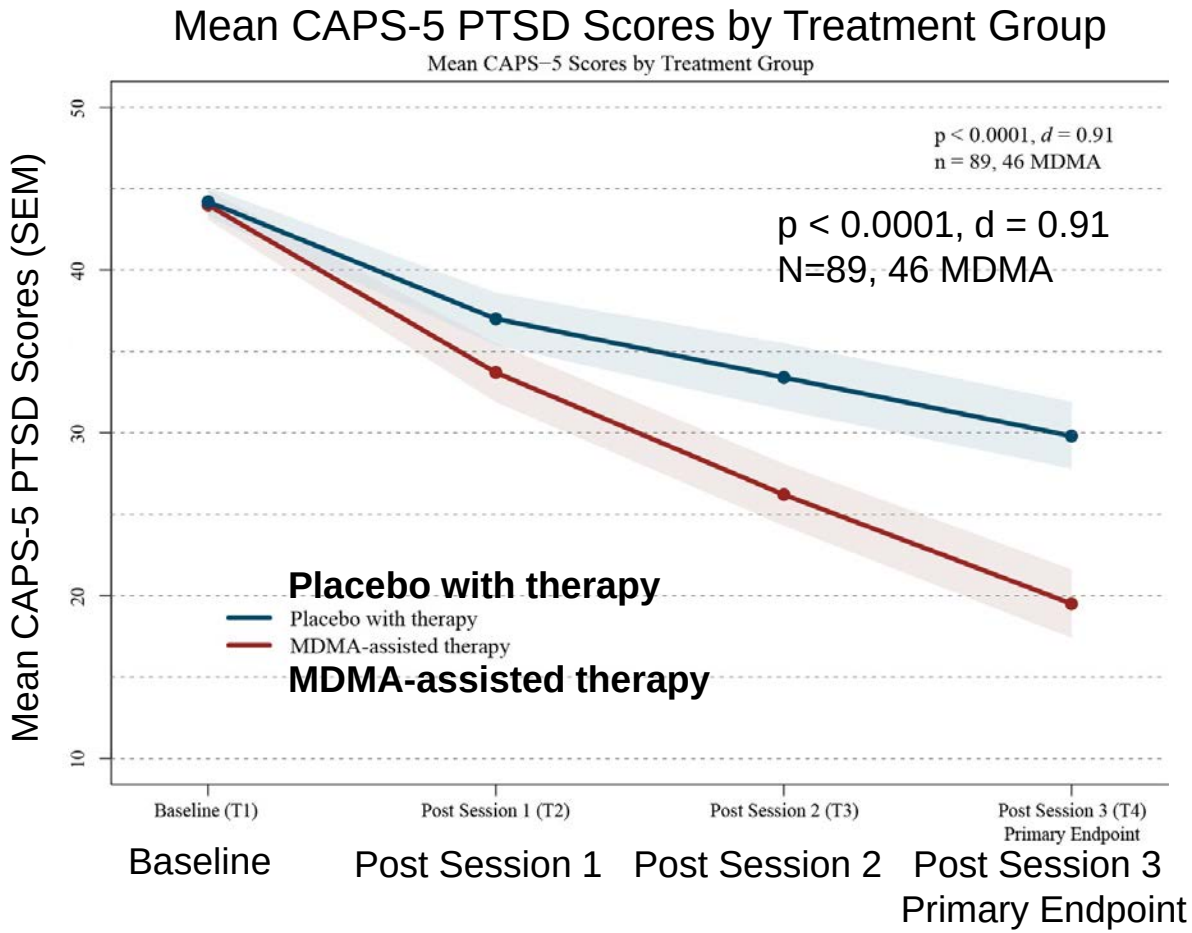
Source: MAPP1 Data on file
PTSD causes derived from the Life Events Checklist for DSM-5 (LEC-5): https://www.ptsd.va.gov/professional/assessment/documents/LEC5_Standard_Self-report.PDF

Suicidality History Prior to Phase 3 Trial



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

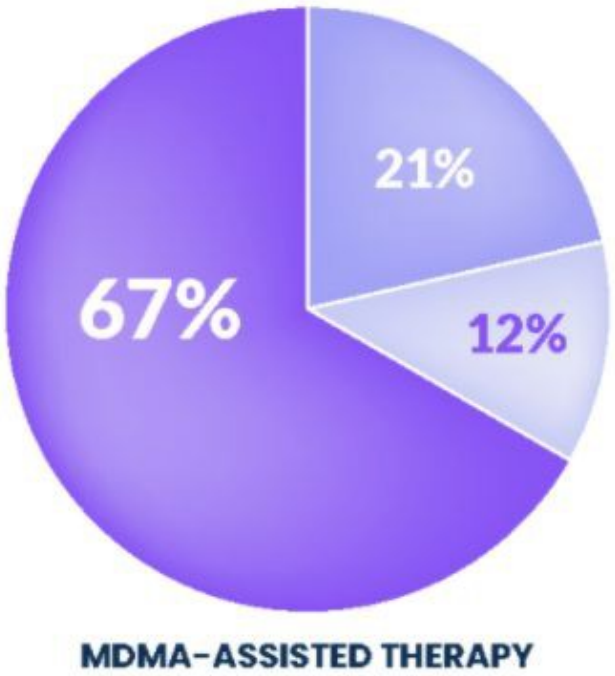


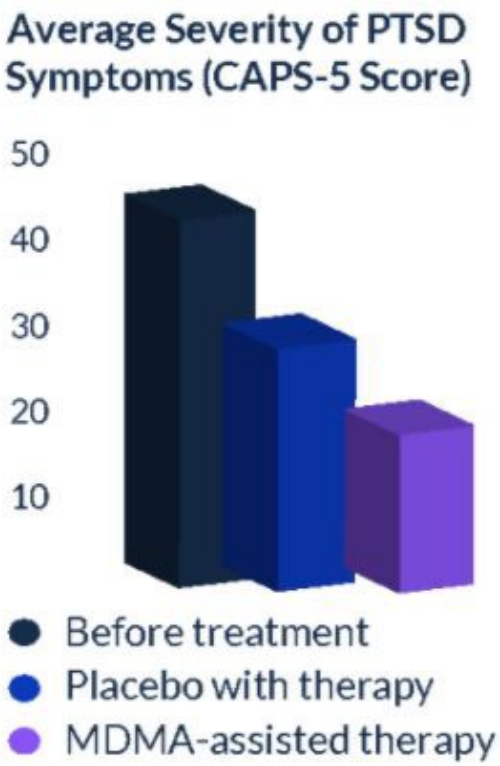
Response & Remission
Post 3 Sessions in Phase 3 Trial

- 88% Treatment Response (10-point drop in CAPS-5)
- 5 non-responders to MDMA
- 14 in remission after MDMA (33%)
  vs. 2 Placebo (5%)

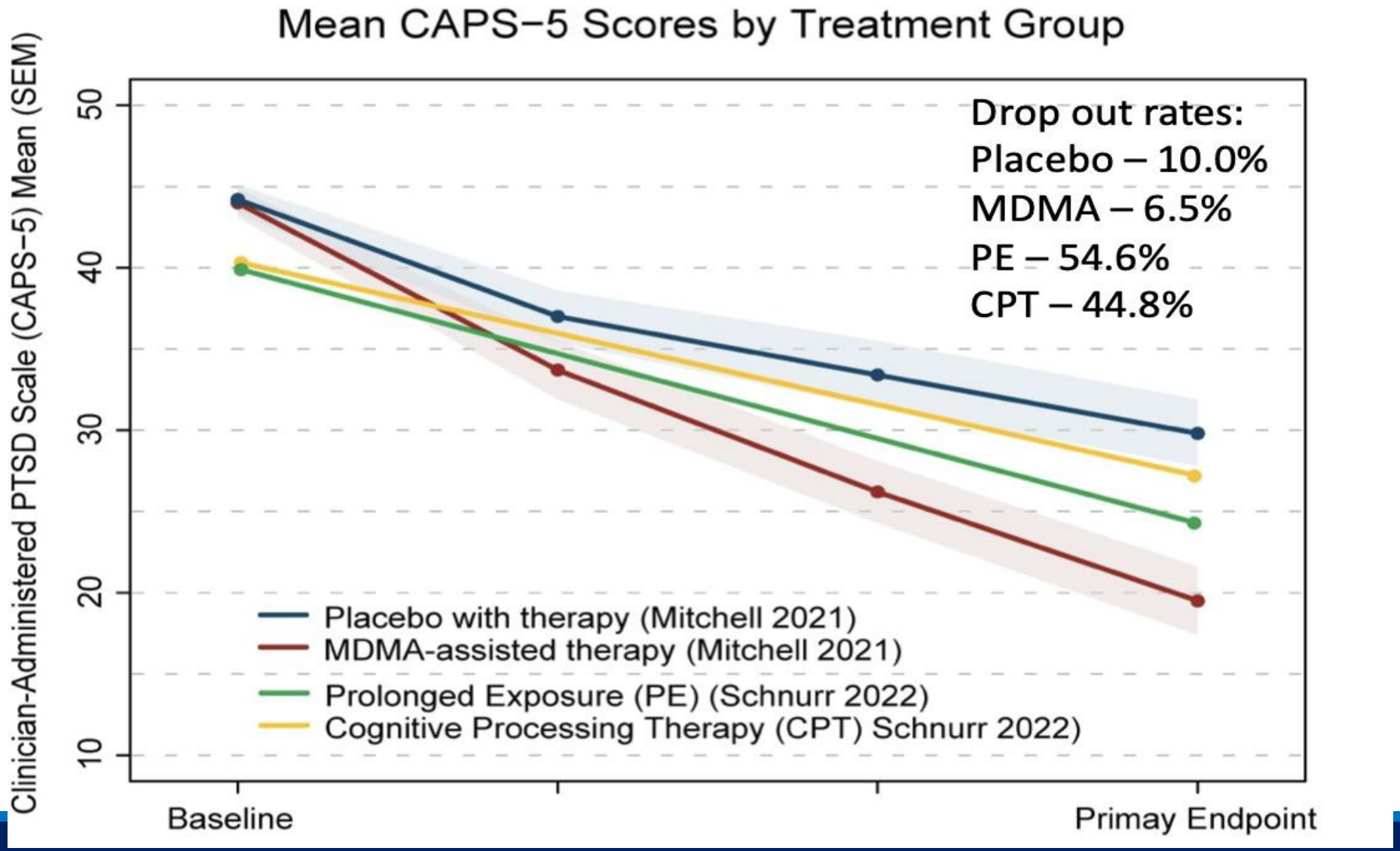
Treating PTSD with MDMA-Assisted Therapy

Phase 3 Trial Results Published in ***Nature Medicine***, May 2021





Results of 1st Phase 3 trial for MDMA-assisted psychotherapy



MDMA Has Large Effect Size in Phase 3 Trial

zoloft (sertraline HCl)

Zoloft Study #640: 0.31

Zoloft Study #671: 0.37

Paxil

Paxil Study #627: 0.09 (failed)

Paxil

Paxil Study #648: 0.45

Paxil

Paxil Study #651: 0.56

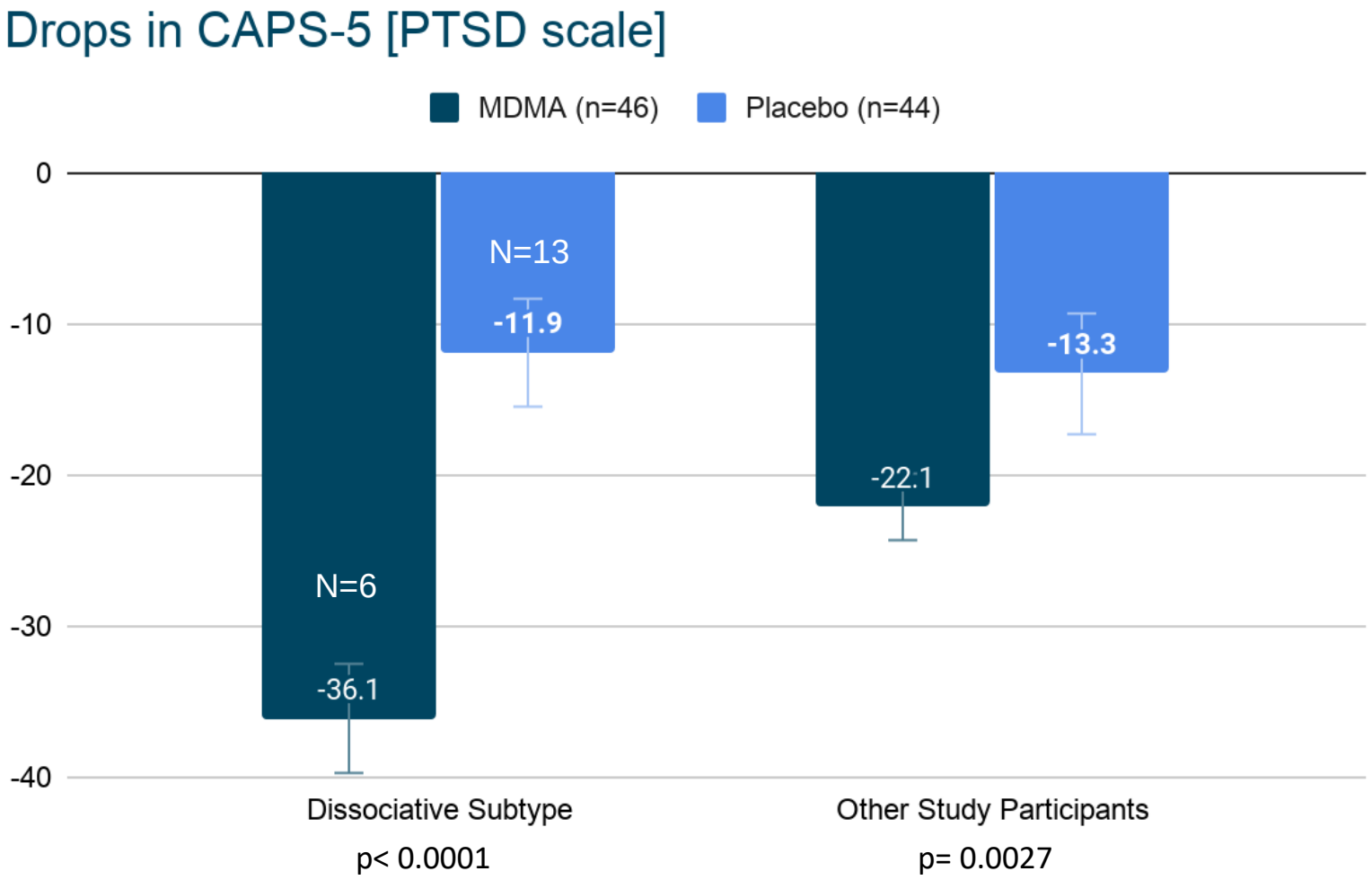
MAPS
MULTIDISCIPLINARY ASSOCIATION FOR PSYCHEDELIC STUDIES

MDMA Therapy Phase 3

0.91[1]
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



Treatment-Related Adverse Events in Phase 3

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

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

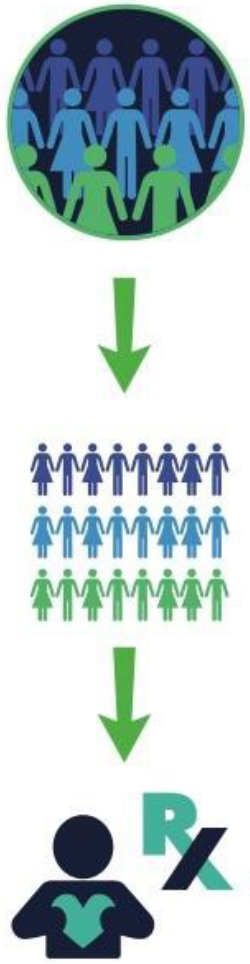
Serious Adverse Events of
Suicidal ideation and/or attempt

- 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

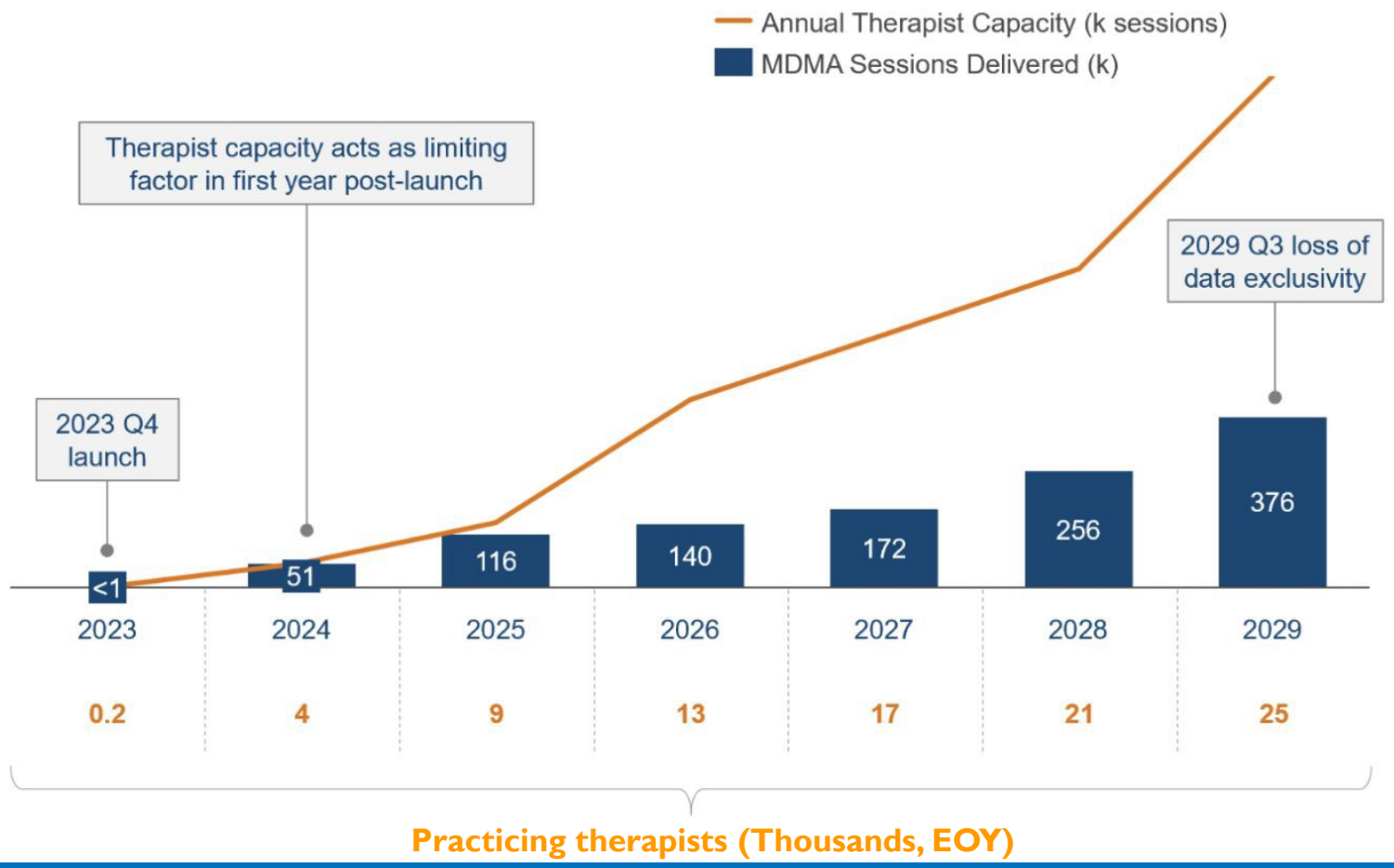
- ☑ Small p-value in 2 Phase 2 studies (0.001 & 0.002) and Phase 3 (0.0001)
- ☑ Large effect size in Phase 2 (0.8) and Phase 3 (0.91)
- ☑ Confirmed efficacy and reproducibility with an adequate well controlled study
- ☑ No site-to-site variability in 15-site Phase 3 study
- ☑ Positive Risk/Benefit Ratio 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

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

The Cost-Effectiveness of MDMA-Assisted Therapy

Elliot Marseille, PhD | Health Economist

- ◎Director for Cost-Effectiveness Analysis in Medicine and Public Health, UCSF
- ◎Principal of Health Strategies International AIDS
- ◎35 years public health management & research experience
- ◎70 peer reviewed publications

Marseille E, et al. PLoS One. 2020;15(10):e0239997.

Next Steps: New Indications & Protocols

PTSD: Cognitive Behavioral Conjoint Therapy & Group Therapy

Social Anxiety Disorder

Anxiety Associated with Life-Threatening Illness

Eating Disorders

Major Depressive Disorder

Substance Use Disorder and Alcohol Use Disorder

Obsessive Compulsive Disorder

Q + A

Thank You!

REFERENCES

Ahmadi, K., Azampoor-Afshar, S., Karami, G., & Mokhtari, A. (2011). The Association of Veterans' PTSD with Secondary Trauma Stress among Veterans' Spouses. *Journal of Aggression, Maltreatment & Trauma*, *20*(6), 636–644.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition). American Psychiatric Association.

Dorrington, S., Zavos, H., Ball, H., McGuffin, P., Rijsdijk, F., Siribaddana, S., Sumathipala, A., & Hotopf, M. (2014). Trauma, post-traumatic stress disorder and psychiatric disorders in a middle-income setting: Prevalence and comorbidity. *British Journal of Psychiatry*, *205*(5), 383–389.

Edmond, T., & Rubin, A. (2004). Assessing the Long-Term Effects of EMDR: Results from an 18-Month Follow-Up Study with Adult Female Survivors of CSA. *Journal of Child Sexual Abuse*, *13*(1), 69–86.

Feduccia, A.A. & Mithoefer, M.C. (2018). MDMA-Assisted Psychotherapy for PTSD: Are Memory Reconsolidation and Fear Extinction Underlying Mechanisms? Prog Neuropsychopharmacology Biol Psychiatry, 84(Pt A): 221-228.

Feduccia, A. A., Jerome, L., Yazar-Klosinski, B., Emerson, A., Mithoefer, M. C., & Doblin, R. (2019). Breakthrough for Trauma Treatment: Safety and Efficacy of MDMA-Assisted Psychotherapy Compared to Paroxetine and Sertraline. *Frontiers in Psychiatry*, *10*, 650.

Hake, H. S., Davis, J. K. P., Wood, R. R., Tanner, M. K., Loetz, E. C., Sanchez, A., Ostrovskyy, M., Oleson, E. B., Grigsby, J., Doblin, R., & Greenwood, B. N. (2019). 3,4-methylenedioxymethamphetamine (MDMA) impairs the extinction and reconsolidation of fear memory in rats. *Physiology & Behavior*, *199*, 343–350.

Jerome, L., Feduccia, A.A., Wang, J.B., Hamilton, S., Yazar-Klosinski, B., Emerson, A., Mithoefer, M.C., Doblin, R. (2020) Long-Term Follow-Up Outcomes of MDMA-Assisted Psychotherapy for Treatment of PTSD: A Longitudinal Pooled Analysis of Six Phase 2 Trials. Psychopharmacology.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *62*(6), 593.

Kibler, J. L., Joshi, K., & Ma, M. (2009). Hypertension in Relation to Posttraumatic Stress Disorder and Depression in the US National Comorbidity Survey. *Behavioral Medicine*, *34*(4), 125–132.

Lukaschek, K., Baumert, J., Kruse, J., Emeny, R. T., Lacruz, M. E., Huth, C., Thorand, B., Holle, R., Rathmann, W., Meisinger, C., & Ladwig, K.-H. (2013). Relationship between posttraumatic stress disorder and Type 2 Diabetes in a population-based cross-sectional study with 2970 participants. *Journal of Psychosomatic Research*, *74*(4), 340–345.

Ly, C., Greb, A. C., Cameron, L. P., Wong, J. M., Barragan, E. V., Wilson, P. C., Burbach, K. F., Soltanzadeh Zarandi, S., Sood, A., Paddy, M. R., Duim, W. C., Dennis, M. Y., McAllister, A. K., Ori-McKenney, K. M., Gray, J. A., & Olson, D. E. (2018). Psychedelics Promote Structural and Functional Neural Plasticity. *Cell Reports*, *23*(11), 3170–3182.

Marshall, W. L., & Marshall, L. E. (2000). The Origins of Sexual Offending. *Trauma, Violence, & Abuse*, *1*(3), 250–263.

Marseille E, Kahn J.G., Yazar-Klosinski, B., Doblin, R. (2020) The Cost-Effectiveness of MDMA-Assisted Psychotherapy for the Treatment of Chronic, Treatment-Resistant PTSD. PLoS ONE.

Mitchell, J et al. (2021). A Randomized, Double-Blind, Placebo Controlled Phase 3 Study Assessing Efficacy and Safety of MDMA-Assisted Therapy for the Treatment of Severe PTSD. *Nature Medicine*, In Press.

Mithoefer, M. C., Grob, C. S., & Brewerton, T. D. (2016). Novel psychopharmacological therapies for psychiatric disorders: Psilocybin and MDMA. *The Lancet Psychiatry*, *3*(5), 481–488.

Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., & Doblin, R. (2011). 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. *Journal of Psychopharmacology*, *25*(4), 439–452.

Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., Martin, S. F., Yazar-Klosinski, B., Michel, Y., Brewerton, T. D., & Doblin, R. (2013). 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. *Journal of Psychopharmacology*, *27*(1), 28–39.

Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., Holland, J., Hamilton, S., Yazar-Klosinski, B., Emerson, A., & Doblin, R. (2018). 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: A randomised, double-blind, dose-response, phase 2 clinical trial. *The Lancet Psychiatry*, *5*(6), 486–497.

Mithoefer, M. C., Feduccia, A. A., Jerome, L., Mithoefer, A., Wagner, M., Walsh, Z., Hamilton, S., Yazar-Klosinski, B., Emerson, A., & Doblin, R. (2019). MDMA-assisted psychotherapy for treatment of PTSD: Study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology*, *236*(9), 2735–2745.

Nardou, R., Lewis, E. M., Rothhaas, R., Xu, R., Yang, A., Boyden, E., & Dölen, G. (2019). Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature*, *569*(7754), 116–120.

Oehen, P., Traber, R., Widmer, V., & Schnyder, U. (2013). A randomized, controlled pilot study of MDMA (±3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *Journal of Psychopharmacology*, *27*(1), 40–52.

Ogden, P., Minton, K., & Pain, C. (2006). *Trauma and the body: A sensorimotor approach to psychotherapy* (1st ed). W.W. Norton.

Ot'alora G, M., Grigsby, J., Poulter, B., Van Derveer, J. W., Giron, S. G., Jerome, L., Feduccia, A. A., Hamilton, S., Yazar-Klosinski, B., Emerson, A., Mithoefer, M. C., & Doblin, R. (2018). 3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial. *Journal of Psychopharmacology*, *32*(12), 1295–1307.

Rauch, S. L., Shin, L. M., & Phelps, E. A. (2006). Neurocircuitry Models of Posttraumatic Stress Disorder and Extinction: Human Neuroimaging Research—Past, Present, and Future. *Biological Psychiatry*, *60*(4), 376–382.

Tarrier, N., & Gregg, L. (2004). Suicide risk in civilian PTSD patients: Predictors of suicidal ideation, planning and attempts. *Social Psychiatry and Psychiatric Epidemiology*, *39*(8).

Young, M B, Andero, R., Ressler, K. J., & Howell, L. L. (2015). 3,4-Methylenedioxymethamphetamine facilitates fear extinction learning. *Translational Psychiatry*, *5*(9), e634–e634.

Young, Matthew B., Norrholm, S. D., Khoury, L. M., Jovanovic, T., Rauch, S. A. M., Reiff, C. M., Dunlop, B. W., Rothbaum, B. O., & Howell, L. L. (2017). Inhibition of serotonin transporters disrupts the enhancement of fear memory extinction by 3,4- methylenedioxymethamphetamine (MDMA). *Psychopharmacology*, *234*(19), 2883– 2895.