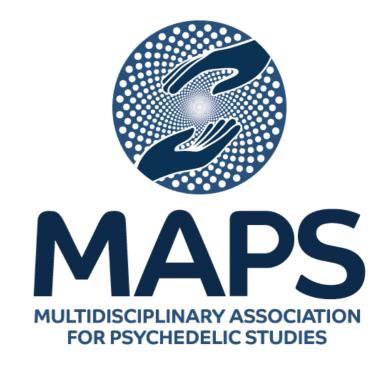
MDMA-Assisted Therapy for PTSD

Potential Need for 25,000 Trained, Educated Therapists

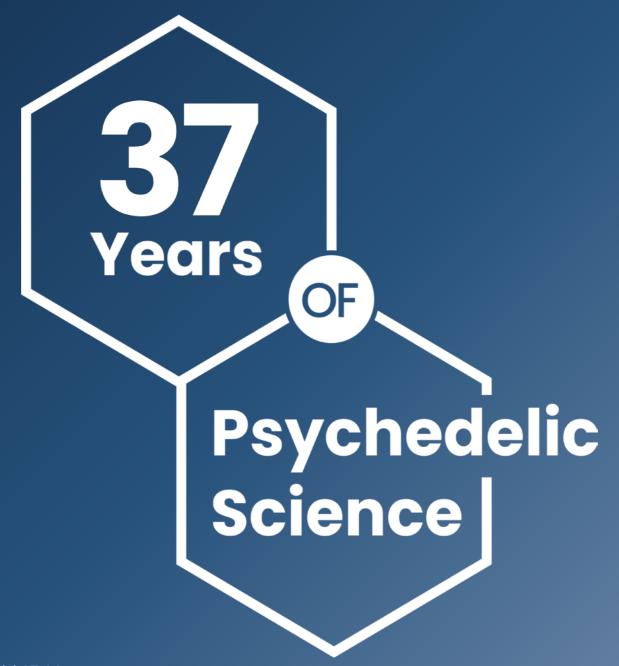
APA 2023

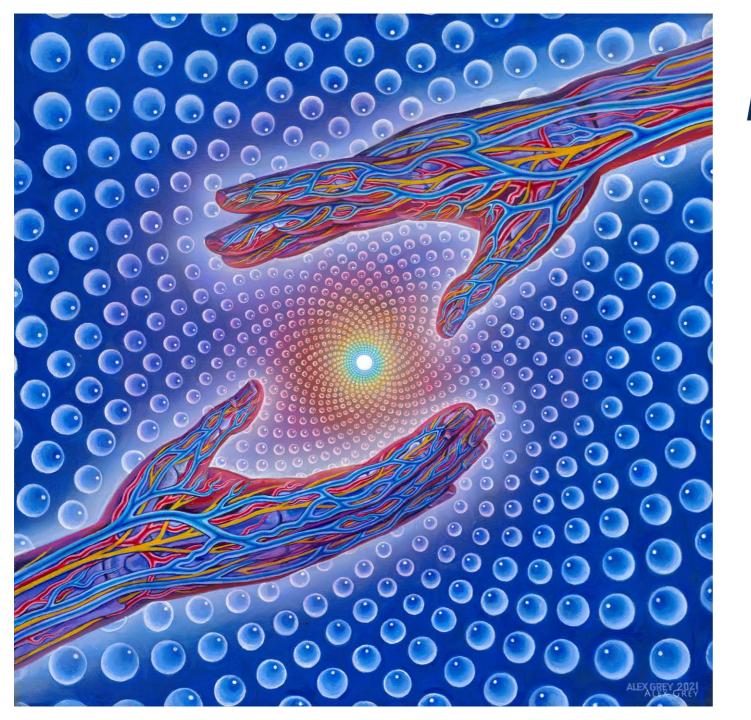
Washington, D.C. | August 5, 2023



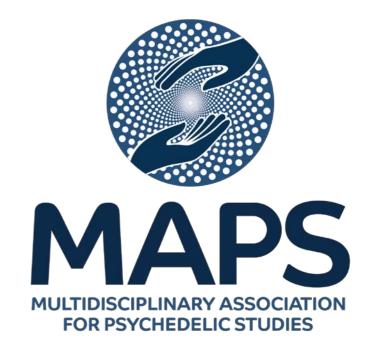
Rick Doblin, Ph.D.

President & Founder





Psychedelic Healing by Alex Grey (2021)





MDMA-Assisted Therapy for PTSD

- Two successful Phase 3 studies completed 1,2
- Submission of New Drug Application (NDA) to FDA planned for Q3 2023²
- Potential FDA approval in mid-2024

^{2.} MAPS PBC Announces Positive Results from Confirmatory Phase 3 "MAPP2" Trial of MDMA-Assisted Therapy for Treatment of PTSD. Jan. 5, 2023. https://mapsbcorp.com/press-releases/maps-pbc-announces-positive-results-from-confirmatory-phase-3-mapp2-trial/ MDMA-AT has not been approved by any regulatory agency. The safety and efficacy of MDMA-AT have not been established for the treatment of PTSD.

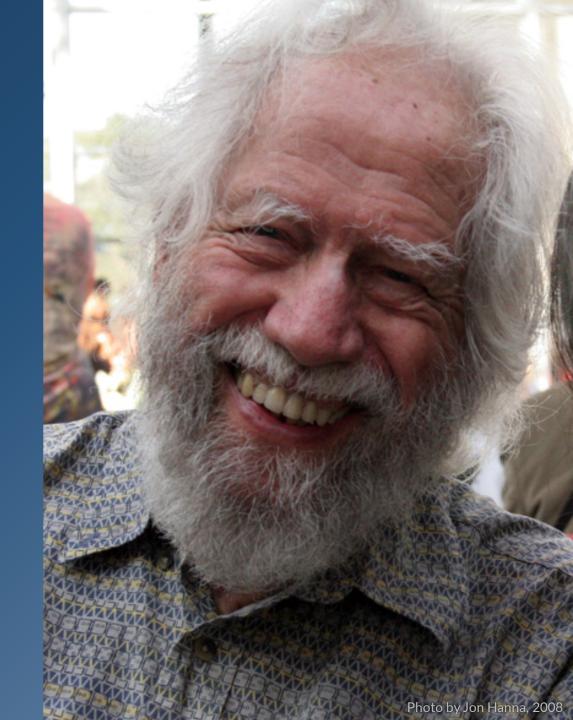


MDMA was first synthesized and patented by the pharmaceutical company Merck as "Methylsafrylamin."

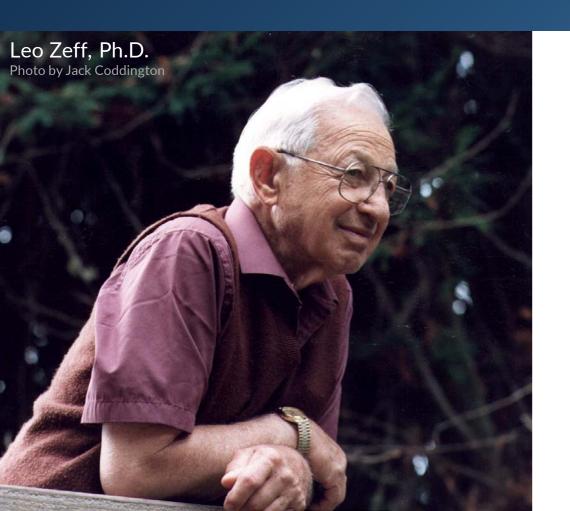
It was an unimportant precursor in a new synthesis for clotting agents.

Mid-1970s Rediscovery of MDMA

American chemist Alexander "Sasha" Shulgin, Ph.D. (1925-2014), resynthesized MDMA and experimented with the drug himself.



Mid-1970s in San Francisco Start of MDMA-Assisted Psychotherapy



- MDMA used in psychotherapy with good results
- Estimated 500,000 doses of MDMA used in therapeutic growth settings from mid-1970s until 1984
- Recreational use of Ecstasy began in late 1970s

^{1.} Stolaroff MJ. The Secret Chief Revealed. 2004. Sarasota, FL: MAPS.

^{2.} Greer G, Tolbert R. J Psychoactive Drugs. 2012;44(4):319-327.

Early 1980s

"Ecstasy" became a popular drug often at dance clubs and raves in the U.S. and Europe.

Initially pure MDMA, "ecstasy" was often adulterated following its criminalization.





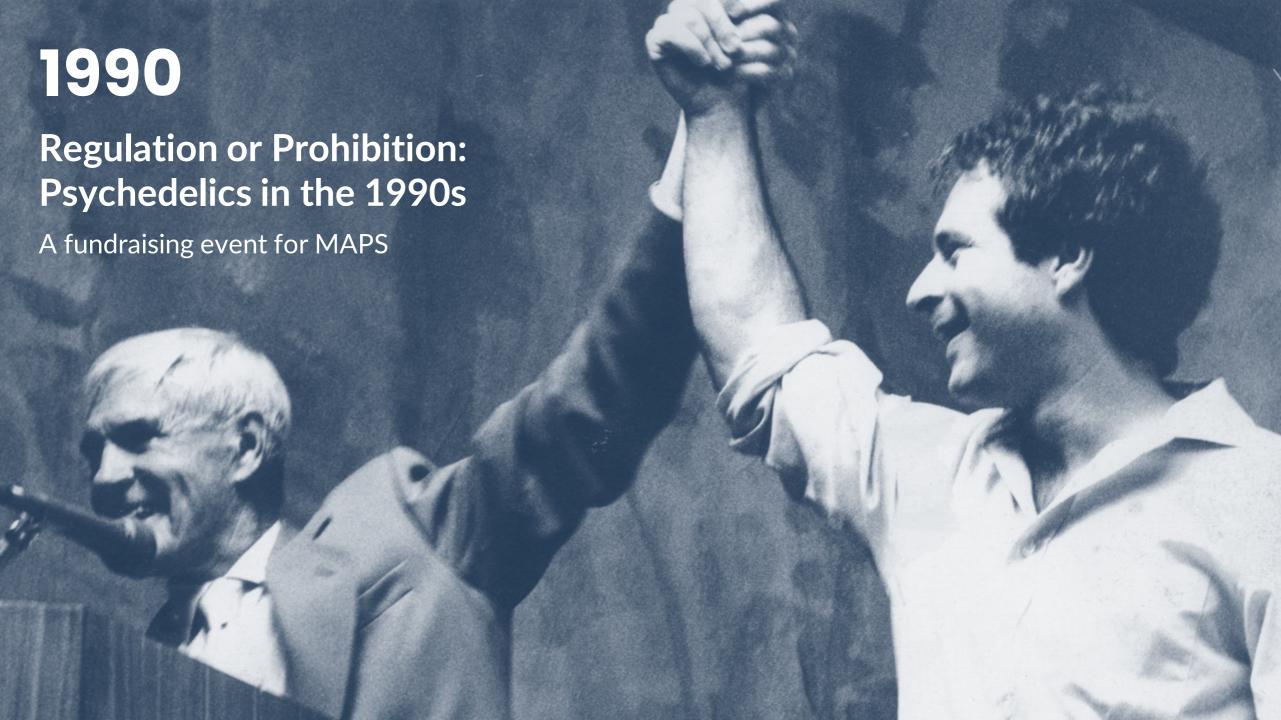
Due to ecstasy use, DEA moved to criminalize MDMA in Schedule I.

Advocates of therapeutic use filed for DEA Administrative Law Judge (ALJ) hearing within 30-day public comment period.

MAPS was founded on April 8, 1986.







FDA allowed first Phase 1 dose response safety study for MDMA in humans.

Charles Grob, M.D.

Harbor-UCLA Medical Center



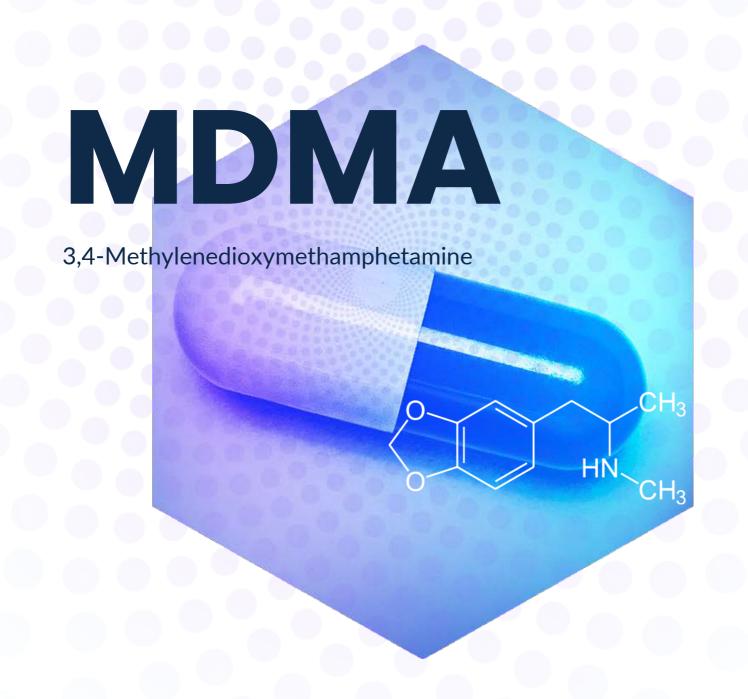
Copernicus Group Independent Review Board approved the first MAPS-sponsored protocol of MDMA-assisted therapy for PTSD.

MAPS initiated contact with Copernicus Group IRB based on their name.

November 29, 2016

MAPS' End of Phase 2 meeting with FDA about MDMA-assisted therapy for PTSD





Increases release of 1,2:

- Serotonin (5-HT)
- Norepinephrine (NE)
- Dopamine (DA)

Enhances release of hormones²:

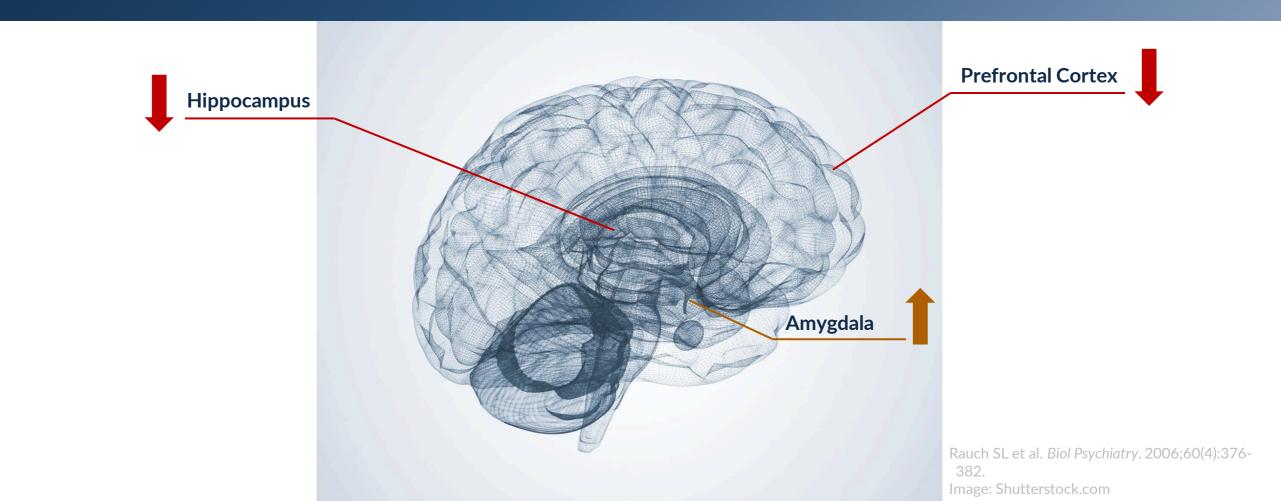
- Oxytocin
- Prolactin
- Vasopressin
- Cortisol

^{1.} Feduccia AA, Mithoefer MC. Progr in Neuropsychopharmacol & Biol Psychiatry. 2018;84(Pt A):221-228.

^{2.} Hysek CM, et al. Soc Cogn Affect Neurosci. 2014;9(11):1645-1652.

Model of Neurological Effects of PTSD

Difficulty in reducing and eliminating fear conditioning responses



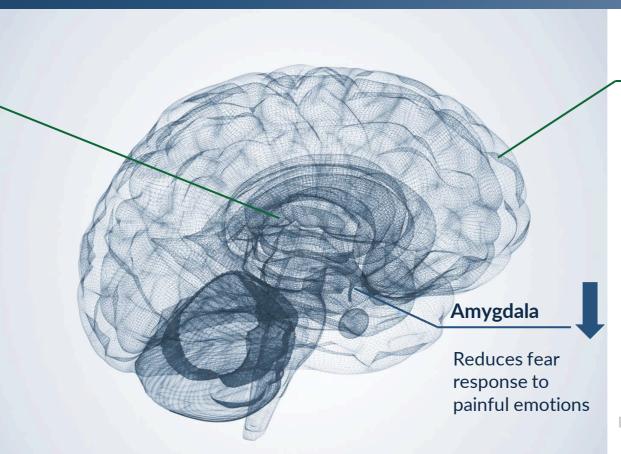
Model of Neurological Effects of MDMA

Increased therapeutic alliance and ability to process traumatic material



Hippocampus

Facilitates long-term storage of traumatic memories



Prefrontal Cortex

Increases cognitive processing of fear response

Feduccia AA, Mithoefer MC. Progr in Neuropsychopharmacol & Biol Psychiatry. 2018;84(Pt A):221-228. Image: Shutterstock.com

SLC6A4 binding site and acute prosocial effects of (+/-)-3,4-methylendioxymethamphetamine (MDMA) are evolutionarily conserved in Octopus bimaculoides

Eric Edsinger & Gül Dölen Current Biology (2018)

nature

Letter Published: 03 April 2019

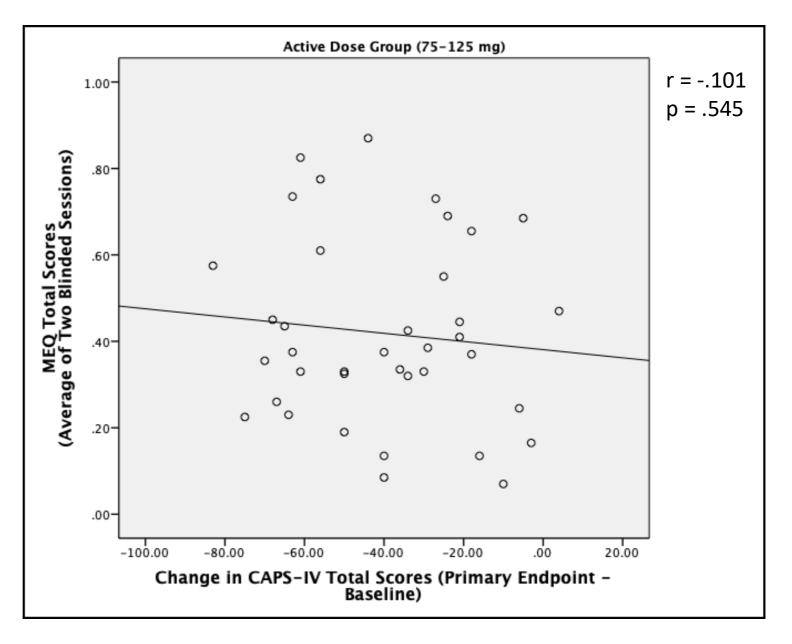
Oxytocin-dependent reopening of a social reward learning critical period with MDMA

Romain Nardou, Eastman M. Lewis, Rebecca Rothhaas, Ran Xu, Aimei Yang, Edward

Boyden & Gül Dölen ☑

Phase 2 Data

Mystical experience scores were not correlated with PTSD symptom reduction in the MDMA active dose group



What Does MDMA-Assisted Therapy Look Like?



An alliance between therapists and participants

- Empathetic rapport & presence
- Support participant's own healing process
- Emphasis on preparation and integration
- Trust in the process

Direction of the session sourced from the participant's experience

An inner-directed therapeutic approach centers on the belief that each person has an intrinsic wisdom and natural ability to heal

maps.org/treatmentmanual

MDMA-AT has not been approved by any regulatory agency.
The safety and efficacy of MDMA-AT have not been established for the treatment of PTSD

A Manual for MDMA-Assisted Therapy in the Treatment of Posttraumatic Stress Disorder

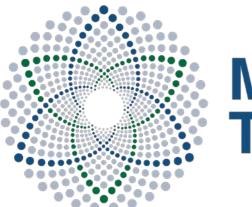
Michael Mithoefer, M.D.
Annie Mithoefer, B.S.N.
Lisa Jerome, Ph.D.
June Ruse, Psy.D.
Rick Doblin, Ph.D.
Elizabeth Gibson, M.S.
Marcela Ot'alora G., L.P.C.
Evan Sola, Psy.D. candidate

Manualized Therapeutic Method

The therapeutic approach is an adaption of the foundation laid by Stanislav Grof, M.D., Ph.D., and others.

maps.org/treatmentmanual

MDMA-AT has not been approved by any regulatory agency. The safety and efficacy of MDMA-AT have not been established for the treatment of PTSD.



MDMA-Assisted Therapy Education

The application is now open for Fall 2023:

mapsbcorp.com/mdma-at-education/ mdma-at-about-the-program

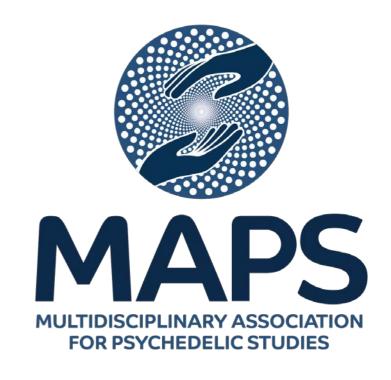
55-hour immersion course

- Live presentations
- Video case presentations
- Enriching discussions
- Scenario-based learning
- Self-reflection
- Small group activities
- Online coursework
- Creative projects



Phase 3 Study Results

Pivotal (MAPP1) and Confirmatory (MAPP2)



nature, medicine

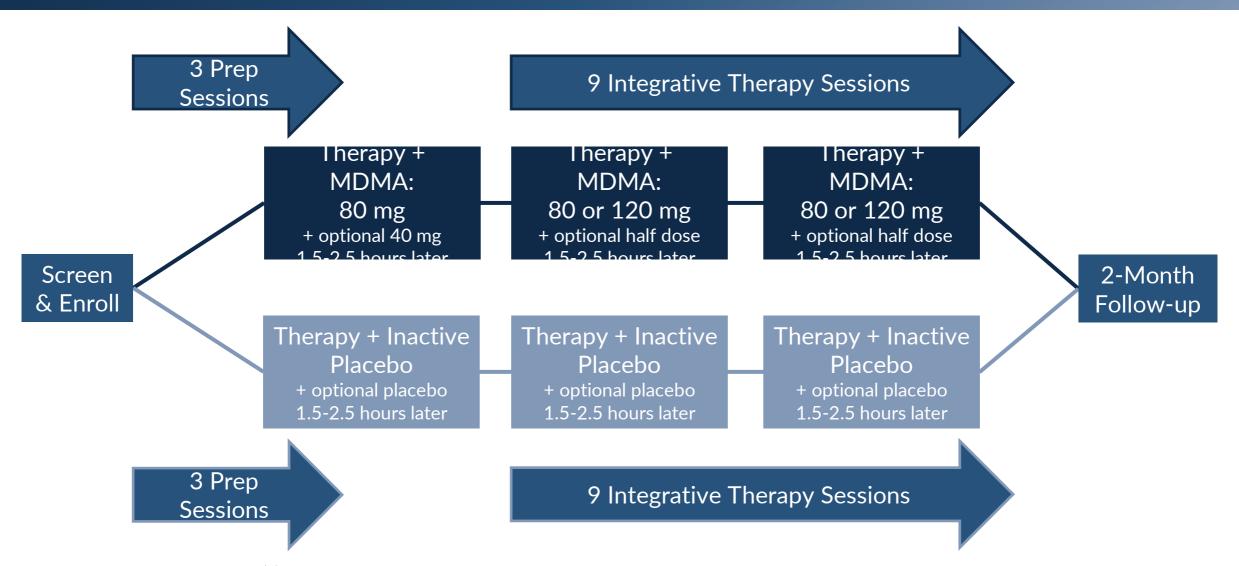
Article Open Access Published: 10 May 2021

MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study

Jennifer M. Mitchell ☑, Michael Bogenschutz, Alia Lilienstein, Charlotte Harrison, Sarah Kleiman, Kelly Parker-Guilbert, Marcela Ot'alora G., Wael Garas, Casey Paleos, Ingmar Gorman, Christopher Nicholas, Michael Mithoefer, Shannon Carlin, Bruce Poulter, Ann Mithoefer, Sylvestre Quevedo, Gregory Wells, Sukhpreet S. Klaire, Bessel van der Kolk, Keren Tzarfaty, Revital Amiaz, Ray Worthy, Scott Shannon, Joshua D. Woolley, ... Rick Doblin

Phase 3 Study Design

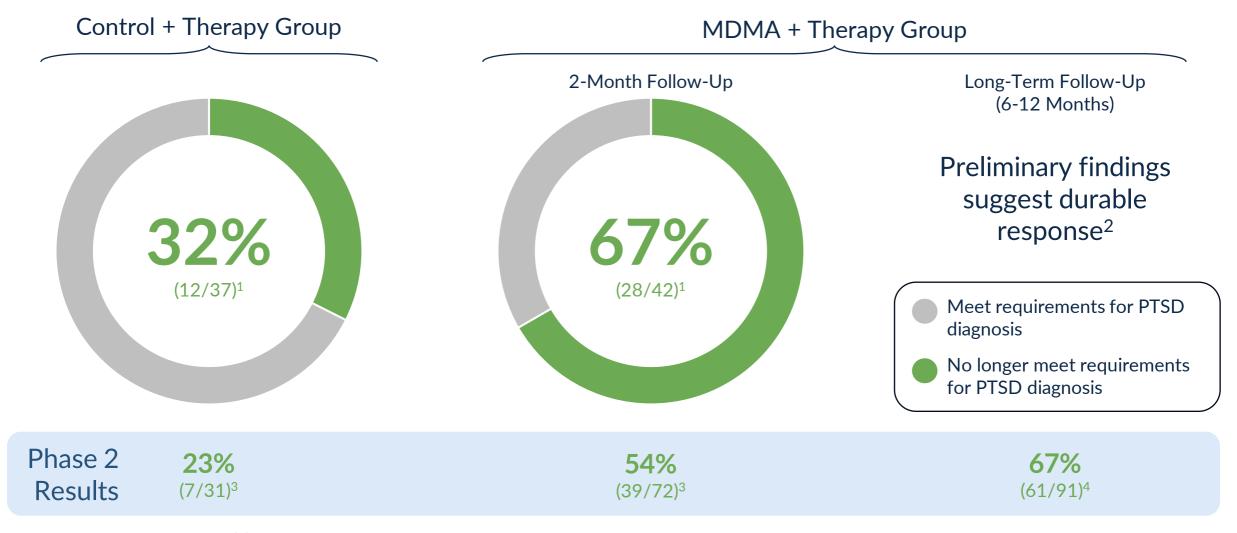
MDMA-Assisted Therapy for PTSD



- 1. Mitchell JM, et al. Nat Med. 2021;27(6):1025-1033.
- 2. Data on file (MAPP2 Protocol IND #063384), MAPS.

Results of MAPP1: MDMA-Assisted Therapy for PTSD

Two-thirds of participants in MDMA group no longer qualified for a PTSD diagnosis



1. Mitchell JM, et al. *Nat Med*. 2021;27(6):1025-1033. 2. MAPS PBC Announces Positive Topline Results from Long-Term Observational Follow-Up Study on MDMA-Assisted Therapy for Treatment of PTSD. Apr. 5, 2023. https://mapsbcorp.com/press-releases/maps-pbc-announces-positive-topline-results-from-long-term-observational-follow-up-study-on-mdma-assisted-therapy-for-treatment-of-ptsd/ 3. Mithoefer MC, et al. *Psychopharmacology (Berl)*. 2019;236(9):2735-2745. 4. Jerome L, et al. *Psychopharmacology (Berl)*. 2020;237(8):2485-2497.

Results From Long-Term Observational Follow-Up Study on MDMA-Assisted Therapy for PTSD April 5, 2023



"According to MAPS PBC, these preliminary findings 'show that participants in this study demonstrated a durable response at least six months, and in some cases a year or more, after their final MDMA-assisted therapy session during the Phase 3 study."

MAPPI Safety Data

Most Common
Non-Serious, Transient,
Treatment-Emergent
Reported Adverse Events

Most frequent non-serious adverse events for the MDMA group:

- Muscle tightness
- Decreased appetite

AE	MDMA n=46	Placebo n=44
Muscle Tightness	29 (63.0%)	5 (11.4%)
Decreased Appetite	24 (52.2%)	5 (11.4%)
Nausea	14 (30.4%)	5 (11.4%)
Hyperhidrosis (sweating)	9 (19.6%)	1 (2.3%)
Feeling Cold	9 (19.6%)	3 (6.8%)
Restlessness	7 (15.2%)	0
Mydriasis (dilated pupils)	7 (15.2%)	0
Bruxism (teeth grinding)	6 (13.0%)	1 (2.3%)
Nystagmus (eye wiggling)	6 (13.0%)	0
Dizziness Postural	6 (13.0%)	2 (4.5%)
Blood Pressure Increased	5 (10.9%)	0
Feeling Jittery	5 (10.9%)	0
Non-Cardiac Chest Pain	5 (10.9%)	1 (2.3%)
Dry Mouth	5 (10.9%)	2 (4.5%)

MAPPI Safety Data

Participants reporting Serious Adverse Events (SAEs)

- 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

Participants reporting Adverse Events of Special Interest

Suicidality

Suicidal thoughts, behavior, self-harm

- 7% (3/46) in MDMA group
- 11% (5/44) in placebo group
- Cardiovascular

Irregular heart rhythm, palpitations

- 0% (0/46) in MDMA group
- 2% (1/44) in placebo group
- Abuse potential

Dependence, substance use disorder

- 0% (0/46) in MDMA group
- 0% (0/44) in placebo group



Results of MAPS' first Phase 3 study

One of Science's **Top 10** Breakthroughs of the Year

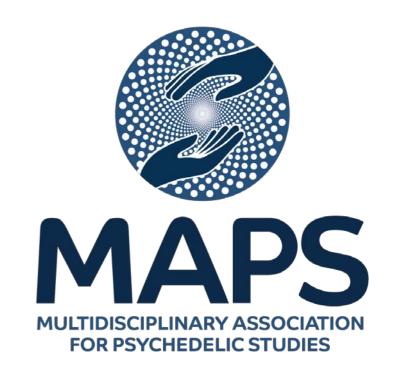
Pennisi E, et al. Science. 2021;374(6574):1428-1433.

MDMA-AT has not been approved by any regulatory agency.

The safety and efficacy of MDMA-AT have not been established for the treatment of PTSD.

January 5, 2023 MAPS Press Release

Prior Positive Results Confirmed in MAPS-Sponsored, Philanthropy-Funded Phase 3 Trial



May 2, 2023

American Medical Association to Issue First New Billing Code for Psychedelic Therapies



Ambitious Goals

Pending potential FDA approval

By 2030, train 25,000 therapists

By 2032, treat **over**1.5 million U.S. PTSD
patients of current
U.S. PTSD population
(13 million¹)

1. VA National Center for PTSD. https://www.ptsd.va.gov/understand/common/common adults.asp

Therapist Training in Clinical Program and Requirement Questions



MAPS' Phase 3 clinical trials have been conducted with a two-person therapy team of which both providers have undergone MAPS PBC's MDMA Therapy Training Program.^{1,2}

If MDMA-AT for PTSD is approved by FDA, what will the provider requirements be?

^{1.} Mitchell JM et al. Nat Med. 2021;27(6):1025-1033.

^{2.} Data on file (MAPP2 Protocol IND #063384), MAPS.
MDMA-AT has not been approved by any regulatory agency.
The safety and efficacy of MDMA-AT have not been established for the treatment of

Formal Dispute Resolution Request

MT2: Phase 1
Study of MDMAAssisted Therapy in
Healthy Volunteers

Optional
Experiential
Component of
MDMA Therapy
Training Program

The protocol to administer MDMA to therapists as part of their training does not pass risk/benefit test.

Clinical hold removed.

The lead facilitator of the two-person therapy team needs to be an MD or PhD.

No. The lead facilitator must be licensed to do therapy, but not MD or PhD. Co-facilitator doesn't need a license but needs 1,000 hours mental health experience or in-program to get a license (+ Bachelor's degree).

A physician needs to be on site, not just on call.

No. Physician screening, then on call.

Evaluation of MDMA-Assisted Therapy With Different Therapeutic Modalities or for Potential Clinical Indications Other Than PTSD

MDMA-Assisted Cognitive-Behavioral Conjoint Therapy (CBCT) in Dyads in Which One Member Has PTSD

Candice Monson, Ph.D. Ryerson University





MDMA-Assisted Therapy in Combination With Cognitive Processing Therapy (CPT) for PTSD

Anne Wagner, Ph.D., C.Psych. Ryerson University

MDMA-Assisted Therapy in Combination With Prolonged Exposure (PE)*

* Two differently designed and independent studies



Barbara Rothbaum, Ph.D.

Emory University

ClinicalTrials.gov Identifier: NCT05746572

Edna Foa, Ph.D.¹ The 2010 *TIME* 100²

1. Internal document, Rick Doblin. Apr. 12, 2022. 2. Kluger J. *TIME*. The 2010 TIME 100. Apr. 29, 2010. https://content.time.com/time/specials/packages/article/0.28804.1984685 1984745 1985506.00.html



MDMA-Assisted Therapy for Social Anxiety in Adults on the Autism Spectrum



Charles Grob, M.D. Alicia Danforth, Ph.D.

Harbor-UCLA Medical Center

Danforth AL, et al. *Psychopharmacology (Berl)*. 2018;235:3137-3148.

MDMA-AT has not been approved by any regulatory agency. The safety and efficacy of MDMA-AT have not been established for the treatment of PTSD.

MDMA-Assisted Therapy for Treatment of Anxiety Associated With Life-Threatening Illness



MDMA-Assisted Therapy for Alcohol Use Disorder (AUD)





Ben Sessa, M.D.
University of Bristol

Sessa B, et al. *J Psychopharmacol*. 2021;35(4):375-383.

MDMA-AT has not been approved by any regulatory agency.

The safety and efficacy of MDMA-AT have not been established for the treatment of PTSD.

MDMA-Assisted Therapy for Adjustment Disorder (AD) in Dyads of Patients With Cancer and a Concerned Significant Other



Principal Investigator: Manish Agrawal, M.D.

To assess the effectiveness of the intervention on Adjustment Disorder and relationship functioning in patients with cancer and a CSO.

The study will assess participants scores on The Adjustment Disorder New Module - 20 items (ADNM-20) and Couples Satisfaction Index (CSI-16) scores from baseline to the primary time point.

ClinicalTrials.gov Identifier: NCT05584826

MDMA-AT has not been approved by any regulatory agency.

The safety and efficacy of MDMA-AT have not been established for the treatment of PTSD.

Studies of MDMA-Assisted Therapy for PTSD Within VA Facilities



Loma Linda VA MDMA-Assisted Therapy for PTSD

ClinicalTrials.gov Identifier: NCT04264026



Shannon Remick, M.D.

October 12, 2021

Historic first dose of MDMA administered to a Veteran with PTSD inside of a VA facility, 26 years after MAPS first offered in 1995 to fund research inside the San Francisco VA

Bronx VA

MDMA-Assisted Therapy: Two MDMA Sessions Versus Three MDMA Sessions



Rachel Yehuda, Ph.D.

Director of the Traumatic Stress Studies Division at the Icahn School of Medicine at Mount Sinai, which includes the PTSD Clinical Research Program and the Neurochemistry, Neuroendocrinology, and Molecular Biology Lab at the James J. Peters Veterans Affairs Medical Center in the Bronx

Portland VA

MDMA-Assisted Group Therapy for the Treatment of PTSD in Veterans (MPG1)

Chris Stauffer, M.D.

Assistant Professor of Psychiatry at the Oregon Health & Science University (OHSU)

Physician Scientist at the Portland VA Medical Center

ClinicalTrials.gov Identifier: NCT05173831 maps.org/mdma/ptsd/mpg1





Palo Alto VA

MDMA-Assisted Therapy Versus Cognitive Processing Therapy (CPT)

Trisha Suppes, M.D., Ph.D.

West Los Angeles VA MDMA-Assisted Therapy Versus Therapy With d-Amphetamine

Stephanie L. Taylor, Ph.D., MPH



San Diego VA and Phoenix VA

MDMA-Assisted
Therapy in
Combination with
Cognitive Behavioral
Conjoint Therapy
(CBCT) for PTSD*

* Two differently designed and independent studies



Leslie Morland, Psy.D.
San Diego VA

Personal communication between Leslie Morland and Rick Doblin. Apr. 19, 2022.



Personal communication between Brandi Luedtke and Rick Doblin. Apr. 17, 2023.







FDA-Required Pediatric Study

- Adolescents ages 13-17 with PTSD
- If successful, then children ages 7-12 with PTSD

Data on file (Agreed Initial Pediatric Study Plan Agreement, ING 63384), MAPS. MDMA-AT has not been approved by any regulatory agency.

The safety and efficacy of MDMA-AT have not been established for the treatment of PTSD.

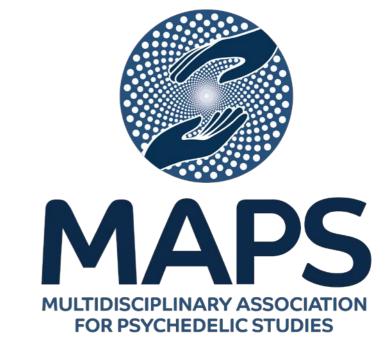
Potential Future Dose Response Safety Study

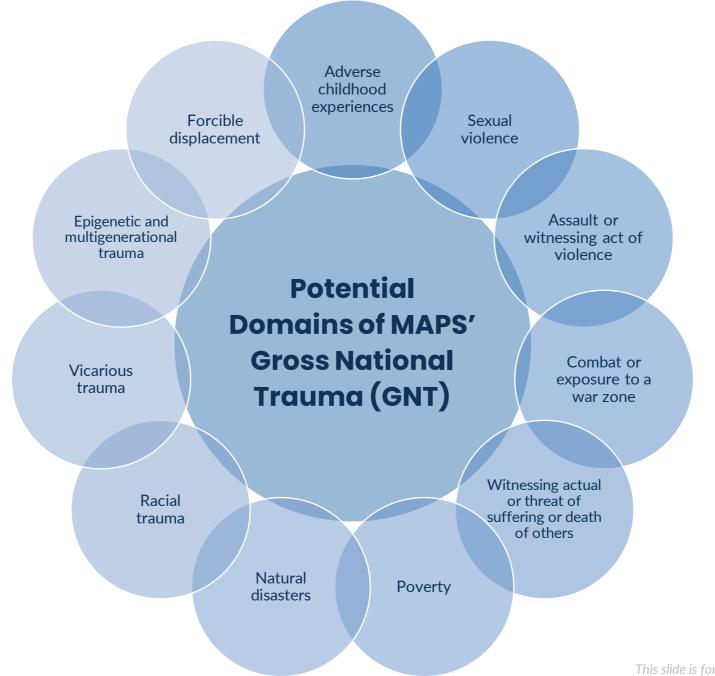


MDMA-Assisted Therapy in PTSD Patients on SSRIs

Toward a World of Net-Zero Trauma by 2070

HEALING FOR ALL









Learn more and apply:

mapsbcorp.com/mdma-ateducation/ mdma-at-about-the-program

Fall Virtual Immersion

6 virtual live sessions via Zoom

- Online course launches September 23
- Live Virtual Sessions: October 7–9,
 November 10–12

Fall Hybrid Immersion

2 virtual live sessions via Zoom + 4.5 consecutive days in-person

- Online course launches September 30
- Live Virtual Sessions: October 14–15
- In-Person Session at Usona Institute in Wisconsin November 8–12