Research News

MDMA-Assisted Psychotherapy

MAPS and MAPS Public Benefit Corporation Announce Positive Result from Phase 3 Trial of MDMA-Assisted Psychotherapy for PTSD

In November 2020, MAPS Public Benefit Corporation (MAPS PBC) completed data analysis of the first of two Phase 3 trials of MDMA-assisted psychotherapy for treatment of posttraumatic stress disorder (PTSD). The results confirmed Phase 2 results and prior expectations from an independent interim analysis which determined there was a 90% or greater probability that the trial, when completed, would be of sufficient size to detect statistically significant results. Further, no unexpected or serious safety signals emerged during the course of the trial.

The results indicate MDMA-assisted psychotherapy for PTSD may be an effective treatment for PTSD resulting from various types of trauma, including trauma occurring in childhood and in patients with dissociative subtype of PTSD, pending assessment by the U.S. Food and Drug Administration (FDA). Based on these results, MAPS will begin discussions with the FDA on ways to accelerate the timeframe for approval of this modality.

The Phase 3 trial, the first of its kind in scope and size, treated 90 participants who received 3 day-long MDMA or placebo sessions one month apart and 12 90-minute non-drug psychotherapy sessions over approximately 3.5 months. The severity of PTSD symptoms was measured using the Clinician-Administered PTSD Scale for the DSM-5 (CAP-5); measurements were taken before and after completion of treatment. Of these 90 participants, approximately half received MDMA-assisted psychotherapy. The other half of participants, the control group, received placebo with identical therapy. A second Phase 3 clinical trial is currently enrolling participants.

Bessel van der Kolk, M.D., a leading PTSD researcher and author of the foundational book on PTSD, *The Body Keeps the Score*, served as Principal Investigator for the Boston site of the study. He noted, "The experience of having been traumatized profoundly alters perceptions; self-experience; and capacity to plan, imagine and anticipate. Since the results of this study mirror previously published results, we can expect to see fundamental shifts in our subjects' perspective on self-capacity, affect regulation, and attitude towards those around them. It takes a great deal of courage to address one's PTSD, particularly when other treatments have failed. These results open the door to a powerful new pathway to healing once MDMA-assisted psychotherapy has been approved as a treatment for PTSD."

Phase 3 Trials of MDMA-Assisted Psychotherapy for PTSD: Seeking Research Volunteers

We are currently seeking research volunteers for our second Phase 3 clinical trial of MDMA-assisted psychotherapy for PTSD. Volunteers will help contribute to scientific knowledge and will help us better understand if MDMA-assisted psychotherapy works for treatment of PTSD. MAPS conducts clinical trials under the guidance and regulations of the FDA in collaboration with federal regulators, including the Drug Enforcement Administration (DEA). To learn more about our clinical trials or apply to be a study participant, please visit our website: **mdmaptsd.org**.

We are recruiting participants in the following locations:

- Los Angeles, California | Private Practice
- San Francisco, California | Private Practice
- Boulder, Colorado | Private Practice
- Fort Collins, Colorado | Private Practice
- New Orleans, Louisiana | Private Practice
- Charleston, South Carolina | Private Practice
- Boston, Massachusetts | Private Practice

Not yet recruiting:

- San Francisco, California | Research Institution
- New York, New York | Private Practice
- New York, New York | Research Institution
- Madison, Wisconsin | Research Institution
- Vancouver, Canada | Research Institution
- Be'er Ya'akov, Israel | Research Institution
- Tel Aviv, Israel | Research Institution

The trials are the final phase of research required by the FDA before deciding whether to approve MDMA as a legal prescription treatment for PTSD. If approved, MDMA will be required to be used in conjunction with psychotherapy in an outpatient setting.

There is now a clear path ahead to make MDMA a legal medicine for millions of people suffering from PTSD. Help heal trauma: **maps.org/donate**

MDMA-Assisted Psychotherapy Will Be Cost-Effective in the Treatment of PTSD

A peer-reviewed study published on October 14, 2020, in the research journal *PLOS ONE* demonstrates that MDMA-assisted psychotherapy is remarkably cost-effective when compared to currently available treatments for PTSD. It is estimated that a public healthcare payer or private insurer making MDMA-assisted psychotherapy available to 1,000 patients with PTSD would reduce general and mental health care costs by $103.2 million over 30 years.

Lead author Elliot Marseille, Dr.P.H., M.P.P., elaborates, "MDMA-assisted psychotherapy is conducted by a licensed psychologist and trained clinician over the course of twelve sessions with three sessions lasting six or more hours. The cost of that time is not inconsiderable, but in just over three years, healthcare providers will break even on the costs of mental health and general medical care. These estimates are promising yet likely too conservative: the study did not measure the value of increased productivity or lower disability payments as patients recover from PTSD and is constrained by the limited availability of data on the long-term trajectory of PTSD. Further research will be needed to determine the full financial, personal, and societal benefits of MDMA-assisted psychotherapy for PTSD."

Berra Yazar-Klosinski, Ph.D., Deputy Director and Head of Research Development and Regulatory Affairs for MAPS PBC and co-author, developed the protocols studying MDMA-assisted psychotherapy. She notes, "A growing body of evidence suggests that MDMA-assisted psychotherapy may be more effective than currently available treatments for PTSD, a notoriously difficult-to-treat condition. Previous research has focused on safety and efficacy and indicates statistically significant improvements over psychotherapy with a control, demonstrating reduction in symptoms for 82% of participants. This study should compel healthcare providers to include MDMA-assisted psychotherapy as a covered treatment for PTSD following FDA approval."

Rick Doblin, Ph.D., Executive Director of MAPS and a study co-author, states, "The profound personal toll of PTSD can include deterioration in physical health, relationships, and ability to participate in social activities along with the anxiety, insomnia, and suicidal ideation that mark the condition. By demonstrating a return of an average of 5.5 quality-adjusted life-years over 30 years, we have shown that MDMA-assisted psychotherapy has the potential to reduce more than the personal burden of PTSD, contributing to improved health outcomes and reduced healthcare burdens for payers and providers."

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The cost-effectiveness of MDMA-assisted psychotherapy from the U.S. healthcare payers' perspective was constructed with a decision-analytic Markov model to portray the costs and health benefits of treating patients with chronic, severe, or extreme, treatment-resistant PTSD. Efficacy was based on the pooled results of six randomized controlled trials with the 105 subjects who participated in Phase 2 trials and a four-year follow-up of 19 of those subjects. Other inputs were based on published literature and on assumptions when data were unavailable. Results are modeled over a 30-year analytic horizon and conducted extensive sensitivity analyses. The model calculates expected medical costs, mortality, quality-adjusted life-years, and incremental cost-effectiveness ratio.

The safety and efficacy of MDMA-assisted psychotherapy is currently under investigation. This treatment has not yet been approved by the FDA, does not work for everyone, and carries risks even in therapeutic settings. To learn more, please visit **mdmaptsd.org**.

MDMA-Assisted Psychotherapy May Have Lasting Benefits for PTSD, Results Published in *Psychopharmacology*

On June 10, 2020, MAPS announced the publication of the long-term follow-up results of six Phase 2 clinical trials of MDMA-assisted psychotherapy for the treatment of PTSD in the peer-reviewed journal *Psychopharmacology*. The paper is the most comprehensive analysis yet published of the safety and durability of treatment outcomes following MDMA-assisted psychotherapy for PTSD.

The results show that for a majority of participants, the benefits of MDMA-assisted psychotherapy for PTSD extended at least 12 months after the treatment sessions. Sponsored by MAPS, the controlled, randomized, double-blind trials found that, two months following their last session, 56% of 100 participants no longer met diagnostic criteria for PTSD. In the newly published analysis, 91 participants were interviewed at least 12 months later. Of these participants, 67% did not qualify for a PTSD diagnosis. One of the studies included data from an average of 3.8 years after treatment.

"Trauma exposure has emerged as one of the most pressing public health issues of our time and is now at the forefront of global consciousness due to the COVID-19 pandemic and rising visibility of systemic oppression," said Berra Yazar-Klosinski, Ph.D., paper co-author and Deputy Director and Head of Research Development and Regulatory Affairs at MAPS. "Although our Phase 3 trials are not yet completed, these long-term data support the hypothesis

that MDMA-assisted psychotherapy may provide significant advantages in treatment outcomes, safety, and durability over available PTSD treatments. This is the breakthrough that the world needs right now."

The trials were conducted by independent investigators in South Carolina (two trials), Colorado, Canada, Switzerland, and Israel. Trial participants included women and men with chronic, treatment-resistant PTSD from a wide variety of causes.

PTSD symptoms were assessed using the Clinician-Administered PTSD Scale (CAPS-IV) at baseline, one to two months after their last MDMA-assisted psychotherapy session, and at least 12 months after their final session. The course of double-blind treatment included one to three eight-hour MDMA-assisted psychotherapy sessions spaced three to five weeks apart, combined with weekly non-drug psychotherapy sessions. Outcomes were assessed by blinded Independent Raters.

Based on these results, in August 2017, the FDA granted breakthrough therapy designation to MDMA-assisted psychotherapy for PTSD, acknowledging that it "may demonstrate substantial improvement over existing therapies" and agreeing to expedite its development and review. The FDA also considered MAPS' prior published Phase 2 results when it agreed to MAPS' expanded access program in January 2020.

The follow-up study found that long-term adverse events were minimal although the benefits were sustained. The most common harm reported at the long-term follow-up was worsened mood, reported by less than 4% of study participants. Further assessment of the long-term benefits and risks of MDMA-assisted psychotherapy is needed in future trials that include control groups.

FDA Agrees to Expanded Access Program for MDMA-Assisted Psychotherapy for PTSD

On December 20, 2019, the FDA agreed to MAPS' application for an expanded access program for MDMA-assisted psychotherapy for PTSD.

The purpose of the expanded access program is to allow early access to the potential benefits of treatment with MDMA-assisted psychotherapy to people for whom currently available treatments have not worked, and who are unable to participate in Phase 3 clinical trials.

The expanded access protocol will allow 50 patients to receive MDMA-assisted psychotherapy, following the MAPS treatment protocol (**maps.org/treatmentmanual**). MAPS hopes to expand the number of patients eligible to receive treatment in the expanded access program in the future. MAPS has proposed to the FDA that after the first 35 patients, patient data will be submitted for the agency to consider whether to expand the program.

The expanded access protocol differs from MAPS' ongoing Phase 3 clinical trials in that it is limited to treatment-resistant patients with moderate to severe treatment-resistant PTSD. Other differences are that the FDA is requiring at least one therapist of each therapy pair to have a medical or clinical doctorate degree (M.D., Ph.D., or equivalent), there is no control group, and patients are responsible for the costs of their own treatment.

Up to 10 qualifying treatment sites will participate in the expanded access program. Over 120 site applications have been received to date. Once the program begins, patients can apply to the individual expanded access sites.

"The resurgence of research into using drugs such as MDMA to catalyze psychotherapy is the most promising and exciting development I've seen in my psychiatric career," said Michael Mithoefer, M.D., Senior Medical Director for Medical Affairs, Training and Supervision for MAPS PBC. "Combining the powerful effects of pharmacology with the potential depth of psychotherapy is a compelling model for harnessing advances in neuroscience and psychopharmacology without ignoring the complexity, richness and innate capacity of the human psyche. I'm delighted that the expanded access program will now allow some patients access to this modality as MAPS' Phase 3 research continues."

MAPS' expanded access protocol received Institutional Review Board (IRB) approval on November 4, 2020, and must still be confirmed by the DEA.

Israel Embraces Research on MDMA-Assisted Psychotherapy for PTSD

On February 3, 2019, Israel became the first government to approve a compassionate use program for MDMA-assisted psychotherapy for PTSD, which will allow 50 patients to receive the treatment outside of Phase 3 clinical trials. Patients with PTSD will be eligible to receive treatment at sites throughout Israel, including Rambam Medical Center in Haifa and psychiatric hospitals in Be'er Yaakov, Lev Hasharon, Be'er Sheva, and Sheba-Tel Hashomer. The U.S. FDA followed Israel on December 20, 2019, when the agency agreed to an expanded access program for MDMA-assisted psychotherapy for PTSD, also for 50 patients with PTSD.

"The Israeli Ministry of Health is constantly looking for new tools to get better results in psychological and psychiatric treatment," says Bella Ben-Gershon, Director of Psychological Trauma for the Israeli Ministry of Health. "After seeing the very promising results of the completed MDMA-assisted psychotherapy research in Israel, we now believe that it is crucial to allow more citizens who suffer from PTSD to have access to this new treatment."

Israel is also the first national government to financially support MDMA-assisted psychotherapy research. In February of 2019, the Israeli Ministry of Health granted $500,000 in medical and hospital services to MAPS in support of the compassionate use of MDMA-assisted psychotherapy for PTSD in Israel.

A Phase 2 Open-Label, Randomized Comparative Effectiveness Study for MDMA-Assisted Psychotherapy in U.S. Military Veterans with Chronic PTSD

On August 25, 2020, the FDA agreed to proceed with MAPS' first randomized clinical trial protocol submitted in partnership with esteemed PTSD researcher Rachel Yehuda, Ph.D., Director at the Mental Health Patient Care Center, James J. Peters VA Medical Center, and Professor of Psychiatry and Neuroscience at the Icahn School of Medicine at Mount Sinai Hospital, through the investigator-initiated research program of the U.S. Department of Veterans Affairs (VA).

The study will be a Phase 2, open-label randomized controlled comparative study on the effectiveness of MDMA-assisted psychotherapy in U.S. veterans with chronic PTSD.

The study will enroll 60 veterans and will collect further information on whether there is a difference in two versus three sessions of MDMA-assisted psychotherapy for safety and therapeutic outcome. This study will also act as a training ground for VA clinicians and therapists on the MAPS modality, and will include blood collection samples for later analysis of hormones, molecules, and other biological markers that may be related to having or recovering from PTSD.

Dr. Yehuda and her team plan to conduct this trial at the VA pending institutional and DEA approvals.

Startle Testing with MDMA: Thirty-Four Veteran Participants Complete Enrollment in Experimental Treatment

On July 30, 2020, MAPS completed enrollment in our study of the effect of experimental treatment with MDMA on startle testing in thirty-four healthy participants. Led by Principal Investigator Barbara Rothbaum, Ph.D., this study was conducted at Emory University in Atlanta, Georgia. Dr. Rothbaum presented a subset of findings at the 36th Annual Meeting of the International Society for Traumatic Stress Studies (ISTSS) on November 12, 2020.

An Open-Label, Phase 2, Multicenter Feasibility Study of Manualized MDMA-Assisted Psychotherapy with an Optional fMRI Sub-Study Assessing Changes in Brain Activity in Subjects with PTSD

Taking place in the United Kingdom, Germany, Portugal, Norway, the Czech Republic, and the Netherlands, this open-label Phase 2 study of MDMA-assisted psychotherapy for PTSD will serve as the lead-in to the planned Phase 3 study in Europe and to validate assumptions made for statistical power calculations supporting the planned Phase 3 clinical trial. This study will also provide cross-cultural validation data on the updated version of the Primary Outcome measure, the CAPS-5, which will be used in the Phase 3 study. In addition, the study will gather supportive data on the safety and effectiveness of manualized MDMA-assisted psychotherapy while providing an opportunity for clinical supervision to planned Phase 3 therapy teams. This study will be the first multi-center study of MDMA-assisted psychotherapy for PTSD in Europe and will explore reproducibility of findings from FDA-regulated Phase 2 trials to confirm the Phase 3 study design.

The study site in the Czech Republic is currently screening participants, screening at the first of two Netherlands sites

will begin imminently, and screening at the Norway site is expected to start before the end of the year. The sites in the United Kingdom and Germany require further permissions before they can begin screening, most likely in early 2021, and the study set-up in Portugal is still in an early stage. Data gathered in European trials would provide support for a planned Marketing Authorization Application for potential approval by the European Medicines Agency (EMA). For more information, please visit: **mapseurope.eu/research**.

Therapist Training Study: New Protocol Amendment Accepted by the FDA

On May 12, 2020, a new protocol amendment that increases the number of study participants to a total of 120 was accepted by the FDA. This protocol amendment was submitted to the IRB on April 30, 2020. This study is our ongoing Phase 1 study of the psychological effects of MDMA when used in a therapeutic setting by healthy participants. Enrollment in this multi-site study is on hold due to COVID-19 and is limited by invitation only to therapists in training to work on MAPS-sponsored clinical trials of MDMA-assisted psychotherapy for PTSD. The Boulder, Colorado, study site is led by Principal Investigator Marcela Ot'alora G., M.A., L.P.C., the Charleston, South Carolina, is led by Principal Investigator Zhenya Gelfand, M.D., and the Santa Fe, New Mexico, study site is led by Principal Investigator George Greer, M.D.

An Open-Label, Multi-Site Phase 2 Study of the Safety and Feasibility of MDMA-Assisted Psychotherapy for Eating Disorders

On May 20, 2020, MAPS received FDA agreement to conduct an open-label, multi-site Phase 2 study for MDMA as an adjunct to psychotherapy for anorexia nervosa restricting subtype (AN-R) and binge-eating disorder (BED), followed by Health Canada's non-objection on October 30, 2020.

This study will explore the safety and feasibility of MDMA-assisted psychotherapy and adjunctive caregiver involvement in the treatment of individuals with AN-R and BED. The addition of a supportive caregiver as a treatment ally with every participant reflects this most recent development in science and practice. Supportive caregivers enrolled in the study will receive non-drug psychotherapy support. The study will enroll 12 participants who meet the Diagnostic Statistical Manual for Mental Disorders Edition 5 (DSM-5) criteria for AN-R, and 6 participants who meet DSM-5 criteria for BED, for a total of 36 participants (12 AN-R, 6 BED, and 18 caregivers).

The study will take place at three study sites. The study site in Vancouver, Canada, will include six BED participants, with Qualified Investigator Christian Schütz, M.D., Ph.D., M.P.H, overseeing the study. The study sites in Toronto, Canada, and Denver, Colorado, will each include six AN-R participants, with Michael Verbora, M.D., overseeing as Qualified Investigator in Toronto, and Co-Clinical Investigators Adele Lafrance, Ph.D., and Mike Rollin, M.D., overseeing the site in Denver.

A Phase 1 Open-Label Study of MDMA Tolerability and Pharmacokinetics in Participants with Moderate Hepatic Impairment Compared to Matched Control Participants with Normal Hepatic Function

MAPS is sponsoring an open-label Phase 1 study of MDMA's effect on hepatic impairment (liver disease). While the study site is prepared, this study has not yet enrolled any participants and enrollment is on hold due to COVID-19.

The primary objective of this study is to evaluate the effect of moderate hepatic impairment on the pharmacokinetics of oral MDMA and its active metabolite. The secondary objective of this study is to evaluate the effect of moderate hepatic impairment on the safety and tolerability of oral MDMA. Led by Principal Investigators Janel Long-Boyle, Pharm.D., Ph.D., and Robert M. Grant, M.D., M.P.H., this study will be conducted at the University of California, San Francisco.

MDMA Therapy Training Program Update

From September 25 - November 1, Marcela Ot'alora G., L.P.C., and Bruce Poulter, M.P.H., delivered a three-weekend course on MDMA-assisted psychotherapy in collaboration with Naropa University. The 9-day course included training in contemplative psychotherapy from Naropa faculty.

Annie Mithoefer, B.S.N., and Michael Mithoefer, M.D., provided an online training from November 5-6 and November 9-12. The November training included trainees from Netherlands, Germany, Norway, Portugal, United Kingdom, Canada, Somaliland, South Africa, and the United States. In October, therapists preparing to work in Europe participated in virtual training calls focused on culturally-informed care for refugee participants, led by Adele Meyer and Nooria Mehraby, M.D.

Over the summer, the training program launched the first of a series of Phase 3 Quarterly Consultation groups. These virtual group supervision calls are facilitated by trainers Marcela Ot'Alora, L.P.C., Bruce Poulter, M.P.H., Annie Mithoefer, B.S.N., and Michael Mithoefer, M.D., and cover therapeutic topics, peer discussion, case presentations, and consultation. Therapists have appreciated gathering in this community of their peers to learn from each other's insights and challenges delivering MDMA-assisted psychotherapy. These are the MDMA Therapy Training Program's first experiment with group supervision; we look forward to offering group supervision on the upcoming expanded access protocol as well, which will be facilitated by Associate Supervisors who have recently completed supervision training.

Sign up for the MDMA Therapy Training Program Newsletter to receive updates on future trainings: **mapspublicbenefit.com/training**.

Participate in Research

MAPS sponsors clinical trials around the world that offer volunteers the opportunity to participate in our research studies. Our studies have strict enrollment criteria based on the goal of the study and the condition the study is investigating.

Phase 3 trial participant enrollment is now open for select study sites: **mdmaptsd.org**.

Please visit our Participate in Research page and check it frequently for updates about participant enrollment: **maps.org/participate-in-research**.