Research News

MDMA-Assisted Therapy

MDMA-Assisted Therapy 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 therapy 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 therapy 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 therapy 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 therapy for PTSD."

Berra Yazar-Klosinski, Ph.D., Deputy Director and Head of Research Development and Regulatory Affairs for MAPS Public Benefit Corporation (MAPS PBC) and co-author, developed the protocols studying MDMA-assisted therapy. She notes, "A growing body of evidence suggests that MDMA-assisted therapy 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 therapy 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 therapy 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."

The cost-effectiveness of MDMA-assisted therapy 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.

MAPS-Sponsored Pilot Study: MDMA-Assisted Therapy for PTSD in Couples May Reduce PTSD Symptoms, Improve Couples' Happiness

A pilot trial to assess the safety, feasibility, and efficacy of Cognitive-Behavioral Conjoint Therapy (CBCT) for PTSD and MDMA-assisted therapy for PTSD resulted in significant reductions in PTSD symptoms and relational outcomes for couples, according to a peer-reviewed paper published on December 7, 2020, in the *European Journal of Psychotraumatology*. This initial trial, sponsored by the Multidisciplinary Association of Psychedelic Studies (MAPS) and organized by MAPS Public Benefit Corporation (MAPS PBC), included six couples with a range of baseline relationship satisfaction in which one member was diagnosed with PTSD resulting from a range of traumas including childhood physical abuse, childhood sexual abuse, and active military service.

CBCT for PTSD focuses on the relationship between the participant and their partner, encouraging skill development as a couple. CBCT alone has been shown to improve PTSD, enhance relationship functioning, and improve intimate partner well-being. MDMA-assisted therapy for PTSD, currently in Phase 3 trials to gain approval from the U.S. Food and Drug Administration (FDA), has yielded significant improvements for individuals in PTSD symptoms and other outcomes such

as increased openness to experience, post-traumatic growth, and improvement in comorbid conditions. This study represents the first in which MDMA's potential to facilitate the effects of a stand-alone, empirically-supported therapy — other than the protocol developed by MAPS — for PTSD was tested.

Candice M. Monson, Ph.D., is a Professor of Psychology and Clinical Training Director at Ryerson University. Dr. Monson is an expert on traumatic stress and CBCT, having researched CBCT as a treatment for PTSD since 2012 and MDMA-assisted therapy for PTSD since 2015. She described the treatment as promising because, "PTSD in one partner can cause distress in the relationship and barriers to understanding each other. It seems that MDMA-assisted therapy can engender empathy and connection, opening a pathway to remembering why came together in the first place and a desire to understand the other. The literature that inspired this study suggests that MDMA may allow people to talk about painful experiences without experiencing the pain again. The therapist can guide couples to talk about very difficult things that they've either experienced themselves or experienced together — against the other or with the other — with a greater sense of understanding, openness, connection, and empathy."

It is estimated that a public healthcare payer or private insurer making MDMA-assisted therapy available to 1,000 patients with PTSD would reduce general and mental health care costs by $103.2 million over 30 years.

Participants received the session content comprising CBCT in a condensed format, including intensive weekends and bi-weekly sessions, over seven weeks. The two MDMA sessions were timed to synergize with the CBCT interventions and both members of the couple were administered 75mg or 100mg of MDMA with an optional supplemental dose. Each member of the couple was scheduled for assessment at pre-treatment, mid-treatment, post-treatment, and three- and six-month follow-ups. In addition, participants completed assessments of self- and partner-reported PTSD symptoms and overall relationship happiness at those assessment points, as well as at each treatment occasion. No unexpected adverse events were observed.

This initial study suggests that MDMA-facilitated CBCT holds promise in facilitating trauma recovery and achieving broader relational outcomes not fully realized with individual evidence-based treatment for PTSD. Though the comparison of effect sizes is tentative due to the small sample size, the effects across all outcomes were largest at six-month follow-up, suggesting that MDMA facilitation may confer ongoing benefits. The authors are currently preparing for a Phase 2 randomized trial led by co-author Anne Wagner, Ph.D., C. Psych., to more rigorously investigate the safety and efficacy of MDMA-facilitated CBCT and to address treatment outcomes across a diversity of participant and partner genders, pre-treatment relationship distress, and type of initial trauma.

Study: MDMA-Assisted Therapy May Reduce Anxiety for Those Diagnosed with Life-Threatening Illness

A peer-reviewed study published on November 24, 2020, in the journal *Scientific Reports* provides sufficient evidence to support further research into the palliative effects of MDMA-assisted therapy for anxiety associated with life-threatening illness. The pilot study, sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS) and using protocols developed by MAPS Public Benefit Corporation (MAPS PBC), demonstrated greater reduction in anxiety among participants who received MDMA relative to participants who received placebo with identical therapy. While the difference between the two groups was not statistically significant, this small pilot study demonstrates the addition of MDMA to the intervention had a large effect size and justifies continued research.

Individuals facing a life-threatening illness may contend with anxiety, depression, anger, and despair that often exacerbate the distress already caused by the illness itself. The trauma of a devastating illness is often deep and difficult to integrate, even for those

who recover. As modern medical care improves life expectancy or recovery rates for serious illnesses, the need to address the psychological trauma of diagnosis and treatment is growing.

Phil Wolfson, M.D., served as Principal Investigator and lead author for the study and authored an accompanying commentary. "Through this intensive psychotherapy, with MDMA experiences as a fundamental part of the process, people who have trauma from life-threatening illnesses were able to significantly improve the impact of their traumatic residues, their fears of relapse and death, and their struggle to make recoveries. The traumatic nature of diagnosis with a life-threatening illness and its aftermath contains a multiplicity of manifestations in cognition, motivation, affect, spirit, meaning, relationships, and view of self. Attention to patients' suffering, impacted ways of being, and tension with potential recurrence of illness and death should be considered as fundamental to their complete recovery or hospice care as attention to their physical state; this pilot study validates continued research into MDMA-assisted therapy as a meaningful pathway to addressing their suffering."

Early investigations with psychedelic compounds suggested such psychoactive substances hold promise in addressing distress, pain, and anxiety in people with life-threatening illnesses. Recent studies provide evidence for the use of psychedelic-assisted therapy as an efficacious modality for the treatment of depression, anxiety, and PTSD. MDMA is under investigation as an adjunct to therapy for various anxiety-related conditions; results from six Phase 2 studies led the U.S. Food and Drug Administration (FDA) to issue a breakthrough therapy designation for MDMA-assisted therapy for treatment of PTSD in 2017. Based on these findings, this pilot study was conducted to examine the safety and efficacy of MDMA-assisted therapy to alleviate anxiety and other psychiatric symptoms, including depression and poor sleep quality, related to a life-threatening illness.

"This study presents a new viable pipeline for the clinical application of MDMA-assisted therapy in the treatment of anxiety symptoms in a population in dire need of palliative care options," noted Berra Yazar-Klosinski, Ph.D., who serves as Deputy Director and Head of Research Development and Regulatory Affairs for MAPS PBC. "Patients suffering from a life-threatening illness are often only treated for their primary medical diagnosis; their anxiety and existential distress is neglected in our current healthcare system. MAPS has a strong record of supporting treatments addressing this unmet medical need. The results of this pilot study will enable the design of future well-powered studies to change this treatment landscape, and perhaps even the way we approach life and death in our modern lives."

A total of 18 participants with moderate or severe anxiety symptoms related to diagnosis of a life-threatening illness were enrolled in the study; 17 completed the treatment and follow-up assessments after six and twelve months. Participants had a mean age of 54.9 years; fourteen participants identified as female; and many had been previously diagnosed with an anxiety disorder (83.3%), major depression (77.8%), PTSD (72.2%), or insomnia (61.1%). Notably, after the experimental sessions, participants who initially received a placebo with therapy received additional therapy sessions with MDMA and results for both groups were combined for the six- and twelve-month follow-up assessments. Study limitations included small sample size, demographic homogeny, exceptionally strong positive response from one member of the placebo group, and combination of the experimental and control groups following the experimental sessions. Study results support the feasibility of exploring MDMA-assisted therapy as a novel approach for potential long-term treatment of anxiety related to life-threatening illness and will inform development of future clinical trials with larger sample size and among more diverse populations.

MAPS and MAPS Public Benefit Corporation Announce Positive Result from Phase 3 Trial of MDMA-Assisted Therapy 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 therapy 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 therapy 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 therapy sessions over approximately 3.5 months. The severity of PTSD symptoms was measured using the Clinician-Administered PTSD Scale for the DSM-5 (CAPS-5); measurements were taken before and after completion of treatment. Of these 90 participants, approximately half received MDMA-assisted therapy. 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 therapy has been approved as a treatment for PTSD."

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

We are currently seeking research volunteers for our second Phase 3 clinical trial of MDMA-assisted therapy for PTSD. Volunteers will help contribute to scientific knowledge and will help us better understand if MDMA-assisted therapy 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
- San Francisco, California | Research Institution
- New York, New York | Private Practice
- New York, New York | Research Institution

Not yet recruiting:

- 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 therapy 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**

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

The Institutional Review Board (IRB) has approved MAPS' protocol for a Phase 2, open-label randomized controlled comparative study on the effectiveness of MDMA-assisted therapy in U.S. Veterans with chronic PTSD. Led by 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, the study is moving through the investigator-initiated research program of the U.S. Department of Veterans Affairs (VA). On August 25, 2020, the FDA agreed to proceed with the protocol.

The study will be a Phase 2, open-label randomized controlled comparative study on the effectiveness of MDMA-assisted therapy 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 therapy 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.

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

Taking place in the United Kingdom, Germany, Portugal, Norway, the Czech Republic, and the Netherlands, this open-label Phase 2 study of MDMA-assisted therapy for PTSD will serve as the lead-in to the planned Phase 3 study in Europe providing an opportunity for clinical supervision of therapy teams to complete their training, 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 Clinician-Administered PTSD Scale for DSM-5 (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 therapy. This study will be the first multi-center study of MDMA-assisted therapy for PTSD in Europe and will explore reproducibility of findings from FDA-regulated Phase 2 and Phase 3 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

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.

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 therapy 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 Therapy 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 therapy 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 therapy 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 therapy 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 multiple 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 3,4-methylene-dioxyamphetamine (MDMA). 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: January 2021

The MDMA Therapy Training Program is currently supporting the final segment of training for therapists preparing for the open-label lead-in study for the European segment of Phase 3, researching MDMA-assisted therapy as a treatment for PTSD. A cohort of new supervisors, experienced MDMA-assisted therapy researchers who have met additional training and certification requirements to provide supervision, will be supporting therapists on this protocol.

The training program will deliver trainings entirely online this year. We are excited about the possibility of expanding access to training with the shift to online education. Our program staff and various subject matter experts are continuing to engage in a training curriculum design initiative to support the growth and continued quality of the program. To better support training thousands of future therapists, we are developing training protocols for new supervisors and trainers, who are also contributing their expertise to the curriculum design initiative.

We look forward to re-opening enrollment for the MDMA Therapy Training Program in the coming months. To receive updates on 2021 trainings and training program admissions, sign up for the MDMA Therapy Training Program Newsletter: **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**.

The safety and efficacy of MDMA-assisted therapy 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**