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Towards Breakthrough Healing: A History and Overview of Clinical MDMA Research

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In November 2016, the U.S. Food and Drug Administration (FDA) green-lit Phase 3 clinical trials proposed by MAPS to further investigate MDMA-assisted psychotherapy for the treatment of posttraumatic stress disorder (PTSD). This means we are closer than ever before to the reclassification of MDMA for legal clinical use as a prescribed medication. But how did we get here? Why—over a century since the first synthesis of MDMA—are we still working to demonstrate its safety and efficacy?

MDMA was first synthesized and patented by the German pharmaceutical company Merck in 1912 as one in a series of chemical intermediaries to produce a compound to stop abnormal bleeding. Merck first studied MDMA itself in animals in 1927, and then again in 1952 and 1959, but decided not to initiate research in humans throughout this period. After a brief series of toxicity studies in animals by the U.S. Army in 1953–4, MDMA was largely disregarded and thought to have no potential medical benefit.

In 1976, MDMA was rediscovered by medicinal chemist Alexander Shulgin, Ph.D. Its use was then spread by psychiatrists and psychologists who reported seeing benefits to its use as an adjunct to psychotherapy for individuals and couples in MDMA-assisted therapy sessions. MAPS founder Rick Doblin, Ph.D., learned about MDMA in 1982 as an adjunct to psychotherapy, but at that time it was already gaining in popularity in the party scene, leading the U.S. Drug Enforcement Administration (DEA) to identify it as a drug of abuse. Doblin then embarked on a valiant, but unsuccessful, effort to preserve the therapeutic use of MDMA by petitioning the DEA, but the agency ultimately criminalized the compound in 1985.

Doblin realized that the path to legitimizing psychedelic-assisted psychotherapy would be proving its efficacy via rigorous clinical trials sanctioned by the FDA. This provided Doblin with the motivation for the establishment of a non-profit medical research organization—the Multidisciplinary Association for Psychedelic Studies, or MAPS—in 1986. MAPS began funding animal toxicity studies and human safety studies at Stanford University and Johns Hopkins University in the late 1980s (Emerson et al. 2014).

Nearly a decade later, the first FDA-approved, double-blind, placebo-controlled U.S. Phase I dose-response safety study of MDMA was published by Charles Grob, M.D., in 1996, working with MAPS. Since that time, MAPS has funded and conducted twelve clinical trials around the globe investigating MDMA-assisted psychotherapy for PTSD, anxiety related to advanced-stage illness, social anxiety in autistic adults, and a (still ongoing) study of healthy subjects via the MDMA therapist training program, with plans for additional studies of MDMA therapy for race-based trauma and transgendered people as well.

Because of MDMA's ability to decrease the fear response and increase empathy and interpersonal trust, early clinicians recognized that it could be especially useful in treating PTSD, a disorder characterized by patients' emotional activation when accessing traumatic memories. In hopes of investigating this potential link, MAPS sponsored the first clinical trial of MDMA-assisted psychotherapy for the treatment of PTSD in 2000, with a pilot study of female survivors of sexual assault with treatment-resistant PTSD in Spain. Unfortunately, the study was discontinued in 2002 due to pressure from the Madrid Anti-Drug Authority after only six subjects were treated with a single dose of MDMA ranging from 50 to 75mg (low to medium doses by comparison to current studies).

In 2004, the FDA and DEA approved the first U.S. clinical trial of MDMA in humans as an Investigational New Drug (IND) for the treatment of PTSD. This randomized, placebo-controlled Phase 2 trial, led by Michael Mithoefer, M.D., and Annie Mithoefer, B.S.N., in Charleston, South Carolina, was published in the *Journal of Psychopharmacology* in 2010. The study employed the male/female co-therapist pair method, which has become the standard in MDMA-assisted psychotherapy clini-

Rick Doblin caught a reflection of himself in the window when he petitioned the DEA to preserve the therapeutic use of MDMA in 1984. (left) after learning about the benefits of using it as an adjunct to psychotherapy with Leo Zeff (above).

cal trials, and treated patients with two full-dose MDMA experimental sessions using 125mg (with a 62.5mg supplemental dose offered two hours after the initial dose). The results were impressive. In a sample of 20 subjects with chronic, treatment-refractory PTSD (meaning they had failed two or more courses of conventional therapy), 83% no longer qualified for PTSD as measured by the Clinician-Administered PTSD Scale (CAPS), versus 25% of the placebo group at the end of treatment. In the long-term follow-up study, approximately 75% of patients still showed meaningful sustained reductions in their PTSD symptoms an average of three and a half years later and many patients no longer met criteria for PTSD (Mithoefer et al. 2011, 2013).

In 2006, a second Phase 2 study of MDMA-assisted psychotherapy for PTSD was sponsored by MAPS, this time conducted in Switzerland by Peter Oehen, M.D. This small study treated twelve subjects with three full-dose MDMA sessions (125mg initial dose + 62.5mg supplemental dose) compared with low-dose active placebo sessions (25mg + 12.5mg), and was published in 2012. Though the reduction in CAPS for this group was not statistically significant due to the small size of the study ($p=0.066$), the effect size was similar to the first study by the Mithoefers, with further improvement in CAPS scores at the one-year follow-up.

The positive outcomes and lack of any serious adverse events in these first studies paved the way for the expansion of the MAPS research program and the further investigation of MDMA-assisted psychotherapy for PTSD and other psychiatric disorders. In Colorado, a Phase 2 study of 23 subjects with PTSD led by Marcela Ot'alora, M.A., piloted an intern training program in which one member of the co-therapist team is a healthcare intern, with the other being an experienced clinician. This study also aimed to determine optimal dosing of MDMA by comparing 125mg and 100mg doses of MDMA with a 40mg active placebo, then allowing patients to choose 100mg or 125mg dosing options in the second stage of the study. As of March 2017, this study, along with a separate MAPS-sponsored team in Israel, have nearly completed 12-month follow up visits. In November 2016, the team in Vancouver, Canada led by Ingrid Pacey, M.D., concluded their investigation of MDMA-assisted psychotherapy in six subjects with PTSD. This study compared full-dose 125mg MDMA with inactive placebo and the data will be included in a meta-analysis of MDMA-assisted psychotherapy results. A second Phase 22 study led by the Mithoefer team in Charleston, South Carolina, also recently concluded. This study—MAPS' largest Phase 2 trial—focused on a population of 24 U.S. military veterans, firefighters, and police officers, and compared 125mg and 75mg doses with a 30mg active placebo dose. The results from this study are currently pending publication, and will be presented at Psychedelic Science 2017.

We are in the midst of a ***psychedelic research renaissance.***

While MDMA was used clinically with much success in couples therapy prior to its scheduling, until very recently MDMA-assisted psychotherapy studies focused only on individuals. In 2016, Michael Mithoefer, M.D., and Candice Monson, Ph.D., began an exciting new phase in MDMA research, with a pilot study of MDMA-assisted Cognitive Behavioral Conjoint Therapy (CBCT) in couples. This study, now ongoing, includes one member of a couple with chronic PTSD, a significant other with no PTSD diagnosis, and significant relationship strain related to the PTSD symptoms. This study is expected to exhibit the improved communication and interpersonal connectedness reported in early publications on MDMA therapy.

MAPS has also funded and obtained approval for studies focused on other psychiatric disorders besides PTSD. In 2014, MAPS began a Phase 2 clinical trial of MDMA-assisted therapy as a treatment for social anxiety in adults on the autism spec-

trum, led by Charles Grob, M.D., and Alicia Danforth, Ph.D., at the Los Angeles Biomedical Research Institute in Los Angeles, California. This study has been completed, and a protocol rationale paper was published in 2015. Also ongoing through MAPS is a clinical trial led by Phil Wolfson, M.D., in Marin, California, investigating the safety and efficacy of MDMA-assisted psychotherapy for anxiety in 18 subjects diagnosed with life-threatening illness. Additionally, a recently-approved MAPS-sponsored Phase 1 pilot study at Emory University led by Barbara Rothbaum, Ph.D., is investigating the effect of MDMA on fear extinction learning in healthy volunteers. This study aims to provide important insight into why MDMA may be beneficial for treating PTSD and will supplement an upcoming study combining MDMA with Prolonged Exposure, an evidence-based psychotherapeutic approach to treating PTSD.

Since the classification of MDMA as a Schedule I substance in 1985, there have been over 5,000 articles written about the compound in academic journals, and over 1,100 volunteers have taken MDMA in clinical settings. Many groups across the globe are passionately working to answer important questions developing from this seminal research, such as: How does MDMA produce its benefits in therapy? What changes occur in brain activity while under the influence of MDMA? What are its potential risks and side effects? What is the abuse potential? There have been many studies of the acute effects of MDMA on healthy subjects, highlighting a wide range of results including fMRI data showing specific patterns of increased and decreased cerebral blood flow (Carhart-Harris 2014, 2015), PET scans of neurotransmitter release and receptor activity (Vollenweider 2002), and data demonstrating pro-social and increased emotional verbal content with MDMA (Baggott 2015). As with all carefully designed and implemented research, each question answered leads to more questions to be asked.

Reflecting on the research completed, in-process, and planned for the future, it is particularly notable that these studies detailed above have been wholly the result of private funding, thanks to the heroic efforts of MAPS. Because of the hard work and dedication by the clinicians and scientists noted above, and many others whom we did not have space to list, we are in the midst of a psychedelic research renaissance. For the first time in decades, students are able to pursue careers investigating treatments based on trusting the healing process, and on letting go of expectations. As Stanford neuroscientists Boris Heifets, M.D., Ph.D., and Robert Malenka, M.D., Ph.D., wrote in their compelling commentary paper published in *Cell* in 2016: "The world's populations need more compassion and empathy for one another. The study of MDMA provides one small but potentially important step toward reaching that goal." This approach to healing and healthcare is needed now more than ever.

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