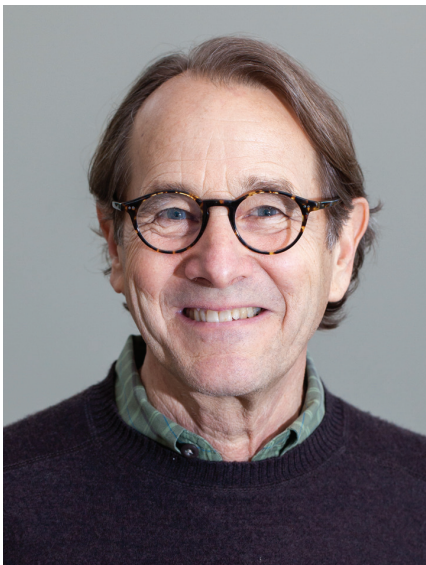


Research Update: MDMA-Assisted Psychotherapy for PTSD

MICHAEL MITHOEFER, M.D.

Reflections on the last 15 years as we conclude our largest study yet of MDMA-assisted psychotherapy for 24 U.S. veterans, firefighters, and police officers with chronic, treatment-resistant PTSD.



Michael Mithoefer, M.D.

In March 2000, Rick Doblin and I had our first conversation. We shared a conviction about the need for a modern era of clinical research looking at the therapeutic effects, as well as the risks, of MDMA and other psychedelics. In the months that followed, we began what turned out to be a four-year process of protocol development and obtaining Food and Drug Administration (FDA), Drug Enforcement Administration (DEA), and Institutional Review Board (IRB, or Ethics Committee) approvals for our first study of MDMA-assisted psychotherapy for posttraumatic stress disorder (PTSD).

Part of what the FDA required was a 350-page summary of all the English language literature on MDMA, which Ilsa Jerome and Matt Baggott expertly compiled (they remain leading experts on this growing literature). Looking back at the number and variety of obstacles that arose during this process, I think it was fortunate that neither Rick nor I ever seriously considered the possibility that we wouldn't be able to accomplish what we had set out to do—though I'm sure many people thought that meant we just didn't understand the situation. For Rick, the effort had started another 15 years earlier when he founded MAPS, and later finally started an MDMA-assisted psychotherapy study in Spain with Jose Carlos Bouso and Marcela Ot'olora, only to have it shut down by the drug police. Nine and a half years after that first conversation, Annie Mithoefer and I completed the study that resulted from it, and published the rather remarkable results in the *Journal of Psychopharmacology*.

Recently, on July 31, 2015, Annie and I facilitated the last MDMA-assisted psychotherapy session in our most recent study. That was our 156th MDMA research session together. In the last 15 years, MAPS' research has also advanced on many other fronts, and it's important to note that while the regulatory process remains rigorous and still takes a number of months, since completing our first study we have not experienced any undue delays in getting DEA and IRB approval for subsequent studies.

EXPANDING RESEARCH

In Charleston, we completed and published a long-term follow-up of the participants in the first study demonstrating sustained improvement for most of them an average of three and a half years later. We also completed a small study showing benefit from an additional MDMA-assisted session for three participants whose PTSD had relapsed more than a year after participation in the first study. In 2013, Peter Oehen and his wife Verena Widmer completed a similar successful MDMA-assisted psychotherapy for PTSD study in Switzerland showing a strong effect size.

After some years in which authorities at The Medical University of South Carolina distanced themselves from our research because they thought it too controversial, we are now collaborating with Mark George and Colleen Hanlon, well-known neuroimaging researchers, to do functional MRI scans (fMRI) before and after treatment in the veteran study.

We have also obtained approval for a Phase 1 trial limited to psychotherapists who have participated in our Research Therapist Training Program, and who choose to have their own MDMA experience in the same therapeutic setting as the clinical trials. When Rick initially broached this idea to others in the psychedelic research community many people discouraged him for fear that even applying to FDA for such a study would give psychedelic therapy a bad name with regulatory authorities. After lengthy consideration, Rick and I still felt strongly that it was important to have a legal way for MDMA research therapists to have their own experience with MDMA in a therapeutic setting in order to better grasp the experiences participants have during research sessions. We knew this was an unusual request for the FDA, but after several productive conference calls with FDA scientists we got approval to proceed. To date, seven therapists working on MAPS Phase 2 trials have completed the protocol, and all have reported that the experience was personally and professionally beneficial.

Additional MAPS sponsored MDMA-assisted psychotherapy for PTSD (MDMA/PTSD) studies are now nearing completion in Israel, with Moshe Kotler, Chief of Psychiatry at Tel Aviv University as Principal Investigator (PI); in Boulder, Colorado, with Marcela Ot'alara as PI and Will Van Derveer as the study physician responsible for MDMA administration; and in Vancouver, Canada, with Ingrid Pacey as PI and Richard Yensen and Donna Dryer as the primary therapy team. These three studies have provided experience coordinating several teams of therapists, many of whom had not previously worked as co-therapists. This is valuable preparation because the Phase 3 trials will have multiple sites with more than one therapist team at each site. More MDMA/PTSD studies are currently under development in England, Australia, and Germany.

In 2011, MAPS came close to initiating a study in Jordan. We made several trips there and trained a team of Jordanian psychiatrists and psychologists, but at the last minute final protocol approval was unexpectedly denied by Jordanian regulators.

Although the main focus of MAPS research is MDMA-assisted psychotherapy for PTSD, there have been several MAPS studies for other conditions. In 2014, Peter Gasser, in Switzerland, completed and published a promising study of LSD-assisted psychotherapy for anxiety associated with life-threatening illness. Phil Wolfson and Julane Andries are currently doing a similar study near San Francisco using MDMA instead of LSD. Meanwhile, Charlie Grob at the University of California, Los Angeles (who had previously done the first US Phase 1 trial of MDMA) and Alicia Danforth are nearing completion of a study of MDMA-assisted therapy for social anxiety in autistic adults.

All these studies, focused primarily on quantitative treatment outcome measures that are of interest to the FDA, have yielded thousands of video recordings of study sessions. These videos are a rich source of information about the nature of the therapeutic process that could be studied with qualitative research methods, and are attracting the attention of a growing number of researchers. Dana Blu Cohen recently completed her

Ph.D. dissertation at the California Institute for Integral Studies analyzing some of the videos, and Ingmar Gorman is currently using videos to conduct a qualitative study at the New School for Social Research in New York. We hope this area of research will continue to expand, because there is much to be learned about the nature of the therapeutic process in MDMA-assisted psychotherapy.

STUDY MONITORING

In September 2002, several months after obtaining it, we lost IRB approval for our first study because of a later-retracted and now infamous “MDMA toxicity” paper by George Ricaurte, a neurologist at Johns Hopkins University. A year after the original publication, the authors revealed that they had inadvertently killed baboons and squirrel monkeys with methamphetamine, not MDMA.

Before the retraction, Rick had spent months scouring the country for another IRB that wouldn't be scared off by Ricaurte's paper. One of the IRBs he spoke to told him MAPS would need to have the study monitored by a clinical research organization (CRO) at a cost of nearly \$300,000. The shock of this figure seemed to jog Rick's memory about an email he'd received a few years before volunteering this kind of monitoring, which he hadn't thought we needed at the time.

He found the old email from Amy Emerson, and luckily for us she was still more than willing to help. Amy was very knowledgeable and experienced in this area through her work for Chiron and later Novartis pharmaceuticals. She taught us a lot and brought our study documentation and accountability to a high level.

Amy went on to help train the increasing number of monitors needed as MAPS research continues to expand: when we started, it was Valerie and Josh Mojeiko, and now Berra Yazarklosinski, Ben Shechet, and Alli Feduccia. As a sign of the rate at which MAPS is growing and maturing, Amy, who like many of us started as a volunteer, is now Executive Director and Director of Clinical Research of MAPS Public Benefit Corporation, and Berra is now Clinical Research Scientist, with a hand in almost everything clinical at MAPS.

STUDY COORDINATORS

When I told a psychiatrist/researcher friend at the medical school in Charleston about our plans for the first study, he asked me if we had a study coordinator. I said it was just a small study, and dismissed it when he said, “Sounds like about the size for one study coordinator to me.” As it turned out, not having a study coordinator was a great way for us to learn about ins and outs of clinical research down to the smallest details, including Annie making food for the participants' overnight stays and taking their sheets to the laundry afterward. We learned the difference between source records and CRFs by filling them all out ourselves. I'm grateful for the adventure of that experience that Annie and I shared, and now I'm even more grateful for Sarah Sadler, our study coordinator, for her welcoming smile and pres-

ence that always helps put new participants at ease, and for all the ways she helps us run the study at our site.

TREATMENT MANUAL AND ADHERENCE CRITERIA

Another important step in assuring the scientific validity of MAPS studies and in progressing toward Phase 3 is the *Treatment Manual* we've written, with contributions from June Ruse and many others (maps.org/treatmentmanual). The *Treatment Manual* describes in detail the essentials of our approach to MDMA-assisted psychotherapy for PTSD. The accompanying set of Adherence Criteria allows a dedicated group of adherence raters, led by Evan Sola, to score video recordings from research sessions in order to document the degree to which study therapists are adhering to the same approach in each of the study sites, and regardless of whether participants received placebo or MDMA.

THERAPIST TRAINING

The *Treatment Manual* is also the basis of our program for training research therapists to use the same method at each MDMA-assisted psychotherapy for PTSD study site. Like everything else at MAPS, the training has evolved over the years. It began with a retreat of researchers in Austria where we shared ideas and videos from the first Charleston study and the Swiss study. Annie and I then went on to develop a five-day therapist training program which included a didactic portion followed by watching and discussing videos from research sessions. We have now done this training in Charleston, Israel, Canada, and England. Marcela Ot'alora has also done trainings in Boulder.

More recently, Annie, and Marcela and I have joined forces to expand the training to seven and a half days. Thanks to the coordinating help of Sarah Braswell and the online training and neuroscience expertise of Alli Feduccia, this new format presents the didactic portions as an interactive online training that participants will complete beforehand. Our first training with this format took place October 4–10, 2015, and additional trainings will take place with increasing frequency as we approach the start of Phase 3 trials in 2017.

SCIENTIFIC PRESENTATIONS

As MAPS' research has grown, so has interest from the scientific community. No longer is the discussion dominated by sensationalism about "Ecstasy" and raves, or by misinformation about toxicity. Since our results have been published in a respected peer reviewed journal, and as we continue to speak at medical conferences, MDMA-assisted psychotherapy is increasingly appreciated as a promising area of research aimed at addressing a major public health problem. Increasingly, MDMA is being discussed as a drug that, like every other drug or procedure used in medicine, has potential risks and benefits that should be evaluated carefully. MAPS' Psychedelic Science conferences have been very well attended, and we have been invited to present the results of our research at many conferences, including The

Royal College of Psychiatrists in England, the American Psychological Association, the U.S. Psychiatric and Mental Health Congress, the European College of Neuropsychopharmacology, the International Society of Traumatic Stress Studies, and others.

The most recent sign of increasing interest from the psychiatric community was the inclusion of our three-hour symposium on psychedelic research at the 2015 annual meeting of the American Psychiatric Association in Toronto, Canada, this spring. Charlie Grob, from UCLA, and I spoke about MDMA clinical research, and Roland Griffiths and Matt Johnson from Johns Hopkins and Michael Bogenschutz from University of New Mexico spoke about psilocybin clinical research, with Tim Brewerton from Medical University of South Carolina as discussant. The symposium was well-received with thoughtful and enthusiastic discussion at the end, and a number of psychiatrists and psychologists in training or who have recently completed their training expressing passion about directing their careers toward this kind of work.

OUTREACH TO VETERANS AFFAIRS AND DEPARTMENT OF DEFENSE

When we applied to the FDA for our first study in October 2001, primarily aimed at treating people with crime-related trauma such as childhood sexual abuse, rape, or other assault, we didn't know that the Afghanistan and Iraq wars would be starting soon. Since then, the need for additional treatments for returning veterans with PTSD has become painfully and increasingly pressing. As we began to add veterans to our first study, and then to design a second study focused mainly on veterans (also including firefighters and police officers with PTSD), a number of psychiatrists and other therapists at U.S. Department of Veterans Affairs (VA) hospitals expressed interest in referring veterans to the studies, and in initiating studies within the VA system.

For years, these efforts were blocked as they moved up the administrative chain, and investigators were told that anything this "controversial" would need to be approved by the Secretary of the VA in Washington, D.C. This was a clear example of politics blocking physicians and therapists from pursuing scientific research methods to discover better ways of helping their patients who were suffering and dying from PTSD. Likewise, in an attempt to collaborate with the Department of Defense (DoD), we developed a research protocol with a psychiatrist in charge of a PTSD treatment center at a Navy hospital, but his Admiral refused to sign off on it.

With the help of the late Richard Rockefeller, who sadly died in the summer of 2014 in a plane crash, we attempted to address the irrational political and administrative resistance to MDMA research. Richard was a physician who understood the ravages of PTSD and the limitations of existing treatments, and he committed himself to helping us advance this research. "Armed" with encouraging data from our studies, Rick, Richard, and I had meetings at the Pentagon, the Defense Health Headquarters, and the National Center for PTSD (which directs all PTSD research and treatment in the VA system). Thanks

to these efforts, after several years and many twists and turns, we are now in the process of developing several MDMA/PTSD research protocols in collaboration with VA researchers, and we have recently submitted the first one of those to the FDA. This will be a study combining our method of MDMA-assisted psychotherapy with Candice Monson's method of Cognitive Processing Therapy for couples.

Ironically, despite the billions of dollars the VA and the DOD have for research, MAPS has committed to funding these pilot studies in order to avoid the uncertainty and several year delay involved in applying for government funding, and in hopes that government funding may follow once we have pilot data from a collaboration with VA researchers. We are indebted to Richard Rockefeller for his political and financial support of the research, and for his wise council, energetic engagement, and warm friendship as we brainstormed with him about our shared passion for the vigorous pursuit of clinical research into the potential of MDMA-assisted psychotherapy for PTSD.

SUMMARY

It's been fascinating and exciting to be involved in this effort, and to see MAPS grow to meet the challenges resulting from successes and growth. When Annie and I started working with MAPS, which had once been Rick's one-man show, communication was easy and emails were limited because Rick, Valerie, and Ilsa were the only people on the clinical team. Now there are many protocols at sites around the world, and a growing MAPS staff to match. It is striking to me that all this has been possible without the benefit of funding from government or the pharmaceutical industry. It's happened because of Rick's vision, knowledgeable guidance, and tireless fundraising efforts tapping the generosity of individual donors, family foundations, and MAPS supporters who understand the importance of this work. I am deeply grateful to have the opportunity to play a role in this compelling work.

My interest stems from seeing the clinical need for better treatments. After 10 years of practicing emergency medicine followed by 25 years of practicing psychiatry with a focus on PTSD, I am well versed in a range of existing treatments. I have respect for treatment models developed in recent years that have been developed and researched by compassionate and committed psychologists and psychiatrists, and I know these treatments are effective for many people. However, millions of people with PTSD do not respond to existing treatments, and presently 26 veterans are committing suicide every day in the US alone. I have not encountered any other treatment approach to helping these people that is nearly as promising and compelling as MDMA-assisted psychotherapy, using a medicine only a

few times in an optimal set and setting to catalyze profoundly healing, often life-changing, experiences. And I appreciate that this is a community effort dependent on committed supporters and a growing number of talented, dedicated and very hard working volunteers, investigators and MAPS staff. I am always encouraged by the number of young people who want to get involved and who have the passion and the credentials to carry this forward.

I'm well aware that it remains to be seen whether our encouraging Phase 2 results will be reproduced in multicenter Phase 3 trials, and I know the importance of maintaining scientific objectivity as the research continues. What is not in doubt is that a great many psychiatrists, psychologists, and other therapists, those in practice and those still in training, clearly recognize the need for new approaches to treatment for the many people whose suffering does not yield to existing psychopharmacologic or psychotherapeutic treatments, and many recognize the potential of novel approaches to drug-assisted psychotherapy.

For those who are suffering, this need is pressing, and is reflected in the fact that over 900 people have contacted us about wanting to participate in our most recent study that had room for only 24 participants. Annie and I deeply appreciate the willingness of study participants to volunteer for our clinical trials, and to allow us to support them in their profound and challenging processes of healing. It's a privilege that always touches us deeply and teaches us a great deal.

Why are people willing to consent to an experimental treatment

that we tell them from the outset may involve revisiting traumatic experiences and feeling more fear, grief and rage during the process? I think it's because, on some level, the understanding that healing comes from catalyzing our own innate wisdom and healing capacity intuitively makes sense to us all, however unfamiliar, and even frightening, it may sound when we've been taught that healing comes from outside ourselves. As we learn more and more about the mechanisms of action of MDMA on the brain and the rest of the body, MDMA-assisted psychotherapy sessions repeatedly confirm the reality that we each have an innate human capacity to heal. 🌀

Michael Mithoefer, MD is a psychiatrist practicing in Charleston, SC, where he divides his time between clinical research and outpatient clinical practice specializing in treating posttraumatic stress disorder (PTSD) with an emphasis on experiential methods of psychotherapy. He is a certified Holotropic Breathwork Facilitator and trained in EMDR and Internal Family Systems Therapy. He can be reached at mmithoefer@mac.com.

A great many psychiatrists, psychologists, and other therapists, clearly recognize the need for new approaches to treatment for the many people whose suffering does not yield to existing psychopharmacologic or psychotherapeutic treatments.
