MAPS-Sponsored Research at the 2017 Annual Meeting of the International Society for Traumatic Stress Studies: Signs of Breaking Through Resistance

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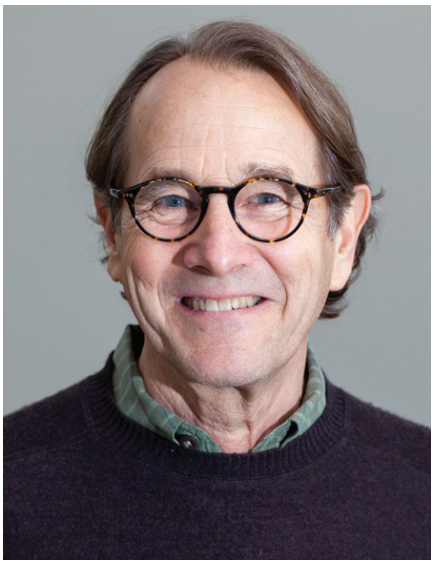

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MDMA-assisted psychotherapy was granted Breakthrough Therapy Designation by the Food and Drug Administration (FDA) only one year after our End of Phase 2 meeting with the agency. I recently heard a Multidisciplinary Association for Psychedelic Studies (MAPS) consultant with many years of experience in the pharmaceutical industry say, "This never happens!"

The fact that it did happen is a result of the expertise and exceptionally hard work of the MAPS and MAPS Public Benefit Corporation (MPBC) teams, the advantages of a relatively small and nimble organization, and the support of so many people who see the importance of this effort. It's also a sign of growing acceptance by the medical and scientific community that this is rigorously conducted and sorely needed research; a far cry from the days when what we heard so often was, "You'll never get approval to do clinical research with MDMA!" Before I discuss other signs of this sea change, a brief review of some of the challenges along the way will illustrate how big a change it is.

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In 1990, Charlie Grob, M.D., Director of the Division of Child and Adolescent Psychiatry at UCLA, published a letter criticizing one of George Ricaurte's MDMA neurotoxicity studies reported in the *Archives of General Psychiatry*. Sasha Shulgin then sent a copy of the letter to Rick Doblin, who promptly introduced himself to Charlie. That's when their respective long-time determinations to pursue psychedelic research came together to bear fruit. Within two years, Charlie, Rick, and Gary Bravo submitted a Phase 2 protocol to the FDA to study MDMA for treating anxiety in patients with terminal cancer. Even for these patients with limited life expectancy, the FDA judged that the possible risk of neurotoxicity was too great to allow the study without more safety data. However, the FDA was willing to consider a Phase 1 trial in healthy volunteers to investigate the physiological effects and pharmacology of MDMA. Later that year, a Phase 1 protocol was accepted, and Grob went on to successfully complete the first of three U.S. Phase 1 trials investigating the effects of MDMA.

This is an example of what we have seen from the FDA consistently regarding psychedelic research—a rigorous approach based on science rather than politics, and a willingness and ability to reply to protocol applications without undue delay. (Responses from other regulatory agencies and institutions have not always been so rational or unbiased.) These Phase 1 studies provided the basis for the Phase 2 treatment trials that were to follow. Despite this success, Charlie judged that (in his words) "the MDMA neurotoxicity campaign run by NIDA was quite intense at that time

and had further poisoned the MDMA debate" (Grob personal communication 2018), so he focused his attention on psilocybin research instead, and did not proceed to a Phase 2 MDMA study for more than a decade.

The first Phase 2 study of MDMA-assisted psychotherapy was started in Spain, sponsored by MAPS and led by Jose Carlos Bouso and Marcela Ot'alora in 2000, the same year we started writing a protocol for a similar study in the U.S. Two years later, for political reasons, the study in Spain was forced to shut down by the drug police. Our U.S. protocol, having been approved by the FDA in November 2001—30 days after we submitted it—had since become mired in other regulatory delays. We had been unable to obtain an Institutional Review Board (IRB) review at the Medical University of South Carolina (MUSC) because MDMA research was still considered too controversial. I was told later by the Chair of Psychiatry at MUSC that they were afraid of a punitive audit by the federal government that, they said, could shut down all the research at the university for months.

We went on to obtain approval from Western IRB without difficulty, but three months later their approval was withdrawn because of concerns raised by a new study from Johns Hopkins University, published in *Science* with an accompanying press release and considerable fanfare, claiming that MDMA caused fatal dopamine toxicity in 20% of primates studied. Our published response expressing skepticism about the study was dismissed by the study authors (among them George Ricaurte, again) and apparently largely ignored by many readers. It seemed they were not persuaded by our scientific reasoning or our assertion that if 20% of people at raves were dying every weekend we probably would have heard about it. Speculation ensued in the medical literature about the looming epidemic of Parkinson's disease expected to result from widespread "Ecstasy" use. As a result, despite Rick Doblin's persistent efforts to find another IRB, we were not able to do so until almost exactly a year later.

On September 12, 2003, Ricaurte's paper was retracted because the researchers discovered that they had mislabeled the bottles, and had not administered MDMA at all in their study. What they had administered to the unfortunate baboons and squirrel monkeys was methamphetamine, a prescription medicine known to cause dopamine toxicity in high doses. Suddenly, when it wasn't MDMA causing the toxicity, the fears about Parkinson's disease seemed to evaporate. Eleven days after the retraction, we received IRB approval from Copernicus IRB in North Carolina.

Meanwhile, my Schedule I research registration application, submitted July 3, 2003, and required for me to obtain and administer MDMA in clinical research, had still not been approved by the Drug Enforcement Administration (DEA). After more than a year of calls, letters, and emails back and forth, and two resubmissions of the approximately 500-page application because it had been misplaced internally at the DEA, I faxed a letter to Senator Fritz Hollings with a chronology of all our communications with the DEA. I said I did not expect the Senator to have an opinion about whether or not the application should be approved, but I was requesting his help with the undue delays that were impeding science. Four days later, I got a call from the South Carolina DEA Field Office to schedule a site inspection.

There was some additional delay as the central DEA office in Washington asked them also to do a background check on the therapist in the adjacent office. They said they were concerned that she could drill through the wall into the back of the safe to steal the MDMA. She was a good sport about my giving them her contact information: "OK," she said, "But tell them I'm not good with tools." Apparently the DEA investigation confirmed this because my Schedule I registration arrived in February 2004. We began screening the first research participant the following month. Since that time, although the regulatory process involved in doing research with a Schedule I drug re-

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mains frustratingly slow at times, we have never again had such extreme delays obtaining approval for any of the subsequent U.S. studies, and we have developed a successful working relationship with the DEA.

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In those earlier days, resistance to accepting the importance and legitimacy of MAPS' research was not limited to the DEA and some IRBs; it also seemed to be widespread in the medical and psychotherapy communities. Happily, this has changed radically in recent years, due in large part to our publishing very promising data in peer-reviewed journals. Media coverage no longer starts every report about the research with images of raves and Ecstasy pills. The public focus has gradually shifted to the results of our rigorously designed and conducted clinical trials, and to the profound stories of the research participants who have courageously spoken publically about their healing.

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A recent sign of this changing attitude was my invitation to speak at the International Society for Traumatic Stress Studies (ISTSS) 2017 Annual Meeting in Chicago. The last time that meeting was in Chicago had been ten years earlier. I applied to speak at the 2007 meeting, but was only accepted to do a poster presentation. While I was in Chicago that first time, I was interviewed on-camera at the CNN studio for one of the reports Sanjay Gupta did on our research, but my poster got relatively little notice at the conference itself. In contrast, in 2017, though I did not apply to speak, I was invited to give one of the "Master Clinician" addresses at the conference. In addition, the conference hosted a symposium entitled "Pharmacologic Agents as Treatment and Adjunct to Psychotherapy for PTSD" with presentations by two psychologists who have collaborated with us on MAPS-sponsored studies.

One of these presenters was Anne Wagner, Ph.D., who organized the symposium and spoke about the promising results of our recently completed pilot study combining MDMA-assisted psychotherapy with Cognitive Behavioral Conjoint Therapy (CBCT) for PTSD. Candice Monson, Ph.D., who developed CBCT and is Director of Clinical Training at Ryerson University and an affiliate of the Women's Health Sciences Division of the Veterans Affairs (VA) National Center for PTSD, was also a co-therapist in the study in which both members of a couple received MDMA together during two MDMA-assisted therapy sessions embedded in a course of CBCT. To my knowledge, this is the first time FDA has allowed an investigational psychiatric drug to be administered to two people at the same time.

The other MAPS collaborator presenting on the panel was Barbara Rothbaum, Ph.D., professor at Emory University and the Atlanta VA Hospital, who spoke about her recent studies of MDMA as an agent to increase fear extinction and her upcoming study combining MDMA with Prolonged Exposure therapy for PTSD. The discussant for the panel was Paula Schnurr, Ph.D., Executive Director of the VA's National Center for PTSD, responsible for directing PTSD research and treatment in the VA system. In her discussion, Schnurr pointed out that she is approached every week with new ideas for better PTSD treatments, most of which she does not consider worth pursuing. She went on to say that MDMA-assisted treatment is an approach she does consider important to pursue, citing our promising data and the plausible mechanisms of action based on what is known about the effects of MDMA and the nature of PTSD.

My "Master Clinician" presentation also seemed to be very well received. Though there was one person in the room who went on a bit of a tirade against the research during the discussion period (with arguments I didn't quite understand), many people expressed excitement about the potential of MDMA-assisted psychotherapy. I explained our study design, our therapeutic approach, and the combined results of MAPS' completed Phase 2 studies, showing a large effect size across six studies at five different sites in four countries. This was an audience of trauma therapists who were trained and experienced in a variety of different methods, so I pointed out that while the format of our therapy with eight-hour sessions and our relatively non-directive (or client-directed) approach is quite different from existing trauma-focused treatments, we have consistently observed that elements of other therapeutic approaches often arise spontaneously in the course of our less directive method of therapy.

For example, our research participants often spontaneously engage in "imaginal exposure," something patients are instructed to do in Prolonged Exposure (PE) therapy, a form of Cognitive Behavioral Therapy (CBT). Our participants also invariably address relationships, family issues, and transference as in psychodynamic psychotherapy; they notice and correct cognitive distortions as in CBT; and they often become more aware of their own inner parts, and bring curiosity and compassion to addressing them, as in Internal Family Systems (IFS) therapy. Our approach includes a focus on the body, as is the case with Somatic Experiencing, Sensorimotor Therapy, Holotropic Breathwork, and other body-centered methods. In addition, there are often Jungian elements, such as powerful archetypal images and processing that resembles active imagination.

One of the challenges I've confronted in discussing possible therapeutic mechanisms of MDMA-assisted psychotherapy has been accounting for this variety of effects observed during PTSD research sessions. How does MDMA-assisted psychotherapy work? Does MDMA work by facilitating imaginal

exposure, by exposing underlying faulty schema and correcting cognitive distortions, by providing psychodynamic insights and increased awareness of transference, by increasing "Self" energy and allowing for effective work with internal parts, by stimulating somatic processing, by mobilizing Jungian archetypal forces, or by engendering mystical or transpersonal experiences? My suggestion to this group of therapists was that we may be in a situation akin to the fabled group of blind individuals describing an elephant according to which part of the elephant each of them could feel.

Parallel to the challenge of making sense of the spectrum of possible mechanisms of MDMA-assisted psychotherapy was the challenge of explaining our relatively non-directive/client-directed approach to a group of experienced trauma therapists and researchers, many of whom were experts in the most widely used manualized treatment methods. Although, these methods are more responsive to individual client differences than one might expect when in the hands of skilled therapists, they are much more standardized, directive, and tied to specific theories about PTSD than is our approach. In our approach, the working hypothesis (which we originally learned from Stanislav Grof) is that the therapeutic process is best directed by the individual's own inner healing intelligence. To many cognitive behavioral therapists, this may seem insufficiently standardized to be consistently effective or even to be studied adequately. Our data demonstrate that this is not the case. In my opinion, our approach is standardized in an important respect, although it is different from what is considered standardization in other treatments, which tend to prescribe the content of each therapy session. Each of our study participants receives the therapeutic experience that arises naturally according to their own healing intelligence, when they are provided a conducive set and setting and a catalyst for this intelligence to express itself. This may be a more relevant form of standardization than one dictated by therapists' assumptions about what may or may not fit a given participant's natural healing process. Instead, the role of the therapist becomes removing obstacles and supporting the healing process as it unfolds.

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As someone with experience practicing MDMA-assisted psychotherapy, all this makes perfect sense to me, but I wondered how it would be received by the ISTSS audience. Happily, I got some unexpected encouragement from an inspiring presentation by Kenneth Kendler, M.D., the day before my talk. Dr. Kendler is a highly respected, widely published professor of psychiatry who has spent decades thoughtfully studying psychiatric disorders. He made an elegant argument against reductionist explanations of etiology (the causes of illness) and in support of the conclusion that "psychiatric disorders are inherently multifactorial." I would add that it follows that if the origin of psychiatric disorders is multifactorial, so too should be their treatment. Our observations and results bear that out. Perhaps that's one reason many people in MAPS-sponsored MDMA-assisted psychotherapy studies who had failed to respond to years of existing pharmacologic and psychotherapeutic treatments for PTSD have responded so robustly to our multifactorial approach.

A few months after the ISTSS meeting, I was delighted to read additional support for this position from another psychiatric elder and leader in developing and teaching psychotherapy, Irvin Yalom, M.D.. Drawing on his many years of research and experience, Dr. Yalom writes, "The therapist must strive to create a new therapy for each patient." I'd take this even further, and say that the therapist must strive to allow and encourage each patient to create a new therapy for themselves. It appears that MDMA, used wisely, can be a powerful ally in this endeavor.

Michael Mithoefer, M.D., *is a psychiatrist practicing in Charleston, SC, where he divides his time between clinical research and outpatient clinical practice specializing in treating PTSD with an emphasis on experiential methods of psychotherapy. He is a Grof-certified Holotropic Breathwork Facilitator and is trained in EMDR and Internal Family Systems Therapy. He and his wife, Annie Mithoefer, recently completed a MAPS-sponsored Phase II clinical trial testing MDMA-assisted psychotherapy for PTSD. A paper about their study was published in July 2010 in the* Journal of Psychopharmacology. *Before going into psychiatry in 1995 he practiced emergency medicine for ten years, served as medical director of the Charleston County and Georgetown County Emergency Departments, and has held clinical faculty positions at the Medical University of South Carolina. He is currently board certified in Psychiatry, Emergency Medicine, and Internal Medicine.*