Update on MDMA/PTSD Research in Charleston:

A New Protocol with Veterans

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TWO YEARS after completing our first study of MDMA-assisted psychotherapy for treatment-resistant PTSD (MP-1), we are now enrolling veterans with PTSD resulting from experiences during military service in a new study entitled, "A Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction with Manualized Psychotherapy in 16 Veterans with Chronic Posttraumatic Stress Disorder (PTSD)" or MP-8.

In November 2008, I presented the results of MP-1 at the International Society for Traumatic Stress Studies (ISTSS) annual meeting in Chicago, and later to the Royal College of Psychiatrists in Liverpool. In July 2010, we published these results in the *Journal of Psychopharmacology*. We have also completed a long-term follow-up of participants in MP1, showing that the marked benefit at the end of the protocol was sustained for most participants one to five years later (average 40 months). I recently presented these long-term results at the American Psychological Association meeting in San Diego and at the ISTSS meeting in Montreal. We are very encouraged by the outcome of this study, including the fact that there were persistent benefits several years later for most people. We were deeply moved by the opportunity to participate in these volunteers' profound experiences, and of course we wish the benefit had lasted for everyone. Over time, we expect further research will yield information about how to optimize the treatment protocol to benefit as many people as possible. We are also aware that that this study is an early step in a long process. The next step is to demonstrate whether or not these results can be replicated in other similar studies, and then ultimately in much larger, multicenter trials. We're looking forward to seeing the results from other MAPS studies by our colleagues in Switzerland, Israel, Canada, and Jordan, as well as our own study in veterans.

There are several reasons we think it's important to put time and resources into the new study with veterans. Most compelling is the fact that there are so many veterans returning from Iraq and Afghanistan who need help with debilitating PTSD symptoms. There are a number of existing treatments for PTSD that are effective for many people, but having just returned from the annual ISTSS meeting, the largest organization in the world of experts in PTSD treatment and research, I am struck by the abiding consensus among these experts that better treatments are urgently needed for the large number of people who do not respond adequately to available treatments and for those who have a high rate of relapse after treatment. I also heard a moving plenary address at the meeting by Canadian Senator and retired General Romeo Dallaire, who commanded the United Nations Assistance Mission for Rwanda. He referred to people with PTSD as "wounded not sick," and emphasized the responsibility we all share to provide effective treatment for their wounds.

The other reasons for this study have to do with refining our design for future large-scale trials. One of the limitations of our first study was that, although we had an effectively blinded independent rater administering the symptom measures, both the investigators and subjects were usually able to guess who got MDMA and who got placebo. This is a weakness in the study design that is common to many drug trials in psychiatry, though one that is not usually measured and discussed openly as it was in our protocol and our paper. In the veteran study, instead of using an inactive placebo vs. a "full" dose of MDMA, we will attempt to strengthen the blind, and therefore the scientific validity, by using three different doses of MDMA: low, medium, and full dose. This design is intended to determine whether one of the lower doses will act as an effective "active placebo," making the subjects and investigators less likely to guess correctly which dose is administered.

We will enroll 16 veterans, twelve with PTSD of less than ten years duration and four with PTSD of any duration, and we hope to recruit eight men and eight women. All must have proved resistant to previous therapy with either medication or psychotherapy. Before enrollment there will be careful medical and psychological screening to rule out contraindications to participation. The enrollment criteria have changed since MP-1, in that now we will be able to include people with histories of hypertension or hepatitis C if they have been adequately screened and treated. Half the participants will receive three sessions with full dose MDMA on three occasions, and the other half will receive either low dose or medium dose MDMA on three occasions. Both the participants and investigators will be blinded to which dose is being administered. At the end of this phase of the study the blind will be broken, and those who received low or medium dose MDMA will have the option to enroll in a second phase

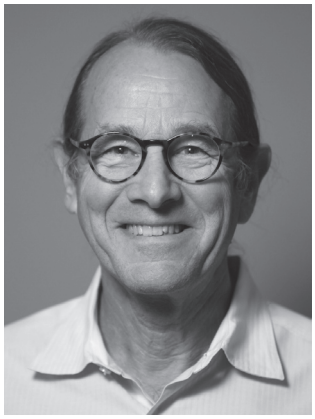
in which they will receive full dose MDMA three times. The MDMA will be administered under direct supervision of a male and female therapist (my wife Annie and I). After the all-day session, participants will spend the night in our office with an attendant on duty. There will be non-drug psychotherapy sessions to prepare the participants for the experience and help them integrate it afterwards. Independent raters (psychologists not involved in the treatment parts of the study) will administer the symptom measures before and after treatment. Our method of therapy will be the same as in MP-1, but we have now refined our treatment manual and have developed manual adherence measures. This will allow outside raters to watch videos of the study sessions and confirm whether or not we are adhering to the manual with each subject. Three highly qualified volunteers have helped us refine the measures and have offered to use them to rate our sessions in MP-8. By applying the measures to recordings from the previous study we are now in the process of establishing inter-rater reliability in their scoring.

Both MP-1 and the Swiss study laid a foundation that allowed us to take these next important steps in MP-8: strengthening the blind, expanding the enrollment criteria, and verifying adherence to the treatment manual. When we began work on the treatment manual over eight years ago, I had doubts that this largely non-directive approach to therapy could be effectively manualized, but we knew a manual would be necessary for the research to move forward into larger trials. Based on what we had learned from the work of others and our own experience treating PTSD, we set out to describe our approach to MDMA-assisted psychotherapy. We did this by reviewing our session videos, with invaluable input from experienced therapists (and occasional cringing on our parts) as we watched. The video review helped us refine our understanding and descriptions of the therapeutic approach, as well as learn more about our own performance. Although we have not completed final editing of the manual, we think it conveys the essential elements of the therapy, while including enough flexibility to support each participant's unique healing process and each therapist's particular skills and intuition.

Using the manual, adherence measures, and video recordings from the first study, we have developed a training program for therapists for use in future clinical trials. We don't claim to have definitively established the best way to conduct MDMA-assisted psychotherapy, but we do have a promising method that grew from the experiences and studies of earlier psychedelic researchers, making it a good candidate for further testing. Meaningful further testing requires that we have a well-described method that can be replicated by other trained teams in different studies, especially in future multi-center trials. Early this year we conducted a training program in Charleston for therapist teams from Jordan, and in January 2011 we will go to Israel to conduct training for new teams who will be joining the MAPS MDMA/PTSD study there.

In addition to obtaining approval for the study with veterans, we have gained FDA, DEA, and IRB approval for a study entitled, "A Phase 1 Placebo-Controlled, Double-Blind Crossover Study to Assess Psychological Effects of MDMA when Administered to Healthy Volunteers." Enrollment will be limited to volunteers who have completed our training program for therapists and intend to work as therapists/investigators in MAPS-sponsored clinical trials. Information about psychological effects of MDMA in healthy volunteers has not previously been obtained in a therapeutic setting, so this study will add to our knowledge of MDMA effects in the same setting we use for clinical studies. It will also provide an option for therapists working in clinical trials of MDMA-assisted psychotherapy to have their own MDMA experience in that setting. We think this is likely to expand therapists' knowledge and skills and give them a more complete grasp of the study drug as experienced by research participants in MDMA-assisted psychotherapy.

So, there's a lot happening in MAPS research and a lot to be done. I'm delighted that more and more young people are expressing interest and becoming involved in research with MDMA and psychedelics early in their careers. These efforts have great potential to teach us about the human psyche and brain, and give us valuable tools for relieving suffering and facilitating healing and growth. •



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