MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder (PTSD): An Update on the Approval Process

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In the fall 2001 issue of The MAPS Bulletin (volume XI number 2), I described the Investigational New Drug Application (IND) that Rick Doblin and I submitted to the U.S. Food and Drug Administration on October 1, 2001. The IND requested permission to conduct a MAPS-sponsored study of MDMA-assisted psychotherapy for the treatment of posttraumatic stress disorder (PTSD). I now have an update about our progress through the approval process since then, including some bumps in the road and at least two pieces of very good news.

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Once an application is formally submitted to the FDA they have thirty days to reply, so we knew we would hear something by the end of October. We also knew it was possible that this initial reply would be the beginning of a process of discussion and negotiation rather than a final decision. On October 29, Rick Doblin got a call from the FDA to tell us that members of the panel reviewing our application wanted to have a conference call in order to address some concerns about the protocol before they made a decision. On October 31, Rick and I had a teleconference with two doctors from the FDA Division of Neuropharmacological Drug Products. We had a useful discussion during which we agreed to make some changes in the protocol.

These changes are as follows: 1) We will measure blood pressure and pulse more frequently during the MDMA sessions and will have lower thresholds for instituting increased monitoring and considering treatment. 2) There will not be an opportunity for subjects who received placebo to be given "open label" MDMA sessions at the end of the study. Although we would have liked to have been able to include these open label sessions, we felt the FDA position on this was reasonable. Since this is the first Phase II study, we presently don't have data to support an argument that an open label dose would be beneficial. 3) Subjects will not be able to take any psychiatric medications until after the final evaluation (two months after the second MDMA or placebo session), including medications they had taken before the study. An exception to this would be a "rescue medication" that I could prescribe if a subject were experiencing severe anxiety or insomnia. 4) Subjects who were in ongoing therapy prior to the study will be able to continue that therapy but will not be able to increase the length or frequency of the sessions and will not be able to start any new therapy during the study period.

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The FDA physicians also wanted to discuss the possibility of excluding subjects who had not previously taken MDMA. This had been a requirement in all the Phase I studies in this country. We argued successfully against adding that exclusion, because restricting inclusion only to people experienced with MDMA or ecstasy would unnecessarily skew and limit the pool of potential subjects. It was agreed that, as requested, we would be allowed to include "MDMA naive" subjects in our study.

The following day. we faxed in a formal version of the changes we had discussed. On November 2nd ,we got a call telling us our application had been approved and we could proceed with the study. We were extremely gratified that the FDA had evaluated our protocol based on the scientific data and had responded accordingly. The process of negotiating with them about some of the details had been straightforward and productive.

The next step was to submit an application to the institutional review board (IRB) at The Medical University of South Carolina (MUSC). In order to do so I needed the signatures of the Acting Chairman and one other full time faculty member from the Department of Psychiatry (I am on the clinical faculty, but not the full time faculty). Although we had elected not to submit a formal application to the IRB until after obtaining FDA approval, I had spoken to a number of people at the Medical University and had found considerable support for the study. Mark Wagner, PhD, a neuropsychologist in the Department of Neurology at MUSC, had agreed to participate as my co-investigator and to conduct the neuropsychiatric testing. Two senior professors of psychiatry had read the protocol and each said they would be willing to sign on as the study "sponsor" for the IRB. I had made an appointment to meet with the Acting Chairman of psychiatry to discuss the study and address any concerns he might have.

On the morning of my scheduled meeting with the Chairman, the first media reports about our FDA approval appeared in the Wall Street Journal. As a result of this article and the additional media attention that followed, I suddenly found myself confronted with a much more difficult climate at the Medical University. I cooperated with the University Press Office in their attempts to deescalate the media response, and hoped that in time my discussions with people at MUSC could get back to addressing matters of science and patient safety rather than media reports. Since November, I have been trying to bring our application before the IRB for a formal review of its merits, however I have not made significant progress in that direction. There appears to be considerable resistance within the university to having this potentially controversial study take place there. Although we remain hopeful that we will be able to do MDMA research at MUSC in the future, we decided in early March to move ahead with pursuing other options in the interest of avoiding further prolonged delays in this project.

On March 14th, 2002 we submitted a formal request to the FDA to change the location of the study from the MUSC General Clinical Research Center to an outpatient setting outside the University. This request provided detailed descriptions of the ways we would handle any potential medical complications, and it included a proposal to have emergency drugs and equipment on hand and to hire an experienced ER nurse to be present in the adjoining room during the MDMA sessions.

On May 10th 2002, we got a phone call from the FDA informing us that a "clinical hold" had been placed on our study because of concerns relating to the provisions for handling medical emergencies outside the hospital. There was some concern about the details of treating hy-

pertensive emergencies in particular, and a more general concern that we would not have an emergency response team comparable to what exists in a hospital setting. Rick and I spent the weekend polling a number of practicing ER physicians about our proposal and working out a response to the FDA's concerns. The ER physicians we spoke to concurred with our approach to blood pressure monitoring during antihypertensive treatment, and Dr. Howard Kornfeld wrote a letter of support to the FDA. On May 13th, we faxed them a response indicating that we understand and appreciate the issues raised concerning the safety of our subjects, and that we agree that, for this pilot study, we need to provide a level of emergency response in the office setting comparable to that which would be provided in the hospital. In keeping with that intent, we proposed to add some additional monitoring equipment, and to hire a currently practicing, board-certified, emergency physician as well as a currently practicing emergency department nurse to be present in the adjoining room during at least the first five hours of each session. These two staff, along with the two cotherapists (me and my wife, Annie), would give us a team of two experienced emergency physicians and two registered nurses. This would allow us to respond to a medical emergency at least as effectively in an office as in a hospital, and arguably more effectively. In addition, from a psychological standpoint, an office has the advantage of being quieter, more comfortable and more aesthetically appealing than a hospital room. (From a financial standpoint, the extra cost of these precautions would be approximately $40,000, which is almost exactly what we would have had to pay MUSC in indirect costs, so they would not add to the overall cost of the study.)

Rick and I had a conference call with the FDA team reviewing our request on May 14th, and were gratified to find that they were very receptive to our revised proposal. They told us that before making a final decision, they wanted an opinion from their cardiology division. On June 11, we received a fax with several recommendations from the FDA Division of Cardiorenal Drugs. These recommendations demanded some fine-tuning of what we had already agreed upon, but required no major changes in our approach. I felt that what they requested was reasonable and was unlikely to interfere with the therapeutic nature of the sessions. Later that day Rick informed the FDA that we would agree to these conditions, thus clearing the way for them to remove the clinical hold on our study.

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With the help of the rest of the original application team, Ilsa Jerome and Matthew Baggott, we've prepared an application to a private IRB. On June 14, we received clearance from the FDA to do the study outside the university. On June 19, we submitted the IRB application. If this process goes smoothly, we should be in a position to start recruiting subjects in August or September.

It's been a sometimes frustrating but always interesting seven months. I've learned something about the intensity and the pitfalls of media attention. I've been not too surprised, but still very sorry to see the degree to which academic freedom in a university can be constrained by prejudice and political pressure. I've been impressed and heartened by the integrity and professionalism of the FDA. And I've really enjoyed the experience of working with Rick and the other people at MAPS to respond to the challenges that have presented themselves. Obviously this project has momentum, and I'm enjoying the ride. ■