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Dear Dr. Bauer:

In further response to your letter of February 4, 2003, I would like to address more fully the committee's concerns "about agitated subjects, or those with suicidal ideation associated with study procedures." In our letter of February 10, Dr. Doblin and I responded to items "a." and "b." in the section on "Protocol – Safety Issues." I will now respond to item "c." regarding controlling "the safety of the post-catalytic reaction" and specifically requesting clarification of our plan to have the therapists stay with an agitated subject, the question of retaining someone against their will and the possibility of relapse hours or days later. Because the question of whether or not bodywork will be used is still under discussion with the committee. I will not include it here (although I do strongly urge that bodywork be retained as an element of the protocol for dealing with emotional distress). If we do reach agreement to retain bodywork as an option, we would use it in conjunction with these other measures as described in Appendix A and in the draft Treatment Manual.

Before drawing a conclusion about how best to deal with anxiety, agitation or distress in the study participant, the investigators will assess the nature of the distress. Some subjects may experience an increase in specific anxiety-related PTSD symptoms such as recurrent trauma-related thoughts, whereas others could experience panic attacks or generalized anxiety. These experiences would be addressed differently according to the type of distress experienced by the subject.

The investigators will deal with recurrent trauma-related thoughts or images, by offering encouragement and supporting continuation and completion of the cathartic experience. In our years of experience treating PTSD patients with other methods, including Holotropic Breathwork and EMDR, both of which often catalyze intense emotional experiences, agitation that persists at the end of a session can usually be resolved quickly with proper focused support. When a patient is agitated and afraid, it can be quite a powerful intervention to have the full attention of two therapists who are able to calmly and compassionately encourage awareness and expression of difficult emotions in order to allow their resolution into a state of greater calm and understanding.

We believe the same will be true for subjects in this study. In fact, it is our hypothesis that the effects of the MDMA will facilitate this kind of resolution.

Our approach to agitation resulting from recurrent trauma-related thoughts at the end of the session would be similar to that during the session itself. If a subject continues to experience strong negative emotional reactions, including a feeling of loss of control, the investigators will encourage the subject to stay with deeper levels of emotion, and to trust that it is safe to face the experience. This may take the form of introducing the previously practiced breathing exercises, (e.g., "use your breath to stay with the experience, breathe into it"), verbal statements assuring the subject that he/she is in a safe place and orienting them to the "here and now" (eg., "stay with what you're experiencing and at the same time remember that it's about old experience. You're safe here with us now and you're remembering this trauma for the purpose of healing."), encouraging the subject to talk about his/her emotions, holding the subject's hand, or providing other nurturing touch. In this way, the investigators help the subject to stay with and move through his/her emotional experience, (i.e., fear, anxiety, shame, confusion, guilt, etc), and to frame the experience as a natural progression of the therapeutic process).

An example of helping the patient with a difficult experience:

> Subject: (looking agitated) "I just keep having images of those men, I try to think of something else but I can't make it stop!"
> Investigator: "We're right here with you. (Perhaps with some nurturing touch) I know this part is hard, but it's coming up now for healing. If you can use your breath to stay with the experience instead of trying to make it stop that will help you move through it. Use your breath, just breathe into it and stay as present as you can with your experience, and express it in any way you need to, crying, making sounds, letting your body move, talking to us about it, however you can express it. We're right here."

At the completion of catharsis in the situation described above, or in cases in which the agitation/anxiety is more generalized, a combination of relaxation techniques and talking (to promote cognitive restructuring and gaining of perspective) will be used. The use of talk therapy, including cognitive-behavioral techniques for anxiety, is beyond the scope of this letter but is well described in the literature (Beck 1988) and is something in which the investigators are well-trained and experienced. The relaxation techniques to be used will be:

1) Slow diaphragmatic breathing which will have been taught and practiced in introductory sessions. The investigators will guide the subject by counting the subject's breaths out loud from 1 – 10 repeatedly and by encouraging subjects to visualize difficult feelings flowing out with the out-breath and calm, healing energy entering with the in-breath.
2) Guided visualizations: either "Streaming Light Visualization" or "Safe Place Visualization" commonly used in conjunction with EMDR and other therapies for PTSD (Shapiro 1995).

If a subject remains agitated after two additional hours of the above interventions, I will have two options:

1) Allow the subject to go home under the following conditions:
    a. The support person will be brought into the room to discuss the situation and plan with the investigators and the subject.
    b. A verbal safety contract will be made in which all parties agree that the support person will remain with the subject continuously until the next day's appointment with the investigators, that the subject will commit no harm to self or others, and that the subject or the support person will page the investigators immediately in the event of relapse.
    c. The 24 hour call number will again be given to the subject and the support person.
    d. A "rescue medication" (a benzodiazepine for anxiety and/or zolpidem for sleep) will be prescribed if deemed appropriate.

2) Hospitalize the subject for stabilization.

The committee has asked about whether or not I would detain someone against their will. In this regard I would act in accordance with the local standard of care and the laws of South Carolina, which mandate that a person can and should be hospitalized against their will if they are deemed by a physician to be in imminent danger to themselves or others. I will have commitment papers on hand and there is a special unit of the Charleston County Sheriff's Department that can be called to transport committed persons in as humane a way as possible. This type of emergency commitment can be carried out on the basis of the signature of one physician and one "applicant" (likely in this case to be the support person or the nurse-investigator). Commitment can be dropped by the hospital physicians at any time within three days, otherwise it is reviewed by a Judge after testimony from a court- appointed psychiatrist. I believe it is very unlikely that agitation or other adverse reaction in a subject will require commitment, but it would be performed if absolutely necessary to assure subject safety.

As you point out in your letter, "there could be some kind of relapse hours or even days later." In the event of this occurring, all subjects will be instructed to contact me immediately via 24 hour pager at any time throughout the study period. Some anxiety, depression or agitation can be dealt with in the weekly scheduled meetings, and if necessary additional meetings may be scheduled either at the investigator's suggestion or through participant-initiated contact between scheduled sessions. In addition, when patients are in ongoing therapy, we will maintain contact with the subject's outside therapist and the subject will be able to see that therapist at previously scheduled intervals. These outside therapists will also be useful allies in helping to recognize any signs of relapse.

In addition to the above interventions, as described in the treatment manual, the subjects will be taught to recognize that experiences encountered and information revealed during the MDMA/placebo sessions serve as a valuable starting point for enhancing their emotional and behavioral repertoire in response to PTSD symptoms. They will be instructed to be mindful of any changes in their perceptions thoughts, feelings, interactions, and other experiences. When confronting emotionally threatening material, subjects will be encouraged to return to or remember

any feelings of intimacy and closeness to others and any sense of reduced fear and self blame originally experienced during the MDMA/placebo treatment sessions, or at other times in their lives. This should give subjects a useful framework within which to handle any anxieties that may arise.

Subjects will be reminded that the investigators are committed to providing them support throughout the study. At the end of each session, investigators will review the procedure by which they can be contacted at any time should the subject or his/her designated support team need to talk with them about any difficulties or concerns.

I believe that the above protocol provides a substantial and adequate safety net for handling any anxiety or agitation that may persist at the end of an experimental session or that may occur hours or days later. I hope this has adequately addressed the committee's concerns. If not, I would welcome the opportunity to respond to any remaining issues.

Thank you for your continued attention to our protocol.

With best regards,

Michael C. Mithoefer, MD

cc: Erica Heath
Don Mayne

References:

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Shapiro, F. (1995) Eye Movement Desensitization and Reprocessing: Basic Principles, Protocols and Procedures. Gilford Press, NY