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MDMA-Assisted Psychotherapy for PTSD: Momentum Towards Phase 3 and Beyond

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Psychology, as a relatively young science trying to deal with some of the most complex issues of human existence, is still in the process of developing effective diagnostic methods and treatment procedures for some of the field's most widespread and debilitating issues. As a result, complicated conditions like posttraumatic stress disorder (PTSD), end-of-life anxiety, and addiction remain highly resistant to most available treatments and lead to a great deal of suffering.

"Counseling and treatment had shown no measurable improvements in my life. I was stuck in an unhappy place" (subject quote). Words like these are probably all too familiar to anyone who has suffered from one of these conditions or knows someone who has. It is that suffering that creates the pressing need for researchers and organizations with a willingness to advance the scientific testing of new procedures for treatment and, more importantly, to utilize the results of that science to find new ways to help people in need.

This is precisely the role that MAPS has filled since 1986. After first acknowledging the vast potential presented by the therapeutic use of psychedelics (a potential that is heavily supported by the medical and psychological research of the latter half of the 20th century), MAPS has sought to apply that potential to a wide range of treatment-resistant conditions. With studies currently underway and in development to test the viability of therapy in conjunction with ayahuasca and ibogaine to treat addiction and compulsive behavior; LSD to treat anxiety in the terminally ill; and with MDMA (and cannabis alone) to treat PTSD, MAPS is currently conducting the promising research that may ultimately lead to more effective treatments for these debilitating conditions (**maps.org**).

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Nowhere is the significant progress MAPS has made toward the development of such treatments clearer than in its work testing the use of MDMA in conjunction with psychotherapy for the treatment of PTSD. As MAPS' top priority, the MDMA-Assisted Psychotherapy for PTSD program seeks to navigate labyrinthine FDA clinical trial procedures with the ultimate goal of seeing MDMA reclassified as a prescription drug for use in conjunction with therapy. The complicated FDA drug trial process requires research to complete three phases: Phase 1 uses healthy volunteers "to determine the drug's most frequent side effects" and how the drug moves through the human body. Phase 2 "aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition." Phase 3 seeks to gather more information about safety and effectiveness from a larger subject population across multiple sites. Altogether, this process can take years, or even decades, to complete and requires a great deal of careful planning, perseverance, and funding to achieve (**fda.gov**).

Over the years, MAPS has shown an abundance of both focus and perseverance (and so far has found sufficient funding) since the inception of its MDMA research program, recently culminating in the completion of its first Phase 2 pilot study in 2010 under the supervision of Dr. Michael Mithoefer. Now, in addition to a protocol training future therapists to use this powerful new tool, MAPS is conducting a series of Phase 2 studies to treat PTSD generally and in veterans, which are expected to be completed the second quarter of 2014. These studies are taking place in countries as diverse as Canada, Israel, Switzerland, Australia, and the U.S. MAPS' MDMA research program could, with funding and a bit of luck, proceed to Phase 3 in the fourth quarter of 2015, with completion of Phase 3 and approval of MDMA as a prescription medicine estimated around 2020. At that point, the field of psychiatry will have gained access to a therapeutic tool with nearly unmatched potential for the first time since it was criminalized in 1985.

The results of MAPS' Phase 2 pilot study and its long-term follow-up (LTFU) were remarkable. PTSD tends to be characterized by a combination of three types of symptoms: fear and hyper-arousal, intrusive re-experiencing of traumatic experiences, and numbing and withdrawal. PTSD is also incredibly difficult to treat and has a high rate of relapse, comorbidity, drug/alcohol abuse, and suicide. Furthermore, there are currently only two FDA-approved medications for the treatment of PTSD and only three treatment procedures recommended by

the American Psychological Association. Altogether, they leave 25-50% of PTSD patients (a group making up between 6 and 10% of the U.S. population, and between 15 and 35% of U.S. veterans) feeling that treatment is ineffective.

When the results of the Phase 2 pilot study (which involved 20 patients with an average PTSD duration of over 19 years) indicated that 83.3% of the experimental group subjects showed a clinical response (defined as a 30% or greater reduction in score on the CAPS test, which is widely used to assess the severity of PTSD symptoms) compared to only 25% in the group that received only therapy and active placebo, there was significant reason to be optimistic *(Mithoefer et al 2010)*. These highly positive results indicate the discovery of—potentially—the most powerful therapeutic model ever found for the treatment of PTSD.

The low availability of effective treatment bears most of the responsibility for the poor prognosis associated with PTSD. Yet even when conventional therapy succeeds in reducing PTSD symptoms, the fact that relapse tends to occur within 18 months must be considered an important—if not equal—part of what makes it such a debilitating disease. The LTFU showed that 14 of the 16 patients who completed the treatment had no statistical differences between their CAPS scores at the end of their second MDMA-assisted psychotherapy session (which were consistent with complete remission of PTSD symptoms) and at the LTFU taken an average of 3.8 years later *(Mithoefer et al 2012)*. Thus, there is strong reason to believe that MDMA-assisted psychotherapy helps more successfully with PTSD treatment—both through initial reduction of symptoms and through maintenance of that reduction over the long term—than any other form of treatment.

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What, specifically, is it about this new model that makes it so seemingly effective in countering these issues? Many elements need to be discussed in order to answer this question (and many will be in what follows), but it is probably best to start with another question: What is so different about MDMA-assisted psychotherapy compared to others used for PTSD treatment?

The answer, again, is "a lot," so perhaps it is even better to begin with what many consider to be the most objective (or at least quantifiable) realm of psychological science: biopsychology (neurology, psychopharmacology, etc.). The symptoms of PTSD are, according to the neurocircuitry model, caused by a deficit in the extinction of conditioned fear responses related to increased activity in the amygdala (the part of the brain responsible for fear, aggression, and most autonomic response) and decreased activity in both the hippocampus and the medial pre-frontal cortex (an area associated with decision making and emotional control/processing). One of the many problems with the medications currently being used to treat PTSD—such as anti-depressant SSRIs—is that very little is known about the mechanism of action of these drugs when used in attempts to confront these issues.

On the other hand, a great deal is known about the pharmacological action of MDMA as it relates to the same problems. Positron emission tomography (PET) scans have shown that MDMA increases blood flow to the medial prefrontal cortex while reducing flow to the amygdala (essentially reversing the neurological effects of PTSD). In other words, MDMA actually seems to create the ideal neurological conditions for a PTSD sufferer to benefit from therapy.

Little is known about MDMA's unique ability to simultaneously speed up the release of serotonin and slow the reuptake of other neurotransmitters into the brain cells where they have their effects, yet this may be one of the qualities that make it so effective as a treatment adjunct. Serotonin contributes to emotional regulation, feelings of well-being and happiness, mood, and some cognitive functions (among other things). As such, the boosting of serotonin levels in the brain may be a positive precursor to the therapeutic state.

MDMA's action on serotonin also causes the body to release increased amounts of the naturally occurring hormones prolactin and oxytocin. Prolactin may play a role in the sense of relaxation that MDMA produces, yet it is oxytocin (commonly referred to as "the cuddle hormone" for its role in pair-bonding) that probably has the largest hand in MDMA's pharmacological benefits for therapy. As a neurochemical that has been shown to increase affiliation, trust, gregariousness, sociability, and accuracy of emotional perception (as well as being partly responsible for the decreased amygdalar activity associated with MDMA ingestion), oxytocin is hypothesized to play a role in MDMA's ability to attenuate the fear response and decrease defensiveness without blocking access to memories or preventing a deep and genuine experience of emotion *(Metzner et al 1988)*.

> *Participants are able to experience and express fear, anger, and grief with less likelihood of feeling overwhelmed by these emotions. MDMA seems to engender an awareness that such feelings arise as an important part of the therapeutic process. In addition, feelings of empathy, love, and deep appreciation often emerge, along with a clearer perspective of the trauma as a past event and with a heightened awareness of the support and safety that exist in the present (Treatment Manual).*

As a result of these qualities, such statements from PTSD patients who have received MDMA-assisted psychotherapy as

"Maybe one of the things the drug does is let your mind relax and get out of the way, because the mind is so protective of the injury," and, "It's helped me in so many ways; it feels like it's gradually rewiring my brain," can be seen played out in neurochemistry.

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If MDMA does all of this on its own, then why bother with psychotherapy? MDMA may be a powerful catalyst, but just as with most pharmacological interventions it is difficult to produce sustained results and without also using therapy to resolve the underlying issues. As one subject in a MAPS study noted: "As interesting as the [MDMA] sessions are, it's more interesting what happens after the sessions when you're making connections." In other words, "MDMA is not in itself the therapy but is rather a powerful tool for both clinician and participant" *(Treatment Manual)*. While MDMA helps create the neurochemical conditions for healing to occur, those conditions are less likely to take root and grow without the care of a therapeutic system.

MDMA is a powerful pharmacological tool requiring the use of a therapeutic model that is distinct from most other methods used in conventional psychotherapy. For example, the use of MDMA requires that a great deal of attention be given to set and setting. The idea that the set (mental and informational preparation, as well as the creation of a safe psychological space) and the setting (the creation of a safe, supportive, and aesthetically pleasing physical environment) are of paramount importance to the therapeutic experience is one of the characteristic elements of any therapy involving the use of psychedelic compounds. This is because these tools produce a state of significantly heightened physical and psychological vulnerability and seem to make important subconscious material more accessible, which can lead to profound—and often intense—emotional and physical effects.

In addition to set and setting, there are numerous aspects of psychotherapy that, without the implementation of careful procedures, could increase the risk of the treatment being problematic or ineffective. The use of MDMA magnifies the importance of these aspects. Key examples of these aspects include (1) the subject's relationship with the psychotherapist (whose sensitivity, talent, and background are all integral to how the patient responds to therapy); (2) the use of somatic procedures (breathwork, focused bodywork, sensory stimulation via music, etc.); and (3) the development of the therapeutic alliance (a relationship between therapist and subject that makes openness, trust, and progress more possible) *(Treatment Manual)*.

MAPS' *Treatment Manual for MDMA-Assisted Psychotherapy for the Treatment of PTSD* outlines these important issues in novel and effective ways. In fact, this manual—which is being independently rated for effectiveness as both an experimental and a training tool—lays out well-developed guidelines for how a two-person male-female therapy team can most safely and productively approach each of the above aspects of MDMA-assisted psychotherapy. With regards to mental preparation, it suggests thorough discussion of session parameters, the making of specific therapist-subject agreements (subject will refrain from self-harm, therapist will provide for all physical needs immediately, etc.), the addressing of specific fears prior to experimental sessions, and general therapist-subject collaboration in creating a safe space for therapy. The manual also makes suggestions about the nature of the setting, wherein the provision of pre-selected musical programs, basic needs reassurance (availability of a kitchen, sleeping arrangements, etc.) eye-shades, privacy, quiet, comfort, and general aesthetic agreeableness are all carefully considered.

Some of the manual's suggestions concern what many consider to be a controversial issue in psychology: the acceptability and utility of physical contact between therapist and subject. Some practitioners worry that such contact is counter-productive to therapy, but with the ability of MDMA to bring to the surface strong emotional forces that can be experienced in the form of physiological tension, physical contact can be an important element of MDMA-assisted psychotherapy. Of course, this contact must always and absolutely be appropriate, beneficial, and driven by the needs of the subject. So, the use of focused bodywork (generally, providing resistance for the subject to push against) and nurturing touch (hand-holding, hugging, etc.) can be an important catalyst for resolving psychological issues caused by a condition like PTSD. Interestingly, subjects' need for physical contact is rare in actual experimental MDMA sessions. More likely are cases in which such physical contact is used to help people work through possible residual effects in integrative sessions following the MDMA session, rather than during the MDMA session itself.

"It's helped me in so many ways; it feels like it's gradually rewiring my brain"—study participant

Along with the possible benefits, there are also risks and challenges involving the use of physical contact by the therapist. Touch may be distracting or misinterpreted by the subject, be motivated by the therapist's conscious or unconscious sexual desires or desire to fulfill the role of therapist, or may even create a feeling in the subject that he/she cannot be healed without the aid of outside intervention. Any of these issues could have deleterious effects on the subject and the therapeutic process. As such, it is imperative to have clear protocols in place in the MDMA-assisted psychotherapy model to guide the acceptable use of bodywork and touch by the therapist. MAPS' *Treatment Manual* provides such a protocol in the form of an 8-step process (designed by Stanislav Grof) specifically for that purpose, as well as suggestions for how to follow the process:

> *The above steps should be offered to participants as possible ways of working with their symptoms if they so*

> *choose. Participants should never be pressured to do focused bodywork or to be touched in any way. Participants should be encouraged to ask for whatever they feel they need, even if it is quite different from what they or the therapists would have predicted (Treatment Manual).*

If the therapist follows these directives, body work or touch can have the greatest possibility of assisting with the therapeutic process.

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The therapeutic alliance (the partnership established between therapist and patient) is one of the most important and difficult-to-measure issues in all of clinical psychology. Almost all therapeutic professionals agree that a safe, trusting, and open therapist-patient relationship is integral to any effective therapy, but problems tend to arise when attempts are made to move toward standardizing this process. This is likely due to the wide variety of therapeutic approaches, and even wider variety of therapist and patient personalities. MDMA-assisted psychotherapy, however, may represent a major step forward on the path to understanding the therapeutic alliance.

MDMA seems (as previously mentioned) to create optimal neurological conditions for the strengthening of the therapeutic alliance, which means that MDMA-assisted psychotherapy may help the world of clinical psychology better quantify that alliance. As a pharmaceutical therapeutic alliance catalyst, MDMA may be able to augment this imperative relationship with consistency.

The MDMA, however, does not work alone—MAPS' treatment approach is specifically designed to maximize the possibility for creating an effective therapeutic alliance. MAPS' MDMA-assisted psychotherapy protocol includes a substantial amount of work with non-drug psychotherapy (in fact, non-drug sessions constitute the vast majority of the treatment protocol)—and this therapy, without the drug, is essential for establishing the alliance. This involves discussing questions and fears, creating plans and agreements, and establishing trust and safety—all of which may improve the effectiveness of the MDMA-assisted sessions.

Letting the patient's internal experience guide the session is an additional aspect of MDMA-assisted psychotherapy that may contribute strongly to the positive outcomes that MAPS has seen in its early studies. Most psychotherapeutic treatments for PTSD direct the patient's attention to the troubling memories and emotions at the heart of their condition; however, this can create problems for the therapeutic alliance (and therapy in general) when it imposes a structure that does not match the patient's own cognitive processes, or when it demands that the patient go places that he/she may not be psychologically prepared to confront. The MDMA-assisted psychotherapy model attempts to solve this problem by repositioning the therapist as someone who is there to support the experiences of the subject as they arise, to provide guidance and comfort when needed, and to ensure a safe and trusting environment in which the experiences can go where they must. Therapists often find that the subject's own consciousness knows best what to reveal and when. In this way, MDMA-assisted psychotherapy aims to create a powerful support system that makes it more possible for the inherent healing process to have a significant and lasting effect.

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This carefully designed form of psychotherapy combined with the powerful effects of MDMA is one of psychiatry's greatest opportunities to confront PTSD and to better quantify the therapeutic alliance. It gives subjects, often for the first time, an opportunity to see their situation in a new light. As one MAPS subject reflected, "I was stuck in an unhappy place…this study changed all that and gave me the possibility of a different outcome." Another stated that "when I let the waves of fear and anxiety come up, it feels like the medicine is going in and bringing them up, and then they dissipate." Another: "It's like PTSD changed my brain, and MDMA changed it back."

It is an exciting time to be part of the journey that MAPS is undertaking to transform psychology and psychiatry. This is true not only because of the historic nature of MAPS' work, but also because of the vast potential that MDMA-assisted psychotherapy has to reduce suffering in instances where conventional therapies have been ineffective. That is the real mission of those working to make MDMA-assisted psychotherapy a legal treatment: the alleviation of suffering and the provision of means for psychological growth. With continued support, MAPS will continue to build momentum as it helps the field of psychology take massive steps toward these ends.

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