Potential Psychiatric Uses for MDMA

BB Yazar-Klosinski[1] and MC Mithoefer[1]

Phase II trials of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy have demonstrated initial safety and efficacy for treatment of posttraumatic stress disorder (PTSD), with potential for expansion to depression and anxiety disorders. In these trials, single doses of MDMA are administered in a model of medication-assisted psychotherapy, differing from trials involving daily drug administration without psychotherapy. This model presents an opportunity to utilize accelerated regulatory pathways, such as the US Food and Drug Administration (FDA) Breakthrough Therapy Designation, to most effectively and expeditiously test such novel approaches.

BACKGROUND

MDMA-assisted psychotherapy employs single doses, administered under continuous medical supervision on two to three occasions a month apart. Drug administration is preceded by preparatory sessions and followed by psychotherapy sessions supporting integration of therapeutic changes into daily life (**Figure 1**). MDMA was placed in Schedule 1 by the Drug Enforcement Administration (DEA) in 1985 on the basis of widespread nonmedical use and concerns of abuse potential, despite a Schedule 3 recommendation by an administrative law judge. The results indicate promising therapeutic applications, but MDMA remains in Schedule 1, defined as having no accepted medical use, high abuse potential, and lack of accepted safety. Data from phase II randomized controlled trials (RCTs) exploring MDMA-assisted psychotherapy were submitted to the FDA as initial indications of safety and efficacy. These studies build on published case reports on clinical use of MDMA prior to DEA scheduling.[1] Completion of successful phase III trials is the remaining requirement for FDA approval of MDMA as a therapeutic agent.

SET AND SETTING

An array of chronic psychiatric disorders share a common core of intractable symptoms that respond favorably to MDMA-assisted psychotherapy, which has been studied in clinical trials treating PTSD, anxiety associated with life-threatening illness, and social anxiety in autistic adults.[2] These studies demonstrate the success of careful approaches to therapeutic set and setting designed to minimize adverse events and maximize benefits with minimal targeted exposure to drug. All recent MDMA-assisted psychotherapy registration studies are RCTs, meeting rigorous standards for drug development regulated by the FDA and overseen by Institutional Review Boards (IRBs). Furthermore, due to the Schedule 1 status of MDMA, compliance with DEA and state-level controlled substance review committees is required, placing these studies in the most regulated area of drug development, and introducing a disincentive to potential researchers. Researchers who are willing to take on the challenge of managing compliance with this complex oversight often only do so because of the potential to relieve suffering that has not responded to existing established treatments, and the hope of providing the field of psychiatry with methods of effectively combining psychopharmacology with psychotherapy in a patient-centered approach that respects and fosters the innate healing capacity of the individual.

MECHANISM AND TARGET INDICATIONS

MDMA produces complex pharmacological effects that may be further influenced by psychotherapy. MDMA potentiates the release of monoamines through reversal of transporter proteins and reuptake inhibition, with the greatest effects on serotonin and norepinephrine.[3] Effects on dopamine release, secondary to serotonin release, are dose- and species-dependent, with less dopamine involvement in humans.[3] Downstream targets include α2-adrenergic and serotonin receptors. Serotonergic signaling triggers a cascade of oxytocin, vasopressin, prolactin, and corticosteroids.[2–4] MDMA also modulates glucocorticoids through the hypothalamic–pituitary–adrenal (HPA) axis,[4] which may have important implications for PTSD treatment, as glucocorticoid hypersensitivity and HPA axis dysregulation are hallmarks of PTSD. MDMA decreases amygdalar and hippocampal activity, and increases prefrontal cortex activity, correlating with subjective effects.[2] In a mouse PTSD model, MDMA administered before training facilitated fear extinction learning, dependent on brain derived neurotrophic factor (BDNF) expression in the amygdala.[1] Recovery from PTSD and extinction learning is dependent on BDNF, which regulates memory reconsolidation after recall in the amygdala–hippocampus circuit.[1] These

[1]Multidisciplinary Association for Psychedelic Studies, Santa Cruz, California, USA. Correspondence: BB Yazar-Klosinski (Berra@maps.org)

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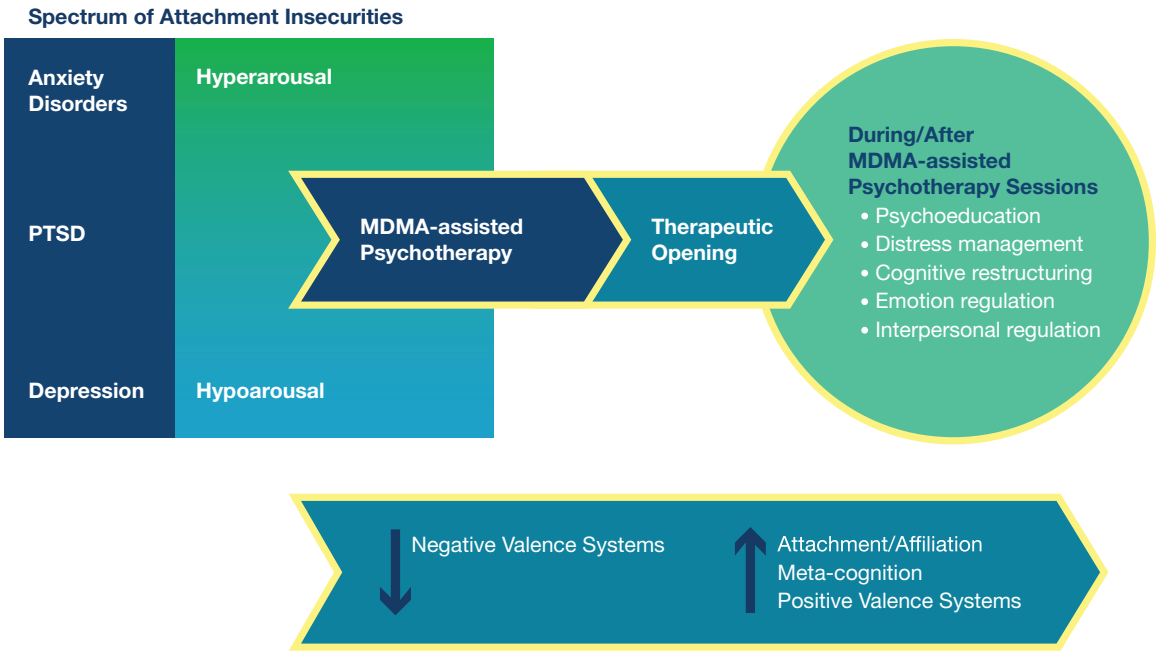

Figure 1 MDMA-assisted psychotherapy catalyzes therapeutic opening, which continues through integration.

neurobiological effects are not specific to PTSD, as reduced emotional impact of fear memories was corroborated in healthy volunteer imaging studies,[2] and BDNF elevations were also observed in recreational MDMA users. MDMA promotes neuroplasticity through BDNF and regulates the HPA axis, improving functional outcomes through effects on learning and memory, which are reinforced in the context of psychotherapy.

In MDMA studies, participants report improved self-knowledge, sleep regulation, accuracy in perceiving mental states of others, coping strategies, emotion regulation, and cognitive insights.[3] Objective measures support attenuated impact of social rejection and reduced amygdalar response to angry or fearful faces.[3] These changes provide insight into potential indications for MDMA-assisted psychotherapy, which may enhance secure attachment and engagement of cognitive and positive valence systems, with corresponding reduction in negative valence. MDMA-assisted psychotherapy could be useful in the treatment of disorders associated with attachment insecurities, including PTSD, depression, anxiety disorders, obsessive-compulsive disorder, suicidality, substance use disorders, and eating disorders.[5] In phase II PTSD studies, 2 months after two to three active-dose MDMA treatments, 55% of chronic PTSD subjects no longer met the PTSD Diagnostic Criteria ($N = 100$) and 66.2% were in remission at least 12 months postdrug ($N = 65$). Clinical effects are rapid-onset but not rapid offset, with durable treatment outcomes reported long after MDMA had been eliminated from the body.

Outcomes of MDMA use are context-dependent, as seen by elevations in BDNF in both recreational settings and fear extinction studies, as well as phase II trial results. While it is true that MDMA has moderate abuse potential and has seen widespread use in nonmedical settings, studies have shown this is self-limiting and typically ceases when life circumstances change, suggesting self-medication or intentional self-exploration as probable motivations for use. Neuroplasticity triggered by BDNF supports the beneficial effects of MDMA in a treatment context, similar to other medication-assisted therapies for treatment of substance use disorders. Consistent with this concept, an upcoming study of MDMA-assisted psychotherapy is planned for treatment of alcoholism. These observations, as well as current phase II results, support utilizing MDMA as a probe of social behavior and the psychopathology of fear, depression, stress, and anxiety.

REGULATORY PATHWAY AND MEDICAL NEED

Following promising results from multiple FDA and DEA-approved phase II studies of MDMA-assisted psychotherapy for PTSD, permission has been requested for a phase III program. These trials utilize a gold-standard objective primary outcome measure and incorporate secondary exploratory measures to better assess benefit in complex clinical cases. Several measures of depression, anxiety, and PTSD are recognized by the FDA, and development of improved objective functional outcome measures is ongoing. Recently, the European Medicines Agency (EMA) revised its opinion on RCTs, advising active-controlled trials rather than placebo-controlled, justifying approvals based on added value rather than absolute superiority. Provided trials are randomized and outcomes are assessed by an objective centralized group, and bias can be effectively minimized. In line with FDA recommendations, proposed phase III success criteria for MDMA-assisted psychotherapy include statistical superiority over psychotherapy with placebo in reducing PTSD symptoms as assessed objectively by a blinded centralized independent rater group at 2-month follow-up.

Unlike most FDA-approved drugs that require a chronic daily dosing regimen for efficacy, with maintenance treatment required to prevent relapse, MDMA is administered as two to three single-dose treatments, frequently with a strong response after the first session. In contrast to maintenance dosing, which can place significant burden on metabolic pathways and increase potential adverse effects, single-dose treatments have a more favorable risk/benefit profile. Therefore, single-dose toxicity studies with assessments for delayed toxicity and reversibility after washout appear more appropriate than repeated-dose toxicology studies. Likewise, pre-postnatal development studies with daily dosing covering development up to sexual maturity, currently required in all countries to support marketing approval, may be beyond the scope of what should be required to demonstrate safety of single-dose treatments. This is especially true if highly effective methods of birth control and a negative pregnancy test just prior to each treatment continue to be required postapproval.

In cases of unmet medical need, the FDA has provided special programs with accelerated pathways for approval that may apply to MDMA, as effect size estimates for PTSD are large, relapse rates are low, and administration under strictly controlled conditions improves compliance over available treatments. In addition, risk evaluation mitigation strategies (REMS) will allow sponsor oversight of certification of treatment providers, to assure that they have the necessary experience and qualifications to administer MDMA-assisted psychotherapy. Appropriate mechanisms to prevent abuse and diversion will likely preclude take-home prescriptions, and may involve restricting use to licensed clinics. Based on coadministration studies with psychiatric medications typically prescribed, MDMA-assisted psychotherapy is unlikely to cause safety concerns within an integrated medication management model, but washout of other medications may be needed for optimal results. The outcome of negotiations with the FDA regarding phase III clinical trials and subsequent marketing remain to be determined.

As MDMA is not patentable and will be difficult to commercialize with single-dose treatments, the most suitable avenue is nonprofit drug development. The nonprofit organization funding and sponsoring clinical trials of MDMA-assisted psychotherapy has made substantial progress using rigorous scientific approaches complying with cautious regulatory requirements. This progress demonstrates that it is possible to study Schedule 1 drugs under the current regulatory structure, but that progress in this area has been undesirably slow. Meticulously establishing safety and efficacy is crucial to evaluating the risk/benefit profile of single-dose treatments as an adjunct to psychotherapy, which may offer improved safety and compliance over available treatments. Fostering open science principles, e.g., prioritizing publishing in peer-reviewed journals and data transparency, will ultimately prove beneficial in shaping and expediting the regulatory environment that applies to MDMA-assisted psychotherapy and similar models with other compounds. Implementation of novel MDMA-assisted therapies could hold the promise of lasting improvements in social and psychological function for patients, and of deeper understanding of psychiatric disturbances across multiple disorders.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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