A Review of MDMA-Assisted Therapy for Posttraumatic Stress Disorder

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Posttraumatic stress disorder (PTSD) is a common chronic and disabling psychiatric disorder that may develop after exposure to a traumatic life event. There are existing evidence-based psychotherapies and pharmacotherapies for PTSD; however, these treatments have significant limitations. 3,4-methylenedioxymethamphetamine (MDMA) was granted "breakthrough therapy" status by the U.S. Food and Drug Administration (FDA) in 2017 for the treatment of PTSD in conjunction with psychotherapy after preliminary Phase II results. This treatment is currently being investigated in Phase III trials with anticipated FDA approval of MDMA-assisted psychotherapy for PTSD in late 2023. This article reviews the evidence base for MDMA-assisted psychotherapy for PTSD, pharmacology and the proposed causal mechanisms of MDMA, risks and limitations of the current evidence, and challenges and future directions for the field.

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Posttraumatic stress disorder (PTSD) is a common and often disabling condition with prevalence in the tens of millions of people in the United States alone (1). It is classified as a "trauma- and stressor-related disorder" in the *DSM-5*, with diagnostic criteria across four symptom clusters: reexperiencing (e.g., recurrent intrusive memories, traumatic nightmares, or flashbacks), avoidance (e.g., avoiding trauma-related thoughts and feelings or avoiding objects, people, and places associated with the traumatic event), negative alterations in cognition or mood (e.g., distorted beliefs about oneself or the world, persistent guilt or shame, emotional numbing, feelings of alienation, or inability to recall key details of the traumatic event), and alterations in arousal and reactivity (e.g., irritability, hypervigilance, reckless behavior, sleep disturbance, or concentration difficulties) (2). To qualify for a diagnosis of PTSD, symptoms must be present for longer than 1 month; result in significant distress or functional impairment; and not be caused by medications, substance use, or a separate medical condition. These symptom clusters were revised from three clusters in the *DSM-IV* to four clusters in the *DSM-5* through splitting avoidance and numbing into distinct clusters of avoidance and negative alteration in mood and cognition. Given the heterogeneity in the application of PTSD diagnoses, familiarity with *DSM* criteria is important in valid diagnosis as well as in tracking treatment response.

PTSD has been associated with a wide range of traumatic events, with variable risk of PTSD symptoms depending on trauma type (3). PTSD develops after exposure to a potentially traumatic event that involves exposure to actual or threatened death, serious injury, or sexual violence. Exposure is defined as either directly experiencing or witnessing the traumatic event or learning that the trauma has occurred to a close family member or friend (2).

Although most people experience traumatic events that result in a transient stress response throughout the course of a lifetime, the majority do not go on to develop PTSD. Approximately 10%–20% of individuals who have been exposed to a traumatic event go on to develop PTSD symptoms that persist with associated impairment (4). The lifetime prevalence of PTSD is estimated at 8.3% (5). In military service members and veterans, the reported incidence rate of PTSD ranges from 5.4 to 16.8 (6, 7).

Risk factors for the development of PTSD include genetic factors, preexisting neuroendocrine and inflammatory pathway alterations, and psychological factors. The heritability of PTSD is estimated to be 30% (8). The most studied genetic risk factors have involved polymorphisms in the hypothalamic-pituitary-adrenal (HPA) axis and catecholamine pathways such as COMT and FKBP5; however, a more recent genomewide association study identified other genes, including PARK2, that were implicated in dopamine regulation (9). There have been epigenetic studies investigating how stress exposure can affect offspring gene expression, conferring risk of PTSD development (10–12). Traumatic exposures activate the HPA axis and stress-response pathways, resulting in downstream inflammatory changes and immune suppression. There is some evidence that preexisting alterations to inflammatory mediators may confer risk for the development of PTSD after exposure to a traumatic event (13). A dose-response relationship has been identified between exposure to traumatic events and subsequent PTSD diagnosis, with higher rates of diagnosis associated with increased number of traumatic exposures (5).

Specifics related to the kind of trauma also appear to confer variable risk of subsequently developing PTSD, with higher rates associated with military combat and sexual assault (14). Several other factors have also been linked to higher risk of developing PTSD after exposure to a traumatic event, including a history of such exposure before the index event, economic and educational disadvantage, and female gender (15, 16).

There are several evidence-based treatments for PTSD—both psychotherapeutic and pharmacologic—that we briefly review here on the basis of the current guidelines from the American Psychological Association (17), published in 2017, and from the Veterans Health Administration and Department of Defense (VA–DoD). Psychological interventions recommended by these organizations are generally divided along "trauma-focused" interventions and "nontrauma-focused" interventions (18). Trauma-focused interventions include prolonged exposure (PE) therapy and cognitive processing therapy. Nontrauma-focused interventions include relaxation exercises, stress-inoculation training, and interpersonal therapy. A large body of evidence supports trauma-focused exposure therapies, particularly PE, including several meta-analyses that support the superiority of PE over nontrauma-focused therapies (19–22). Rates of successful treatment with PE—defined as loss of PTSD diagnosis—is in the range of 41%–95% (23). However, trauma-focused therapies suffer from high rates of treatment discontinuation and dropout: Rates of dropout for exposure-based therapies are approximately 36% (24). Exposure to a traumatic event and subsequent PTSD can problematize the ability to form the stable, trusting interpersonal relationships required for a sustained working alliance between patient and therapist that is thought to be critical for therapeutic change (25–27). Trauma-focused therapies also often involve aversive reexperiencing related to the traumatic event that can overwhelm a patient's capacities. As such, remission of symptoms with these therapies accounting for rates of dropout is only around 44% (28). Even after a course of cognitive processing or PE therapy, up to two-thirds of patients will retain their diagnosis after treatment (29) Furthermore, there is a limited evidence base, to date, to suggest that current evidence-based trauma-specific psychotherapies are superior to other non–evidence-based interventions (30).

Evidence-based pharmacological treatments for PTSD center around selective serotonin reuptake inhibitors (SSRIs). Of note, the VA–DoD and National Institute for Health and Care Excellence treatment guidelines have both unequivocally designated exposure-based psychotherapy as the first-line treatment for PTSD, meaning that psychopharmacological treatments—which have smaller effect sizes—are recommended as second-line (31, 32). Sertraline, paroxetine, fluvoxamine, and citalopram have received U.S. Food and Drug Administration (FDA) support for the treatment of PTSD symptoms (33–39). Treatment response to these agents is estimated at 15%–30%, with small effect sizes (40). There is also a tendency for patients to relapse on discontinuation of the medication (38, 39). There are several other agents used in the treatment of PTSD symptoms, including prazosin, a noradrenaline alpha-blocker agent that has shown efficacy in PTSD-related sleep disruption and nightmares. Although early studies that investigated prazosin (41, 42) were encouraging, subsequent randomized controlled trials (RCTs) have failed to show a significant effect (43, 44). Polypharmacy is common among patients with PTSD, involving frequent use of second-generation antipsychotics (despite minimal evidence supporting efficacy) as well as benzodiazepines, which demonstrably worsen outcomes related to PTSD (45, 46).

In sum, the evidence base for current standard-of-care pharmacological and psychotherapeutic interventions for PTSD suggests significant limitations. As such, there is a significant need for new strategies for treating this condition. MDMA-assisted therapy for PTSD has emerged as a promising intervention that combines a pharmacological approach with an embedded psychotherapeutic protocol.

3,4-methylenedioxymethamphetamine (MDMA) is a ring-substituted amphetamine with structural similarities to mescaline (47, 48). Although it can produce consciousness-altering effects similar to those of classic psychedelics (understood as agonists at the serotonin 5-HT_{2A}-receptor) MDMA is often referred to as an "entactogen," given its prosocial effects and the relative absence of perceptual alterations compared with classic psychedelics (49). MDMA was first synthesized by Merck in 1912 as an intermediate substance in the synthesis of a hemostatic drug (50). It was largely shelved until the 1950s and emerged briefly as a chemical of interest during the mind-control experiments of the CIA project MK-ULTRA. There was limited recreational use of MDMA during the 1960s; however, after the rescheduling of LSD and psilocybin in the late 1960s, there was a renewed interest in the therapeutic use of MDMA. MDMA was used frequently through the 1970s until 1985 (when MDMA was rescheduled by the Drug Enforcement Administration to Schedule I) in conjunction with psychotherapy, in particular with couples therapy, given its empathogenic qualities (51). The first Phase I trial with MDMA was completed in 1995 by Charles Grob and involved the administration of two doses of MDMA and one dose of placebo to six normal volunteers to track physiological and safety variables (52). The first controlled study of MDMA-assisted psychotherapy for PTSD was published in 2010 (53). This study included 20 patients with treatment-refractory PTSD symptoms and demonstrated an 80% remission rate sustained at 3 years after two or three sessions. The Multidisciplinary Association for Psychedelic Studies (MAPS) has supported research into MDMA-assisted psychotherapy, including six FDA Phase II trials and ongoing FDA Phase III trials (with one published study to date, which we discuss later). In response to promising results from initial trials, on August 15, 2017, the FDA designated MDMA-assisted psychotherapy as a "breakthrough therapy

designation" for the treatment of PTSD on the basis of criteria for treatment of a life-threatening illness and greater safety and initial efficacy than that seen with existing approved medications (i.e., sertraline, paroxetine). This intervention involves the use of a medication in conjunction with a psychotherapeutic process, which is a novel model that challenges the standard model of FDA approval (which historically has only applied to medications alone) as well as standard models of mental health care delivery and reimbursement.

Therapeutic mechanisms of MDMA can be explored at several different levels of explanation. From a neurobiological standpoint, MDMA interacts with several neurotransmitter systems but predominantly exerts its pharmacological action by means of the monoaminergic system, with the strongest affinity at the serotonin transporter, followed by norepinephrine and dopamine transporters (54). MDMA also binds directly at the alpha-2 adrenergic, serotonin, H1 histamine, beta-1 adrenergic, and D_1 and D_2 dopaminergic receptors (55). Acute effects of MDMA involve elevation in extracellular serotonin, both through increased release into the synapse through reuptake inhibition. There are concomitant increases in extracellular dopamine and norepinephrine. MDMA is absorbed by the gastrointestinal tract, has an onset of action typically at approximately 30–45 minutes, and reaches peak brain levels at 60–180 minutes. It is metabolized primarily by CYP450 2D6 and 2C19 pathways with an elimination half-life of 8–9 hours (56, 57).

MDMA also causes an increase in oxytocin release (58). This neuropeptide has been implicated in social bonding, trust, and prosocial behaviors (59). MDMA increases levels of oxytocin through action on the serotonin transporter and 5-HT_4 receptors on oxytocin neurons (60, 61), which has been shown in animal studies to mediate the prosocial effects of MDMA (62). Changes in oxytocin signaling and prosocial feelings have also been correlated in healthy volunteer humans (63), and there is evidence that intranasal oxytocin administration can normalize deficits in social reward processing in terms of neural sensitivity to social reward in patients with PTSD (64). However, at least one study in humans failed to show a significant correlation between plasma levels of oxytocin and the prosocial effects of MDMA (65), although the authors noted that plasma concentration may not be representative of the central availability of oxytocin. The relationship between the prosocial and empathogenic effects of MDMA and oxytocin is incompletely characterized with demonstrated divergent effects when administered individually in subjects (58): As such, it appears that the effects of MDMA on social reward processing are not likely to be due solely to alterations in oxytocin.

From a psychological standpoint, one rationale behind MDMA-assisted psychotherapy is the idea that MDMA acts as a catalyst of sorts for psychotherapy by reducing the fear response, enhancing interpersonal trust and openness, and allowing for the exploration of content and past traumatic experiences that are otherwise difficult to engage with (66) and that have historically problematized adherence to exposure-based therapies alone. MDMA has been shown to increase emotional empathy (67), prosocial behaviors (68), and interpersonal trust (60, 69). There is preliminary evidence that the direct effects of MDMA on the personality trait of openness moderate the effects of MDMA-assisted psychotherapy on the reduction of PTSD symptomatology (70). These changes are hypothesized to facilitate therapeutic engagement, rapport building, and exploration of difficult psychological terrain. There is evidence to suggest that enhanced sociability with MDMA may be related to diminished response to threatening stimuli through attenuation of the amygdala response as well as enhanced responses to social reward signals related to enhanced ventral striatum response (71). The ventral striatum plays a central role in reward processing, and enhanced ventral striatum response is associated with social approach behavior (72). It has been hypothesized that MDMA may reduce PTSD symptoms through the two distinct processes of memory reconsolidation and fear extinction (73). Other research on memory reconsolidation during psychotherapy suggests that feelings of safety and trust are critical elements to reconsolidating emotional memories in the treatment of trauma (74)—MDMA may facilitate this process.

A more recent—albeit preliminary—explanatory model for the therapeutic effects of MDMA (as well as of classic psychedelics) examines the effects of MDMA on neuroplasticity and the opening of a "critical period," or "critical window," for new learning. Although this model is still early in development and based on animal models, it provides a bridge between psychological and neurobiological levels of explanation and supports the importance of embedding MDMA administration within a thoughtful psychotherapeutic framework for therapeutic effect. A critical period is a period of heightened neuroplasticity when the brain is increasingly receptive to environmental stimuli, flexible in laying down new neurocircuitry pathways, and more open to engaging with learning. These periods occur naturally developmentally, and they can explain the often significant longitudinal effects that early life trauma can have over the course of a lifetime. It is hypothesized that, in disease states, the closure or constraints on synaptic plasticity afforded by critical periods limit adaptation and therapeutic change, even in the context of optimizing environmental conditions (1). Although there are many different forms of critical periods (i.e., critical periods for language development), the social reward learning critical period informs durable changes in social cognition, emotion regulation, and attachment—all domains heavily implicated in the pathogenesis and symptomatology of PTSD. Animal model studies have demonstrated that MDMA opens a critical period for social reward learning that appears to be mediated by changes in oxytocin-dependent synaptic plasticity in the nucleus accumbens (75). It is interesting that this effect was only present for mice in social contexts (76). MDMA has been shown to increase neuroplasticity by stimulating the expression of immediate-early gene transcription factor c-Fos, which is a marker for

neuroplastic populations in the brain. Additionally, there is evidence that MDMA results in an increase of brain-derived neurotrophic factor (BDNF) in areas related to fear extinction and that this increase is dependent on 5-HT_{2A} receptors (77).

MDMA downregulates amygdala activity (78) and has direct effects on fear extinction pathways (79). This is, in part, due to effects on neurotrophic factors implicated in neuroplasticity. Effects of MDMA administration on the enhancement of fear extinction pathways appear to be dependent on increases in BDNF expression in the amygdala (80). MDMA has also been shown to raise BDNF levels in cortical regions of rodents, which is reflected in increased spine density and heightened neurogenesis of cortical neurons. Genetic polymorphisms associated with reduced BDNF expression have been shown to predict reduced response to exposure-based therapies for PTSD (81).

MDMA-assisted therapy for PTSD—as instantiated in recent Phase II and Phase III trials—involves a robust psychotherapeutic protocol that involves approximately 40 hours of therapist time (with two therapists present; typically, a male-female dyad) for the complete course of treatment. This has involved a manualized protocol that is supportive in nature, is nondirective, and uses the following core principles: safety, support, inner healing intelligence, inner-directed process, beginner's mind, trusting the process, somatic manifestation, therapeutic alliance, and trust (73). The therapeutic approach emphasizes the interaction of the medication and the therapeutic setting and relationship with the therapy team. Although unique insofar as involving a catalyzed form of psychotherapy, many aspects of the therapeutic approach are similar to those of other models of psychotherapy for PTSD and may include elements of exposure therapy, stress-inoculation training, anxiety management, and cognitive restructuring. However, the emphasis of the therapeutic approach is nondirective, and these therapeutic elements are not incorporated in an explicit fashion. MAPS has developed a five-part therapy training program that comprises in-person trainings, role-plays, video-recorded MDMA sessions, e-learning modules, and readings.

The therapy protocol involves three preparatory sessions before any MDMA sessions to establish trust with the therapist team, provide psychoeducation as to the expected MDMA effects, and begin to explore material related to the exposure to trauma, again with a predominantly nondirective approach. There is a significant emphasis on the importance of these nondrug preparatory sessions to establish safety and maximize the therapeutic potential of the subsequent MDMA sessions. The MDMA sessions (2, 3) are 8 hours in duration, again with two therapists present for the session. Typically, this has involved a male therapist and a female therapist present for the sessions; however, it has been recognized that this may not be the most appropriate default in increasing the access, safety, and acceptability of this treatment to transgender and gender-diverse individuals (82). These sessions use a music playlist and eyeshades to encourage an internal experience. Although there may be intermittent interaction to process the psychological material that may arise, these MDMA sessions are largely nondirective, with the encouragement that patients "go inward." Music is emphasized as a critical component of the therapy that assists patients as they move into difficult emotional terrain. Dosing has typically involved an initial dose of 75–125 mg MDMA followed by the possibility of a "booster" dose of half of the initial dose at 1.5–2 hours. After each MDMA session, three integration sessions all take place within a comfortable, living room–style clinical setting with an emphasis on "set and setting." "Set" refers to the patient's intentions, mindset, and psychological approach to the treatment; "setting" refers to the environment of the session. These integration sessions again follow a nondirective therapeutic model and focus on processing and incorporating emotional and psychological content that arose in the MDMA sessions within the broader framework of the individual's illness symptoms, functioning, and life.

EVIDENCE BASE

The first randomized placebo-controlled trial of MDMA-assisted therapy for PTSD was published in 2011 (53). This study involved 20 patients with chronic PTSD, with 12 patients undergoing two MDMA sessions (125 mg plus the option of an additional booster of 62.5 mg) and the remaining eight receiving placebo. The primary outcome measure was the Clinician-Administered PTSD Scale for *DSM-IV*, and by study completion, 83% of patients in the MDMA arm no longer met PTSD diagnostic criteria versus 25% in the placebo arm. This study included a long-term follow-up over 3.5 years that demonstrated stability in treatment effect. These results were then replicated in two subsequent studies (1, 83).

In total, there have been six Phase II RCTs on MDMA-assisted psychotherapy for PTSD. An analysis of the 105 patients pooled across these studies, published in 2019 (84), demonstrated that, after two MDMA sessions, 54.2% of the patients no longer met diagnostic criteria for PTSD, compared with 22.6% in the placebo condition. This suggests that MDMA more than doubles the remission rate, compared with placebo (85).

At this point, there has been a single published Phase III study on MDMA-assisted therapy for PTSD (86). MAPS recently reported that a second Phase III study has been completed, but these results are not currently available. The first Phase III study, by Mitchell et al. (86)—published in *Nature Medicine* in 2021—was a randomized, double-blind, placebo-controlled trial that included 90 participants (mean age, 41 years) across sites in the United States, Canada, and Israel. Forty-four participants were randomized to the MDMA condition, and 46 were randomized to placebo. The primary outcome measure was the Clinician-Administered PTSD Scale for the *DSM-5* (CAPS-5), which is a 30-item,

scale (with items rated from 0 to 4) that is considered the gold standard in PTSD assessment utilizing *DSM-5* criteria. The mean CAPS-5 score for participants was 44.1 at baseline. A "response" on CAPS-5 assessment required a decrease of 10 points or more on the CAPS-5. "Remission" was defined as a loss of diagnosis and a CAPS-5 score less than 11.

Participants in the placebo arm of this trial completed the same therapeutic protocol as those in the MDMA arm, which included three 8-hour placebo sessions (in place of MDMA sessions). This study did not formally evaluate blinding in participants, and the study describes that at least 14% of those in the placebo arm incorrectly guessed that they had received MDMA and that at least 4% in the MDMA group incorrectly guessed that they were in the placebo group (86).

There are a few interesting features of study participants worth discussing.

The participant sample was predominantly White—an important limitation that arises across most current studies on psychedelic-assisted therapies and that raises important questions about equity and inclusion as well as culturally informed care (87, 88). This participant sample was also predominantly female (65.6% female at birth)—although it was unclear whether this was intentional in the study design, it does reflect the higher rates of PTSD diagnoses in women than in men, with a lifetime prevalence of 10%–12% in women versus 5%–6% in men (89). Thirty-two percent of participants reported prior lifetime use of MDMA compared with an estimated 7% in naturalistic samples in the United States as of 2017, for instance (90), which suggests a degree of selection bias. A surprisingly small number of participants (N=1) had completed a course of PE therapy. It is interesting that this study included participants with features that are typically considered markers for treatment resistance, including a total of 19 participants with a dissociative subtype of PTSD, as well as participants with a history of multiple traumas dating back to childhood (as opposed to, e.g., specifically combat-related PTSD). Similarly, participants with alcohol use disorder and other substance use disorders were included and did not show any apparent difference in treatment efficacy. The mean duration of the PTSD diagnosis for participants was 14.8 years.

There were only two recorded serious adverse events, both in the placebo arm, and there were no major safety issues reported in the MDMA arm of the study. Abuse potential, cardiovascular risk, and suicidality were tracked as adverse events of special interest; however, MDMA was not shown to induce any of these phenomena. At the 18-week endpoint, the study demonstrated a large effect size (d=0.91) for MDMA on the CAPS-5 score, with 67% of participants in the MDMA arm no longer meeting criteria for PTSD (vs. 32% in the placebo arm). Considering the proportion of participants that still met the criteria for "severe" or "extreme" PTSD at the primary endpoint, this study showed clinical benefit surpassing the pooled Phase II study results, with 14.3% of the participants meeting the criteria versus 37.8% (91). It has been hypothesized that this is due to the incorporation of a third MDMA session in this trial, compared with two sessions in the Phase III studies (91), and this is supported by the data, which show a significant drop in mean CAPS-5 scores between Sessions 2 and 3 (26.2 to 19.5) (86). It is interesting that MDMA-assisted therapy was equally effective in participants with comorbid conditions that are typically associated with treatment resistance (e.g., alcohol and substance use disorders, dissociative subtype of PTSD, multiple traumas from childhood). However, it should be noted that the relationship between comorbid substance use disorder and PTSD is complex, and substance use can be a marker for severity of PTSD symptoms (92). Notably, there is preliminary evidence for MDMA-assisted therapy as an integrated treatment for PTSD and alcohol use disorder (93). The robust reduction in PTSD symptoms observed in the study in the MDMA arm was accompanied by significant improvement in scores on the Sheehan Disability Scale (SDS). The SDS is a clinician-administered scale for assessing functional impairment across domains. The MDMA arm demonstrated a 3.1 (SD=2.6) reduction in the SDS versus a 2.0 (SD=2.4) in the placebo arm. The Beck Depression Inventory–II was used as an exploratory endpoint, with a mean reduction of 19.7 (SD=14.0) in the MDMA arm and 10.8 (SD=11.3) in the placebo arm, for an effect size of 0.67.

Despite promising early results, studies on MDMA-assisted psychotherapy have had several limitations. Although longitudinal data have been collected from Phase II study results for 3.5 years, there are limited longer term follow-up data from more recent Phase III trials, in terms of both efficacy and safety data. There are also several methodological challenges and limitations worth discussing. Studies that use psychedelic-assisted psychotherapies are notoriously difficult to blind; given the pronounced and unique consciousness-altering effects of classic psychedelics, as well as of MDMA, both study participants and study personnel are unlikely to maintain a blinding condition. This has been the case with studies that use MDMA-assisted psychotherapy, and it problematizes controlling for expectancy effects. The Phase III trial that was published in 2021 did not formally assess blinding during the study. However, the authors commented that, in contacting participants to inform them with regard to treatment assignment, "at least 10% had inaccurately guessed their treatment arm" (86). Anecdotally, in the article, this involved 15.9% in the placebo arm and 4.3% in the MDMA arm. Selection bias also arises in several ways: studies on MDMA-assisted psychotherapy have demonstrated an overrepresentation of subjects with prior lifetime exposure to MDMA in excess of what would be predicted from population-based surveys. The 2021 Phase III trial showed a 32.2% rate of lifetime reported MDMA use. This may suggest an increased degree of expectancy effects and subsequent inflated effect sizes. Studies on MDMA-assisted psychotherapy have also been largely homogenous in terms of the racial-ethnic backgrounds of the study populations, an issue also seen in other trials of psychedelic-assisted therapies (87).

It has been suggested that these limitations may be compounded by several other factors that are specific to psychedelic medicine; namely, allegiance bias underlying the decades of advocacy work required to drive this research program as well as the concomitant influence of public messaging and promotion that may contribute to inflated expectations (94, 95). We are, indeed, living in a time of considerable hype surrounding psychedelic medicine, which places an ethical onus on adhering to claims supported by available evidence so as to move forward with a clear determination of risk and benefits (96).

SAFETY AND RISKS

MDMA causes transient and self-limited elevations in body temperature, heart rate, and blood pressure. To date, these parameters are predictably elevated across clinical studies in transient fashion, without documented serious adverse events. These changes are estimated to be similar in degree to the effects of moderate aerobic exercise and well tolerated by healthy individuals, with the peak difference between placebo and 125 mg MDMA being 44 mmHg for systolic pressure, 25 mmHg for diastolic pressure, and 30 beats per minute for heart rate (97). Although MDMA has been demonstrably safe in clinical trials when accompanied by appropriate screening for patients with preexisting cardiac disease, hypertension, or other associated risk factors, this does suggest a degree of cardiac risk for certain patient populations. In the therapeutic context, acute adverse effects include nausea and vomiting, muscle tension or tremulousness, jaw clenching, headache, dizziness, sweating, and diminished appetite (98), which are typically self-limited. In the context of the controlled clinical trials that have been conducted thus far, there have been no reported persisting study drug–related harms in over 850 participants (45, 65, 68). The first published Phase III trial reported side effects of mild to moderate severity (e.g., muscle tightness, decreased appetite, nausea, hyperhidrosis, and feeling cold) in the active MDMA arm of the study (86).

There have been anecdotal reports of subsequent decline in mood in the days after MDMA administration in recreational settings—so-called "blue Mondays"—presumably caused by a relative decline in levels of synaptic monoamines. The extent to which this is a phenomenon in clinical trials remains unclear. A recent paper by Sessa et al. reported the results of an open-label study of MDMA in the treatment of alcohol use disorder and concluded that there was "no observable decline in mood after dosing of MDMA in clinical settings" (99). However, in subsequent responses, researchers have taken exception to this claim, arguing that the study in question was underpowered as well as methodologically limited in assessing this phenomenon (100).

Although there have been no documented instances of subsequent MDMA abuse or misuse in the context of published trials, MDMA has abuse potential when used in uncontrolled and nontherapeutic settings. This is supported by animal studies that have demonstrated reliable self-administration (101). This is in notable contrast to classic psychedelics (agonists at the serotonin 5-HT_{2A} receptor such as psilocybin, LSD, mescaline, or DMT), which do not demonstrate similar abuse potential. Repeated heavy use of MDMA has been shown to be associated with several psychobiological deficits, including worsening of declarative memory and a heightened risk for mood disorders (102), which is thought to be related to the decrease in serotonin transporter density. However, it should be noted that much of the data obtained naturalistically surveyed recreational "ecstasy" users, who frequently ingest uncontrolled dosages of impure samples containing a range of other substances, including amphetamines and designer cathinones: A recent study using calorimetric reagent assays of recreationally obtained "ecstasy" showed that only 60% of 529 obtained samples actually contained MDMA (103). As such, it is important to distinguish between the pharmaceutical-grade MDMA used in clinical trials and "ecstasy" obtained and used recreationally. There have been no recorded persistent psychobiological deficits in study participants.

A subsequently retracted paper published in *Science* in 2002 (104) initially caused significant concern regarding MDMA-induced neurotoxicity in dopaminergic neurons in a study of 10 primates. However, it was discovered that nine out of the 10 animals had actually been administered methamphetamine, not MDMA. This contributed to several popular press articles on the brain-damaging effects of MDMA that were invalid but, nonetheless, influenced popular perception.

CHALLENGES AND FUTURE DIRECTIONS

MDMA-assisted therapy for PTSD shows significant promise for rapid and sustained reduction in PTSD symptoms, improvement in functioning and disability status, and improvement in depressive symptoms associated with the diagnosis. Provided that the remaining Phase III trials show consistent evidence to the studies completed to date—we anticipate that this treatment will be approved by the FDA in late 2023 or early 2024. MDMA-assisted therapy has the potential to transform the treatment landscape for PTSD, but there are several challenges and unanswered questions at present.

Given that the presence of the therapy dyad results in 40 hours of therapy time (for each individual therapist; hence, 80 hours total), scaling this intervention within the constraints of current health care models will be a significant challenge. There are questions as to how this will work within health care insurance models and within the Centers for Medicare and Medicaid Services. Several recent economic analyses on MDMA-assisted therapy—the most recent one using data from the 2021 Phase III trial (91, 105)—have suggested that MDMA-assisted therapy is ultimately cost saving from a payer's perspective, given the significant improvement in remission rates of PTSD with this form of

treatment for a condition that is otherwise enormously costly on the U.S. health care system. This analysis (91) estimated that the treatment in the 2021 Phase III trial cost $11,537 per patient. Comparing this with the standard of care for 1,000 patients utilizing a Markov model, this form of treatment would save $132.9 million over 30 years, accruing 4,856 quality-adjusted life-years and averting 61.4 premature deaths. According to this analysis, MDMA-assisted therapy breaks even, with standard of care at 3.8 years.

It remains unclear how to optimize MDMA-assisted therapy in terms of the number of MDMA sessions, intensity of the associated psychotherapy, modality and directedness of the associated psychotherapy, and ongoing therapeutic follow-up. It is also unclear whether two therapists present for the duration of the psychotherapeutic process is requisite for full therapeutic effect. However, it should be noted that this model does offer some degree of protection against boundary violations that are consequential in an altered state. The 2021 Phase III trial showed a significant improvement in remission rates from the second to the third MDMA session. Proposed neurobiological mechanisms for long-term positive effects of MDMA-assisted therapy for PTSD, such as critical period plasticity and fear extinction learning, provide a strong rationale for the combination of a robust therapeutic approach with medication administration. However, historical pressures within health care delivery will likely seek to increase efficiency and scalability of the treatment, with uncertain effects. A window of neuroplasticity may afford opportunity for therapeutic growth in the right context but may also introduce the possibility of harms without careful attention to associated environmental factors. Balancing the prioritization of treatment outcomes with scaling the intervention to increase access will present challenges. Similarly, there has been little work to date examining the effect of alterations on the associated psychotherapeutic protocol. Arguments have been made to utilize gold-standard, evidence-based psychotherapies in the context of psychedelic-assisted therapy trials (106) to maximize efficacy.

Another significant challenge with MDMA-assisted therapy for PTSD is the strong likelihood that concomitant SSRIs may dampen response to this medication. Although there are limited empirical data to inform this concern at present, there are significant pharmacodynamic interactions that may blunt the response to MDMA (107). This will present difficulties for many patients who are currently treated with these agents, particularly given the frequency of prescription of SSRIs for PTSD symptoms and the dearth of other meaningful pharmacologic agents.

Although the most recently published Phase III trial on MDMA-assisted therapy included participants with a broader range of PTSD symptomatology and comorbid conditions, it remains the case that studies to date have involved strict inclusion and exclusion criteria. Similarly, intensity and consistency of the therapeutic approach are easier to control in the context of clinical trials. Presumably, with a broader sampling of patients across clinical settings and increased heterogeneity in psychotherapeutic approach and rigor, these initial effect sizes in treatment response may diminish somewhat. Notably, given the history of MDMA-assisted therapy in couples work, there have been recent trials exploring MDMA-assisted therapy for couples in which one member of the partnership has a PTSD diagnosis (108), which may be a promising direction.

With the anticipated FDA approval of MDMA-assisted therapy, there are a host of related ethical questions with regard to ensuring access to underserved, vulnerable, and minority populations; minimizing harms and ensuring fidelity to appropriate screening practices; and minimizing risk of therapist boundary violations. Although the process is still in its early stages, it is anticipated that the FDA, in granting approval, will mandate the provision of Risk Evaluation and Mitigation Strategy programs to ensure that the benefits of treatment outweigh the risks. These would presumably specify details as to context and supervision of drug administration, monitoring parameters, oversight and record keeping, as well as required training. There are ethical questions related to the relative importance of therapist or researcher personal experience with MDMA (or other psychedelic substances) insofar as conducting therapy and research without bias (109). However, the MAPS therapist training protocol notably includes an optional experiential component in which researchers are provided with an MDMA experience with the support of two therapists to facilitate empathy and understanding for the process of study participants. The enhanced openness and suggestibility of patients undergoing an MDMA experience increases vulnerabilities to boundary violations. This has already been identified as a problem in one of the MAPS-sponsored clinical trials on MDMA-assisted therapy (110) and highlights the importance of ethical oversight, quality control, training, and video recording of drug administration sessions.

Some methodological limitations of the current research deserve careful attention to better characterize risks and benefits. These include challenges with blinding conditions (and associated expectancy effects), possible selection and allegiance bias, challenges with the replicability of the largely nondirective MAPS therapeutic protocol, and the expectancy effects influenced by the intensity of public messaging and associated hype. Careful and rigorous ongoing research is needed to better characterize this emerging treatment approach.

In sum, MDMA-assisted therapy is an emerging novel and likely effective treatment for PTSD, a condition in which there is a clear need for improved treatments. There are studies underway that are investigating MDMA-assisted therapy for other psychiatric indications; however, initial clinical applications will likely focus on the treatment of refractory PTSD symptoms. This intervention presents some unique conceptual and practical challenges for the field that anticipate similar challenges with other forms of psychedelic-assisted therapies.

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