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REVIEW

Progress and promise for the MDMA drug development program

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Abstract Pharmacotherapy is often used to target symptoms of posttraumatic stress disorder (PTSD), but does not provide definitive treatment, and side effects of daily medication are often problematic. Trauma-focused psychotherapies are more likely than drug treatment to achieve PTSD remission, but have high dropout rates and ineffective for a large percentage of patients. Therefore, research into drugs that might increase the effectiveness of psychotherapy is a logical avenue of investigation. The most promising drug studied as a catalyst to psychotherapy for PTSD thus far is 3,4-methylenedioxymethamphetamine (MDMA), commonly known as the recreational drug "Ecstasy." MDMA stimulates the release of hormones and neurochemicals that affect key brain areas for emotion and memory processing. A series of recently completed phase 2 clinical trials of MDMA-assisted psychotherapy for treatment of PTSD show favorable safety outcomes and large effect sizes that warrant expansion into multi-site phase 3 trials, set to commence in 2018. The nonprofit sponsor of the MDMA drug development program, the Multidisciplinary Association for Psychedelic Studies (MAPS), is supporting these trials to explore whether MDMA, administered on only a few occasions, can increase the effectiveness of psychotherapy. Brain imaging techniques and animal models of fear extinction are elucidating neural mechanisms underlying the robust effects of MDMA on psychological processing; however, much remains to be learned about the complexities of MDMA effects as well as the complexities of PTSD itself.

Keywords 3,4-Methylenedioxymethamphetamine · PTSD · Psychoactive effects · MDMA

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Introduction

Over a century after the discovery of 3,4-methylenedioxymethamphetamine (MDMA), a significant milestone has recently been reached in the unique history of this compound. Based on favorable results of a series of phase 2 studies, MDMA is now advancing to phase 3 clinical trials as a pharmacological agent to enhance psychotherapy. First synthesized in 1912 by the German pharmaceutical company Merck (Freudenmann et al. 2006), its potential as a treatment for psychological disorders was not recognized at that time. It was the subject of only minimal research in animals over the next 50 years. In the mid-1960s, an American chemist Alexander "Shasha" Shulgin resynthesized MDMA and performed self-experimentation, calling it his "low-cal martini" due to the positive psychoactive effects he experienced while under its influence. Recognizing the potential psychotherapeutic applications that might stem from its neurobiological actions as an "entactogen" (Nichols 1986), Dr. Shulgin gave MDMA to his psychologist friend, Dr. Leo Zeff, who began using the drug in psychotherapy sessions. Having good results, he shared his findings with other therapists who also reported that MDMA could increase communication during sessions and was especially useful in couples' therapy (Stolaroff 2004). Shulgin and Dr. David Nichols published the first paper on MDMA's psychoactive properties in 1978, reporting an "easily controlled altered state of consciousness" and encouraging human studies (Shulgin and Nichols 1978).

By the early 1980s, "Ecstasy" (tablets purported to contain MDMA) became a popular drug at all-night dance parties and raves in the USA and Europe. Due to the widespread use of "Ecstasy" in mainstream culture, the Drug Enforcement Administration (DEA) pushed for stiff regulation of its use, leading to MDMA being classified as a Schedule I controlled substance in 1985. At the time, no controlled clinical trials had been conducted, but collection of therapists' observations and subjective reports from 29 individuals administered MDMA in a clinical setting was underway when scheduling occurred (Greer and Tolbert 1986).

This review outlines the current status of the FDA-regulated MDMA drug development process, starting with the filing of an Investigational New Drug (IND) Application in 1985 and continuing through the projected approval of a New Drug Application (NDA) in 2021. Following the recent completion of six phase 2 clinical trials of MDMA-assisted psychotherapy for posttraumatic stress disorder that provided ample safety and efficacy data, the FDA has agreed to large-scale phase 3 trials. The pharmacology and subjective effects of MDMA are well-understood from hundreds of articles in the literature; the neurobiological mechanisms responsible for the large effect sizes observed in phase 2 studies are not completely understood, but are hypothesized and detailed herein, based on the neural circuitry affected by PTSD, the pharmacodynamic parameters of MDMA, and transformations observed during MDMA-assisted psychotherapy research sessions.

Commencement of MDMA research for therapeutic use

The Multidisciplinary Association for Psychedelic Studies (MAPS) was founded in 1986, shortly after MDMA was placed on the Schedule 1 list of controlled substances. Later in 1986, MAPS funded a 28-day toxicity study in rats and dogs (Frith et al. 1987), in accordance with FDA guidance for starting a drug development program to gather data to test the safety of MDMA administration in healthy humans. Subsequent clinical investigation of the safety and effectiveness of MDMA-assisted psychotherapy has been conducted under an open FDA Investigational New Drug (IND) application with MAPS as sponsor. After overcoming many obstacles and delays related to working with a Schedule 1 substance, the first double-blind, placebo-controlled phase 1 study of MDMA sanctioned by the FDA was conducted in 1994. Findings showed that MDMA administered in a controlled clinical setting was well tolerated by healthy volunteers, causing a transient, clinically insignificant increase in body temperature and heart rate in some subjects (Grob 1998; Grob et al. 1996). Subsequent trials confirmed that MDMA produced increases in heart rate and blood pressure (Clark et al. 2015; Kirkpatrick et al. 2014a; Liechti et al. 2001; Liechti and Vollenweider 2000) that would be well tolerated by healthy individuals, similar in degree to moderate aerobic exercise. Peak differences between placebo and MDMA 125 mg were 44 mmHg for systolic blood pressure, 25 mmHg for diastolic blood pressure, and 30 beats/min for heart rate (Mas et al. 1999).

MDMA-assisted psychotherapy for PTSD phase 2 trials

The first randomized, placebo-controlled, double-blind study investigating MDMA-assisted psychotherapy commenced in 2000 in a MAPS-sponsored, dose-response pilot study in Spain in women survivors of sexual assault with PTSD. Six women were enrolled and treated in this study without any adverse events or signs of deteriorating mental health; they showed mild signs of improvement, with single doses ranging from 50 to 75 mg (Bouso et al. 2008). Unfortunately, this study was not completed because it was closed in 2002 due to political pressure from the Madrid Anti-Drug Authority.

In 2000, MAPS began developing the first placebo-controlled phase 2 study of MDMA-assisted psychotherapy for the treatment of chronic PTSD (MP-1, NCT00090064). The FDA cleared the protocol in 2001, but long delays in IRB approval resulted from a paper published in Science that incorrectly claimed that MDMA caused dopamine neurotoxicity and was later retracted because methamphetamine was inadvertently administered instead of MDMA (Ricaurte et al. 2002; Ricaurte et al. 2003). After subsequent delays in the DEA approval process, the study began enrolling subjects in 2004. The study was designed with three non-drug preparatory sessions, and two 8-h experimental psychotherapy sessions with MDMA or inactive placebo, each followed by four non-drug integrative sessions. The MDMA dose was 125 mg plus an optional supplemental 62.5 mg dose 2–2.5 hours later. PTSD symptom severity was assessed with the Clinician Administered PTSD Scale (CAPS-4) at baseline, 4 days after each experimental session, and again 2 months after the second experimental session. The MDMA-treated group ($n = 12$) had significantly lower CAPS-4 scores than the placebo group ($n = 8$) after only one MDMA session and associated non-drug therapy visits, and scores from subjects who completed treatments in the MDMA group remained significantly lower 2 months after the second MDMA session (Mithoefer et al. 2011). To assess the durability of treatment, 16 of the 19 subjects who had received MDMA in either the blinded sessions or in the open label crossover completed CAPS-4 and Impact of Events Scale-Revised (IES-R) measures during a long-term follow-up 17–74 months after the final MDMA session. Mean scores at the long-term follow-up were not significantly different than the 2-month Exit scores, showing

that gains in PTSD symptom mitigation were sustained over time for most participants (Mithoefer et al. 2013).

The next study (MP-2, NCT00353938) conducted in Switzerland had 12 participants with chronic PTSD who completed sessions through the primary endpoint. After undergoing 3 blinded drug-assisted sessions and 12 non-drug therapy sessions, the group that received full dose MDMA (125 mg) had a mean (SD) point drop of 15.6 (18.1) in CAPS-4 Total Severity Scores compared to the active placebo (25 mg MDMA) group with a 3.2 (15.3) point decrease. Although group comparisons of CAPS-4 scores did not reach statistical significance ($p = 0.066$) at the 2-month follow-up, there was a significant change over time (at 1 year follow-up) for the full-dose group only. The Posttraumatic Diagnostic Scale (PDS), a self-report measure of PTSD symptoms, detected a significant decrease in severity in the full-dose group compared to placebo ($p = 0.014$) (Oehen et al. 2013).

Safety outcomes from the MP-1 and MP-2 studies were favorable, with no drug-related serious adverse events or adverse neurocognitive effects. Transient increases in physiological vital signs were mostly moderate and did not require any medical interventions. Most adverse events and spontaneously reported reactions (expected events as ascertained through examination of phase 1 studies) were mild to moderate, and generally remitted within 7 days of the experimental treatment. Data from these two studies (Mithoefer et al. 2011; Oehen et al. 2013) provided an acceptable risk/benefit ratio to expand investigations into a larger PTSD sample.

Four other MAPS-sponsored phase 2 double-blind, dose-response studies (MP-4, NCT01958593; MP-8, NCT01211405; MP-9, NCT01689740; MP-12; NCT01793610) that followed a similar design were completed by 2016. Results from these studies are currently in preparation for publication, but have yet to be peer-reviewed. All data were submitted in an End of phase 2 package and reviewed by FDA, leading to agreement for phase 3 trials. Safety outcomes were in line with favorable published findings. Pooled analysis of CAPS-4 Total Severity Scores in the intent-to-treat set ($n = 103$) showed a large Cohen's d placebo-subtracted effect size (0.9) and significant group differences at the primary endpoint (1-2 months post 2-3 blinded drug sessions). Beyond clinically meaningful symptom severity reductions, 52.7% of subjects that received active doses of MDMA ($n = 72$) no longer met criteria for PTSD according to the CAPS-4 compared to 22.6% in the placebo/comparator group receiving the same psychotherapy ($n = 31$), suggesting that MDMA more than doubles the positive effects of psychotherapy (Feduccia et al. 2016; Mithoefer 2015). Safety outcomes were replicated in this larger sample of people with PTSD, providing evidence that limited doses of MDMA in controlled clinical settings are physiologically and psychologically well-tolerated by participants with PTSD who have been screened to exclude serious medical problems. Similarly, the safety of single dose administration of MDMA has been documented in healthy subjects (Vizeli and Liechti 2017). Through spontaneous reports during follow-up and a clinician-administered unstructured interview 12-months post-MDMA, there were no adverse events related to substance abuse or self-report of compulsive drug seeking for "Ecstasy" after subjects participated in these trials; therefore, abuse potential after MDMA administration in a clinical setting was low in participants who met inclusion criteria for these trials. In addition to self-report data, urine drug screens for MDMA were performed at random and 2, 6, and 12 months after the final experimental session during one study (MP-2, $n = 12$). All were negative, supporting the observation that subjects in MP-2 did not seek out MDMA or "Ecstasy" after taking part in the study (Oehen et al. 2013). At the 12-month follow-up visit in a self-report questionnaire [across the six phase 2 trials ($n = 91$)] that asked about "Ecstasy use," seven subjects, of whom six had used "Ecstasy" prior to enrollment, reported using Ecstasy once or twice after the study. The potential for abuse of MDMA in nonmedical settings is considered moderate (Bershad et al. 2016a; Kamilar-Britt and Bedi 2015).

Therapeutic and pharmacological mechanisms of action

PTSD may arise after a traumatic event, with symptoms manifesting in a variety of ways that can negatively affect a person's wellbeing, daily functioning, and physical health. Pharmacotherapies aimed at reducing symptom severity and several types of talk therapies are currently used in treating PTSD, yet only 40–60% of patients respond adequately. Existing pharmacologic treatments can improve symptoms, but do not offer definitive treatment, and often require continued daily dosing of medications with significant side effects (Bradley et al. 2005; Brady et al. 2000; Steenkamp et al. 2015). Significant symptom reduction has been reported months after prolonged exposure (PE) and cognitive therapy (CT); however, when followed up 3 years later, CAPS total scores were equivalent across groups that received PE, CT, SSRIs, placebo, and no interventions (Shalev et al. 2016). The use of MDMA as an adjunct to psychotherapy is a novel approach based on the theory that a drug of this kind could facilitate therapeutic processing of traumatic memories and could also be helpful in addressing the broad array of psychological and psychosocial difficulties that accompany PTSD and contribute to the detrimental effects on patients' lives and relationships. A primary characteristic of PTSD is a heightened fear response to environmental stimuli, whether from an actual current threat or not, which is reflected in neuroimaging as hyperactivity of the amygdala and reduced prefrontal modulation of this fear-activated region (Etkin and Wager 2007; Rauch et al. 2006). The neurobiological

underpinnings of PTSD symptoms can make revisiting memories with congruous emotional engagement during therapy sessions difficult, impossible, or counter-productive. Therapeutic benefits are thought to arise from MDMA's complex pharmacologic profile that promotes synaptic efflux of serotonin, norepinephrine, and dopamine via the respective monoamine transporter (Feduccia and Duvauchelle 2008; Han and Gu 2006; Hysek et al. 2012b; Verrico et al. 2007) and by subsequent release of oxytocin, vasopressin, cortisol, and prolactin (de la Torre et al. 2000; Dolder et al. 2017; Dumont et al. 2009; Hysek et al. 2012a; Hysek et al. 2014a; Kirkpatrick et al. 2014c; Kuypers et al. 2017; Murnane et al. 2010; Schmid et al. 2014; Seibert et al. 2014). The synergistic activity of these neurochemicals and hormones may act through several receptors within different brain networks to enhance the therapeutic alliance, reduce fear and defense mechanisms surrounding trauma memories, and allow for an alternative, present-moment perspective of the trauma memory.

Delineating the role of receptor subtypes and neural circuitry underlying MDMA's effects has been the subject of investigations in both clinical and nonclinical models. Serotonin is robustly released by MDMA into the synaptic cleft where it binds to post-synaptic 5-HT receptors throughout multiple brain regions to alter normal consciousness. In the clinical setting, the resulting shift in perspective provides an opportunity to engage in focusing on the trauma without overwhelming anxiety and fear. Increase in emotional empathy for oneself and one's situation can result from deep internal reflection that is mediated by the serotonergic effects of MDMA (Hysek et al. 2014a; Kuypers et al. 2014; Kuypers et al. 2017). In addition, MDMA reduces the decoding of negative emotions (Bedi et al. 2010; Dolder et al. 2017; Hysek et al. 2012a; Hysek et al. 2014a; Hysek et al. 2014b; Schmid et al. 2014) and also reduces the amygdala response to angry facial expressions (Bedi et al. 2009). Given the neuromodulatory role of 5-HT for mood, and its association with depression and anxiety disorders, targeting this system with MDMA during therapy to enhance positive emotions and therapeutic alliance through 5-HT(2)R activation (van Wel et al. 2012) presumptively allows for an opening into the psychological processes underlying the triggering of and response to trauma memories. In healthy individuals, MDMA (100 mg) ingestion altered response to favorite and worse autobiographical memories compared to placebo. Worst memories were perceived less negatively after MDMA, without changing the strength of emotion, and correlated with significantly lower activation (BOLD) of the left anterior temporal lobe and greater activation of the superior frontal gyrus/dorsal medial prefrontal cortex (Carhart-Harris et al. 2014). Attenuating activity in the temporal lobe may neutralize perception of traumatic memories (Meyer et al. 2013; Musser et al. 2012) while still permitting painful emotions to be fully processed through enhanced mPFC activation during MDMA-assisted psychotherapy. On the other hand, favorite memories were experienced under MDMA with greater vividness and more intense positive affect, accompanied by more activation of hippocampal regions, bilateral fusiform gyrus, and somatosensory cortex than observed with recall of negative memories (Carhart-Harris et al. 2014). Given the modulatory role of serotonin on mood (Davidson et al. 2002), the observed shift in subjective ratings and neural activity is likely due, at least in part, to augmentation of serotonergic signaling by MDMA.

Recent studies with a different imaging technique have shown that in healthy volunteers, MDMA causes a decrease in resting state functional connectivity (RSFC) between prefrontal cortex and hippocampus and an increase in RSFC between hippocampus and amygdala. This may lead to what the authors refer to as a "less constrained repertoire of functional connectivity" (Carhart-Harris et al. 2015), possibly allowing for more flexibility in previously rigid patterns of cognitive and emotional response, and a new, more balanced perspective about trauma memories. This finding is particularly interesting in light of a study showing decreased amygdala-hippocampal RSFC in combat veterans with PTSD. The authors speculate this "may relate to an impaired ability to contextualize affective information in PTSD" (Sripada et al. 2012).

The exact role MDMA-stimulated enhancement of oxytocin may play in potentiating the therapeutic process is under investigation. The neuropeptide oxytocin regulates the autonomic nervous system's fear response, and centrally mediates complex social behaviors involving pair bonding (Insel 1992), sex (Carter 1992; Witt 1995), affiliative behavior (Insel 1992), and pro-social feelings (Dumont et al. 2009; Hysek et al. 2014a). MDMA can reduce subjective anxiety and enhance feelings of trust, closeness toward others, and openness (Bershad et al. 2016a; Dolder et al. 2017; Hysek et al. 2014a; Schmid et al. 2014). MDMA induces the release of oxytocin secondary to MDMA-stimulated 5-HT efflux or by direct affinity to 5-HT receptors, which is deemed important for the prosocial effects of MDMA (Thompson et al. 2007). MDMA reliably raises peripherally measured oxytocin levels (Dumont et al. 2009; Hysek et al. 2014a; Thompson et al. 2007). Over time and within subjects, correlations were detected for higher oxytocin levels and stronger MDMA-induced prosocial feelings (Dumont et al. 2009). Further, oxytocin receptor gene variation predicts subjective responses to MDMA (Bershad et al. 2016b). Oxytocin modulates key neural substrates, namely the amygdala and prefrontal cortex, implicated in PTSD, learning and memory, and fear extinction. Oxytocin can attenuate activity in the amygdala (Eckstein et al. 2015), a possible mechanism of the MDMA-induced amygdala suppression seen in neuroimaging studies (Carhart-Harris et al. 2015; Gamma et al. 2000).

Oxytocin has been investigated as an adjunct to psychotherapy because of its established effects on prosocial behavior, its potential to augment the therapeutic alliance, and its enhancement of fear extinction in rodents (Dolder et al. 2017; Hysek et al. 2012a; Kirkpatrick et al. 2014b; Kuypers et al. 2017; Schmid et al. 2014). Administration of oxytocin to humans has paradoxically been shown to either enhance (Guastella et al. 2008; Rimmele et al. 2009; Savaskan et al. 2008) or decrease (Ferrier et al. 1980; Heinrichs et al. 2004) memory and learning, with evidence showing the bidirectional effects are related to whether or not learning is socially reinforced (Hurlemann et al. 2010). The supportive attention from two therapists during MDMA-assisted psychotherapy sessions provides robust social reinforcement through empathetic rapport that may enable oxytocin signaling to promote, rather than inhibit, memory reconsolidation during trauma recall.

On the other hand, more recent papers have failed to provide evidence that MDMA-induced enhancement of emotional empathy is related to peripheral oxytocin levels or 5-HT_{1a} receptor activation (Kuypers et al. 2014). In a paper that pooled data from multiple trials (n = 118), oxytocin concentrations were elevated after MDMA administration but were not associated with subjective effects between subjects (Kuypers et al. 2017). According to Kuypers, oxytocin did not affect measures of empathy and social interaction, and changes in emotional empathy were not related to oxytocin plasma levels (Kuypers et al. 2014). However, interpretation is limited because Kuypers et al. (2014, 2017) did not measure within-subject correlation of subjective effects with multiple post-MDMA oxytocin levels as in the study design that showed a positive within-subject correlation after MDMA for oxytocin and prosocial effects (Dumont et al. 2009).

Observations during phase 2 clinical trials indicate that with the support of two therapists during MDMA-assisted psychotherapy sessions, individuals who have not been able to successfully process trauma during prior psychotherapy are often able to remember details of traumatic events more clearly and to revisit and talk about them without becoming emotionally overwhelmed, emotionally numb, or dissociated. This may extinguish fear connected to the memory, and possibly activate memory reconsolidation processes that would allow new emotional content to be overlaid in a way that modifies the past memory trace. fMRI imaging of healthy adults after MDMA administration showed a decrease in activity in the amygdala as well as the increased functional connectivity between the amygdala and hippocampus mentioned above (Carhart-Harris et al. 2015), supporting the hypothesis that emotional memory systems are targeted by MDMA. The long-term durability of treatment may be explained by the decreased salience of trauma memories that have been processed during MDMA and integrative therapy sessions. The hypothesis that MDMA may interact with memory processes and facilitate fear extinction is corroborated by the first published report of MDMA tested in a rodent training paradigm (Young et al. 2015), and replicated in a fear-potentiated startle paradigm in mice (Young et al. 2017). Brain-derived neurotrophic factor (BDNF) plays a crucial role in hippocampal synaptic plasticity and learning (Hall et al. 2000; Thoenen 1995), and regulates adult neurogenesis (Lu and Chang 2004). In mice, MDMA (7.8 mg/kg) administered before extinction training increased fear extinction through enhanced expression of *BDNF* in the amygdala and increased *Fos* in the medial prefrontal cortex (mPFC) and amygdala. BDNF signaling in the basolateral complex of the amygdala (BLA) was crucial for the enhancement of extinction, demonstrated by microinfusion of MDMA (1 μg) into this region and blockade of its effects through inhibition of BDNF (Young et al. 2015). Administration of antidepressants also increases BDNF expression (Chen et al. 2001; Nibuya et al. 1995), reversing BDNF deficits associated with anxiety (Ford et al. 2013). Glucocorticoid activation of the BLA by emotionally arousing stimuli enhances long-term memory (Liang et al. 1986; Roozendaal et al. 2006), and presumably creates an optimal level of arousal for engagement with the therapeutic process (Foa et al. 2009) which may attenuate hypervigilance and emotional numbing—symptoms that are hallmarks of PTSD.

The mechanisms described above are primarily oriented toward the current predominant conceptual models of PTSD and PTSD treatment (such as imaginal exposure or cognitive behavioral therapies) and the ways in which MDMA may catalyze elements of these recognized models of treatment. While these models point to therapeutic factors that play an important role in PTSD recovery for many patients, it would be a mistake to assume that the benefits of MDMA-assisted psychotherapy are necessarily limited to bolstering these effects. The impact of trauma, especially early childhood trauma, on individuals' lives goes beyond the core PTSD symptoms described in the Diagnostic and Statistical Manual of Mental Disorders (DSM) to include profound effects on relationships, somatic experience, and overall development. This clinical reality is reflected in a proposed diagnosis of Developmental Trauma Disorder (D'Andrea et al. 2012; van der Kolk 2009). In a long-term follow-up study of participants who had completed participation in a clinical trial of MDMA-assisted psychotherapy for PTSD for an average of 42 months prior to follow-up, a large percentage reported positive sequelae in areas such as improved relationships, enhanced spiritual life, enriched community involvement, augmented empathy for others, and increased creativity (Mithoefer et al. 2013). It is likely that MDMA-assisted psychotherapy contributes to these improvements directly, as well as indirectly through decreases in PTSD symptoms. Qualitative studies on video data collected during MAPS-sponsored MDMA trials have begun and will continue to explore this area further (Cohen 2015). A factor to be considered is that MDMA is administered in

conjunction with a manualized therapy but relatively non-directive form of psychotherapy that includes elements of existing therapies, such as imaginal exposure or cognitive restructuring, but does not prescribe when or how these elements must occur (Mithoefer 2017), and that also presents an opportunity to focus on any areas of concern for the individual. This approach takes into account the complexity and variability of trauma-related symptoms and allows flexibility for each individual to work with the material that naturally arises for them. A panel of experts in trauma has pointed out the importance of looking beyond the "fear based model" of PTSD (which has yielded important advances but has limitations) and of avoiding an "exaggerated view of the specificity of (existing) treatments" in order to discover new treatments that can effectively address the "multidimensional facets of our complex patients" (Yehuda et al. 2016). Based on observations during phase 2 studies, it appears that one of the strengths of MDMA-assisted psychotherapy is that it facilitates a multidimensional experience.

Status of MDMA development program

Safety and efficacy data collected from six MAPS-sponsored phase 2 studies conducted in the USA, Canada, and Israel were submitted to the FDA as part of a briefing package for the End of phase 2 meeting between the FDA and MAPS that occurred in November 2016. The CAPS-4 efficacy results, and the safety profile (as determined by adverse event rates, physiological vital signs, and severity of suicidal ideation and behavior), both supported expansion of the drug development program into phase 3 trials. The FDA agreed to MAPS's plans to conduct two phase 3 trials (approx. 100 subjects/trial) at 16 study sites in the USA, Canada, and Israel to meet requirements for filing a New Drug Application, if phase 3 results replicate those of phase 2 studies. In addition, MAPS will sponsor a series of nonclinical safety studies concurrently with phase 3 (reproduction toxicity, genotoxicity, repeated-dose CNS toxicity) and phase 1 clinical studies (pharmacokinetic, effects of food on MDMA metabolism, subjects with hepatic impairment, and effects on QT interval prolongation) in order to complete the battery of tests required by FDA for all drugs under development for NDA and drug labeling. Several supportive pharmacokinetic and pharmacogenetic studies have been conducted previously by academic researchers (de la Torre et al. 2012; Peiro et al. 2013; Schmid et al. 2016; Vizeli and Liechti 2017; Yubero-Lahoz et al. 2012), but do not meet the specific FDA guidelines. With agreement from FDA, completing these ancillary studies has been deferred until now because pregnant or nursing women do not meet inclusion criteria for phase 2 or 3 MDMA studies, and published reports from nonclinical models support a large margin of safety for the dose ranges used in single-dose administrations in the therapeutic setting. MAPS has gained approval for the phase 3 protocol after engaging in FDA's Special Protocol Assessment (SPA) program. Subsequently, on August 15, 2017, the FDA granted Breakthrough Therapy Designation for MDMA-assisted psychotherapy for treatment of PTSD, based on the criteria for treatment of a life-threatening illness and greater safety and initial efficacy than approved medications, i.e., sertraline and paroxetine. MAPS plans to submit an Expanded Access Treatment Protocol in the winter of 2018. If the FDA approves the Expanded Access program, patients with PTSD who cannot enroll in the parallel phase 3 trials could be eligible to receive MDMA treatment with data collection limited to safety measures. Good manufacturing practice (GMP) MDMA is being synthesized by a contract manufacturing company in preparation for phase 3 trials. By request through study proposals, MAPS will encourage further research by providing MDMA to collaborators for FDA-regulated trials or nonclinical mechanistic investigations.

In preparation for phase 3, MAPS has developed a 5-part therapy training program to teach study clinicians how to use MDMA in conjunction with psychotherapy based on "A Manual for MDMA-assisted Psychotherapy in the Treatment of PTSD" (Mithoefer 2017). The training is comprised of online e-learning modules, reading assignments, in-person trainings to review and discuss video-recorded sessions from phase 2 MDMA studies, and co-therapy team-building and role-playing exercises. New therapy teams for MAPS-sponsored phase 3 trials will each treat one subject with open-label MDMA in a phase 2 study with supervision from the clinical training team in the fall of 2017. To understand the psychoactive effects through experiential learning, therapists who will work on MDMA trials are eligible to participate in a double-blind, phase 1 MAPS-sponsored study (MT-1, NCT01404754) to receive both MDMA and placebo in a therapeutic context. The training program will at some point be open to more practitioners in preparation for an Expanded Access Treatment Protocol and/or post-approval clinical use of MDMA (Fig. 1).

Other MDMA studies and potential indications

In addition to clinical trials of individual therapy for PTSD, MDMA-assisted psychotherapy is currently being investigated in three pilot studies to test efficacy for (1) reducing anxiety related to a life-threatening illness (MDA-1, NCT02427568) (Wolfson 2015), (2) reducing social anxiety in adults on the autism spectrum (MAA-1, NCT02008396) (Danforth 2013; Danforth et al. 2015), and (3) combining MDMA-assisted psychotherapy with cognitive behavioral conjoint therapy for PTSD by treating both members of a couple or other dyad (MPVA-1, NCT02876172) (Wagner 2017). These studies and

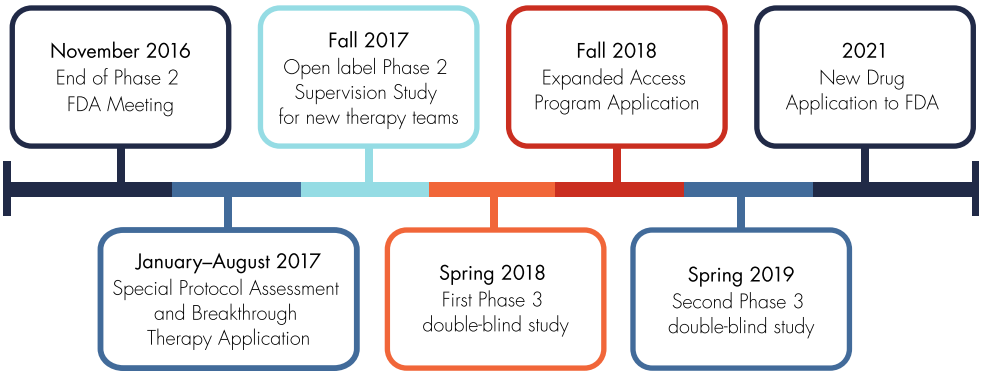

Fig. 1 Timeline for MDMA drug development program

others being planned will address the question of whether or not the utility of MDMA as an adjunct to psychotherapy is specific for PTSD, or whether it could also be effective for other psychological disorders. It is hypothesized that MDMA may be useful for anxiety and depressive disorders for the same reasons described above, namely that it can be a potent catalyst to the therapeutic process and can enhance the therapeutic alliance (Yazar-Klosinski and Mithoefer 2017). In addition, a MAPS-sponsored study in healthy individuals at Emory University will evaluate how MDMA affects startle response (MPVA-4, NCT03181763) which may provide a rationale to study MDMA in conjunction with prolonged exposure. Treatment of substance use disorders may also be enhanced with MDMA-assisted psychotherapy through resolving underlying psychological issues that drive compulsive drug-seeking behaviors (Jerome et al. 2013). A study in the UK is planned to test MDMA therapy in individuals with alcohol use disorders, which will provide initial data on safety and efficacy for use in this patient population. Other mental health disorders for which psychotherapy is an important element of treatment, including eating disorders, mood disorders, and relational problems, may show improved treatment response from MDMA as a therapeutic adjunct, and deserve investigation of safety and efficacy through randomized controlled trials.

Limitations of research

As with all treatments and research designs, evaluation of limitations and risks should coincide with interpretation of treatment efficacy. Because the psychoactive effects of MDMA may be noticeable to participants and therapists through subjective effects or changes in vital signs, maintaining blinding during these trials can be difficult. Bias was minimized in phase 2 MDMA trials by having blinded independent raters who are not present during therapy sessions administer primary outcome measures and, in some studies, using low doses of MDMA as an active placebo/comparator. For phase 3 trials, inactive placebo will be utilized because low doses of MDMA reportedly stimulated some subjects to a degree that provoked anxiety and an anti-therapeutic effect. A blinded independent rater pool will administer CAPS-5 through telemedicine sessions to reduce bias.

Although results have been very promising for MDMA-assisted psychotherapy, the conditions of administration during clinical trials offer potential benefits and drawbacks. For example, in the therapy model under study, participants gain from the safety and support of male/female co-therapy teams, yet having two therapists adds to treatment cost. Future research and the flexibility that would come with clinical use are likely to present opportunities to increase cost effectiveness. Even without such economies, MDMA-assisted psychotherapy may still be more cost effective than existing treatments because of the limited dosing regimen and durability of symptom remission over time. One must consider the costs and limited effectiveness of long-term treatment with available drugs and psychotherapies for chronic PTSD. The only two FDA-approved medications for PTSD, sertraline and paroxetine, have small to medium placebo-subtracted effect sizes (0.31–0.37 and 0.45–0.56, respectively), according to results from pivotal studies that supported the FDA designation for PTSD indication (GlaxoSmithKline 2001; Pfizer 1999), and require continuous daily dosing with ongoing medication management. Unlike MDMA (effect size 0.9), which is only administered in a clinical setting without any take-home doses, existing medications pose the risk of improper use (Amoroso and Workman 2016). Thousands of accidental and intentional overdoses have occurred from take-home prescriptions of SSRIs (Mowry et al. 2016), and the dangers of other commonly used prescription drugs such as benzodiazapines and other hypnotics, mood stabilizers, and antipsychotics are even greater. Increased suicidality and worsening of depression have been reported with SSRI treatment (Healy and Whitaker 2003), which was not detected in clinical trials of MDMA. The single MDMA dose regimen produces fewer, less enduring side effects and greater compliance compared to daily dosing of paroxetine or sertraline. Thus, MDMA treatment may be more effective and less expensive over the long term compared to SSRIs and traditional

therapy. MAPS is collecting data throughout phase 2 and phase 3 trials to explore the economic impact of MDMA-assisted therapy as a basis for attaining insurance coverage if MDMA becomes an FDA-approved medication.

Conclusions

Following decades of sparse research, renewed interest in the use of psychoactive agents such as MDMA and other psychedelics is growing rapidly across the globe as findings from randomized controlled trials bring evidence of safety and efficacy in treating PTSD, depression, anxiety, and addictive disorders. Large studies in diverse populations are called for to replicate the results from the relatively small sample sizes in phase 2 trials. The accumulated historical and modern-day scientific evidence points to the reemergence of psychedelic compounds as extremely promising tools for patients and for a psychiatric profession in serious need of a wider range of innovative, more effective treatments. Despite the growing forward momentum, lack of government or industry funding and regulatory obstacles to researching Schedule 1 substances continue to slow the pace of discovery and delay the utilization of psychedelics in the clinical practice of medicine. It is quite remarkable that, over the past 20 years, a handful of small, non-profit organizations have been able to bring this research all the way to phase 3 trials. Through continued research, education and de-stigmatization, a greater awareness of the healing potential of these compounds should lead to increasingly widespread understanding of both the risks and benefits of psychedelic-assisted therapies.

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