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MDMA-Assisted Psychotherapy for PTSD: A Review of the Literature

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Abstract

Many people suffer from chronic, treatment-resistant posttraumatic stress disorder (PTSD). Some treatments, including exposure therapy, may not be effective for some people, and treatment dropout and suicidality are high among people for whom therapy is minimally effective. Thus, researchers are investigating 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy as a possible treatment for PTSD. MDMA has recently been studied in therapeutic contexts to find out whether its psychedelic effects can significantly benefit people with chronic, treatment-resistant PTSD. Several studies have indicated positive results—both short-term and long-term—following MDMA-assisted psychotherapy for people with PTSD. This review examines some of the published literature about MDMA-assisted psychotherapy, including a meta-analytic comparison of exposure therapy and MDMA-assisted psychotherapy as well as two clinical trials. Evidence present in this literature suggests that MDMA-assisted psychotherapy may reduce symptoms by improving patients' mood, promoting a strong therapeutic alliance, and catalyzing fear memory extinction. Although much more research is necessary to establish its efficacy and safety among a variety of populations, MDMA-assisted psychotherapy appears to be a viable treatment for some people with PTSD.

MDMA-Assisted Psychotherapy for PTSD: A Review of the Literature

Effectiveness of psychotherapy, or non-pharmacological treatment for psychological distress and disorders, is contributed to by clients' openness with therapists, willingness to confront and examine discomfort, and competence in processing emotion (Cloitre, Stovall-McClough, Miranda, & Chemtob, 2004; Doukas, D'Andrea, Doran, & Pole, 2014). For some individuals, psychotherapy involves psychological arousal, such as nervousness in front of a therapist or intense emotion during a discussion about sensitive issues (Doukas et al., 2014; Eftekhari et al., 2013). For a subgroup of clients, however, arousal may rise to an uncomfortable level (Doukas et al., 2014). This kind of arousal—or anxiety—is a symptom of posttraumatic stress disorder (PTSD) and often leads clients to avoid the triggering thought or emotion, because sympathetic nervous system arousal may feel like panic (Amoroso & Workman, 2016). However, despite efforts to suppress triggering memories and feelings of anxiety, they may still often surface. Unpredictable bouts of anxiety can interrupt one's work performance, personal relationships, and ability to relax or feel safe. PTSD can be very disturbing, but treatment may help to relieve persistent and bothersome symptoms.

One of the most popular treatments for PTSD is exposure therapy, in which a client recalls a trauma in a therapeutic setting (Amoroso & Workman, 2016; Oehen et al., 2013; Eftekhari et al., 2013). While recalling a traumatic experience in great detail, a client may consciously associate the safety and calm of the therapy setting with the memory. Over time, the traumatic memory loses some of its negative emotional energy (Dèbiec, Bush, & LeDoux, 2011) and adopts the non-triggering feeling of a client's surroundings during recall (van den Hout, Eidhof, Verboom, Littel, & Engelhard, 2014). This phenomenon is called fear memory extinction (Dèbiec et al., 2011; Young et al., 2017). Exposure therapy is effective for many people with

PTSD but for not all; sometimes, recalling the trauma triggers such a high level of arousal that the arousal itself distracts from any intervention (Amoroso & Workman, 2016; Mithoefer et al., 2011).

Between the lower threshold, at which a client experiences manageable arousal, and the upper threshold, at which a client experiences heightened anxiety and distraction, is a level of emotional engagement that is favorable for processing emotion. This zone is called the window of tolerance or optimal arousal (Mithoefer, Wagner, Mithoefer, Jerome, & Doblin, 2011; Oehen, Traber, Widner, & Schnyder, 2013). People who suffer from trauma-related disorders such as PTSD often struggle to remain within this window of tolerance (Amoroso & Workman, 2016; Buoso, Doblin, Farré, Alcázar, Gómez-Jarabo, 2008; Mithoefer et al., 2011). Some clients may attempt to remain somewhat calm while processing triggering content, but if discomfort eventually overwhelms them, the experience may be more painful than helpful and lead to avoidance of the triggering content altogether (Amoroso & Workman, 2016; Eftekhari et al., 2013). This hyperarousal complicates the therapy process, because clients worry about accessing emotionally fraught memories and catapulting themselves into a state of high arousal in which they feel only fear (Amoroso & Workman, 2016; Buoso et al., 2008; Mithoefer et al., 2011). Although exposure therapy is intended to trigger some arousal, hyperarousal can interrupt the therapy process and trap clients in a cycle of avoidance.

The cycle of accessing emotionally charged content, experiencing arousal, and promptly practicing avoidance may render psychotherapy impossible, thus frustrating clients (Amoroso & Workman, 2016). This discomfort may lead some clients to quit treatment to avoid the experiences involved in treatment (Amoroso & Workman, 2016; Oehen et al., 2013; Cloitre et al., 2004; Eftekhari et al., 2013). In other cases, even clients who keep seeking treatment avoid

disclosing personal memories, thoughts, and feelings (Amoroso, 2015; Amoroso & Workman, 2016; Oehen et al., 2013; Corey, Pisano, & Halpern, 2016). These factors contribute to the prevalence of chronic, treatment-resistant PTSD (Buoso et al., 2008; Oehen et al., 2013).

One possible augmentation to assist with the difficulties that can accompany exposure therapy for people with PTSD is 3,4-methylenedioxymethamphetamine (MDMA). MDMA is a Schedule I psychedelic that can produce feelings of empathy, intimacy, affection, and trust (Hysek et al., 2014; Wardle & de Wit, 2014). The unique effects of MDMA can lift a user's mood by boosting the positive impact of positive facial expressions and memories while simultaneously softening the negative impact of negative facial expressions and memories (Carhart-Harris et al., 2014; Wardle & de Wit, 2014). Recalling emotional memories while under the comforting influence of MDMA weakens the memory's power to induce fear (Buoso et al., 2008; Carhart-Harris et al., 2014; Mithoefer et al., 2011; Oehen et al., 2013). In addition, MDMA can strengthen interpersonal relationships, including the alliance between therapist and client (Corey et al., 2016; Hysek et al., 2014; Wardle & de Wit, 2014). Feeling less afraid and close to one's therapist primes a client for reprocessing traumatic memories (Buoso et al., 2008; Mithoefer et al., 2011). Thus, MDMA-assisted psychotherapy may promote especially effective and durable fear memory extinction in exposure therapy, and the potential risks have thus far not outweighed the associated benefits (Carhart-Harris et al., 2014; Mithoefer et al., 2011; Mithoefer et al., 2013). The effects of MDMA distinguish it as a potentially efficacious drug adjunct for psychotherapy, especially in the treatment of PTSD.

MDMA has recently been studied in therapeutic contexts to find out whether its effects can significantly benefit people with chronic, treatment-resistant PTSD. Several studies have indicated positive results—both short-term and long-term—following MDMA-assisted

psychotherapy for people with PTSD (Buoso et al., 2008; Carhart-Harris et al., 2014; Corey et al., 2016; Mithoefer et al., 2011; Mithoefer et al., 2013). The relatively high prevalence of PTSD, especially among soldiers (Amoroso & Workman, 2016; Mithoefer et al., 2011), can be associated with difficulties in maintaining employment, resisting substance abuse, and managing one or more debilitating psychological or medical disorders. More efficient and effective treatment will serve many people, both those who suffer from the disorder and the people surrounding them. However, partly due to abuse of MDMA among recreational users, concerns about post-treatment substance abuse exist. Some researchers have warned against exposing clients to MDMA, citing effects of long-term drug abuse such as aggressive behavior and depression (Parrott, 2014; Reid, Elifson, & Sterk, 2007). Indeed, MDMA brings powerful positive feelings but may also bring some potential negative effects, including acute physiological reactions (nausea, numbness, dizziness, headache, fatigue, sweating, decreased appetite) and some neurocognitive effects (disturbed sleep, higher-order cognition, memory, confusion, depressive thoughts) (Thal & Lommen, 2018). The difference between harmful and helpful effects of the drug appears to lie in controlled dosage and pairing of drug use with psychotherapy (Bouso et al., 2008; Mithoefer et al., 2011). Although recreational abuse of MDMA can have adverse effects, limited and carefully administered doses of MDMA in conjunction with psychotherapy may benefit people with chronic and treatment-resistant PTSD because it improves mood, strengthens the therapeutic alliance, and facilitates fear memory extinction. This review on MDMA-assisted psychotherapy will provide an overview of some challenges in psychotherapy for PTSD, including the debilitating mood symptoms of PTSD, challenges in forming an effective therapeutic alliance, and interruptions in fear memory extinction caused by hyperarousal. Finally, this review will consider points against MDMA-

assisted psychotherapy's suitability as a solution to the aforementioned difficulties.

Mood Symptoms of PTSD

One pervasive and painful aspect of PTSD is a cycle of fear and anxiety, in which people with PTSD experience flashbacks and nightmares punctuated by extreme anxiety at the prospect of another episode (Amoroso & Workman, 2016; Mithoefer et al., 2011; Oehen et al., 2013; Wicking et al., 2016). In the absence of fear and anxiety, many people with PTSD experience emotional numbing (Amoroso, 2015; Mithoefer et al., 2011; Oehen et al., 2013; Wicking et al., 2016). This pattern can seem inescapable and can lead to persistent depression (Eftekhari et al., 2013). In fact, many clients with PTSD wait to seek treatment until it is clear that their symptoms are persistent and disruptive (Giummarra, Lennox, Dali, Costa, & Gabbe, 2018). PTSD symptomatology is associated with high rates of functional impairment and disability, such as paralyzing fear, distracting paranoia, pervasive suicide ideation, and varied comorbid medical complications (Eftekhari et al., 2013; Mithoefer et al., 2011; Oehen et al., 2013). Furthermore, the most effective and commonly practiced psychotherapies—such as prolonged exposure therapy, Eye Movement Desensitization and Reprocessing (EMDR), cognitive or cognitive-behavioral therapy, relaxation training, and stress inoculation—can be emotionally exhausting (Amoroso, 2015; Mithoefer et al., 2011; Oehen et al., 2013). Associating the therapy process with a negative feeling—like the anxiety, fear, and helplessness involved in many traumatic memories or embarrassment or shame for seeking help—may lead some clients to discontinue treatment and suffer chronic PTSD (Amoroso & Workman, 2016; Cloitre et al., 2004; Oehen et al., 2013; Eftekhari et al., 2013; Lancaster, Teeters, Gros, & Back, 2016). Even when clients do attend therapy, they may feel distressed by the very exposure that should help them, and they often struggle to engage effectively (Eftekhari et al., 2013; Mithoefer et al., 2011). Thus, the

persistent poor mood associated with PTSD not only disables victims in their everyday lives but stands as an obstacle to effective psychotherapy.

MDMA offers hope in dealing with two issues: resistance and hyperarousal during the therapy process as well as poor mood and therapy-related anxiety outside of therapy sessions (Amoroso & Workman, 2016; Hysek et al., 2014; Mithoefer et al., 2011; Oehen et al., 2013; Wardle & de Wit, 2014). Adding the drug to psychotherapy blunts arousal and allows clients to explore their traumatic memories in greater breadth and depth (Carhart-Harris et al., 2014; Wardle & de Wit, 2014). The amphetamine-like effects of MDMA also allow a client to continue the therapy process for longer than he or she could normally tolerate it (Amoroso, 2015). After taking MDMA, study participants can react more quickly to positive stimuli and less quickly to negative stimuli, suggesting a higher tolerance for processing difficult content in therapy (Wardle & de Wit, 2014). Clients experience a calm, relaxed mood under MDMA, and this mood may enhance the process of exposure therapy by producing and maintaining positive emotions in moments when a client usually experiences anxiety (Hysek et al., 2014; Reid et al., 2007; Wardle & de Wit, 2014). Clinical trials have tested the effects of MDMA in the therapeutic setting (Mithoefer et al., 2011; Oehen et al., 2013) and have found that the drug seems to encourage openness and self-disclosure, operationalized as patterns of speech that consider one's self-concept, emotions, and experiences (Carhart-Harris et al., 2014; Corey et al., 2016; Hysek et al., 2014; Wardle & de Wit, 2014). These results suggest that MDMA dampens hyperarousal and resistance in psychotherapy clients, especially those with otherwise treatment-resistant symptoms. These effects allow for progress in treatment. A positive treatment experience may offer hope to clients whose lives were previously dominated by despair and may encourage them to return for future treatment (Amoroso & Workman, 2016). Therefore, MDMA facilitates

healing, which may increase treatment effectiveness as well as clients' willingness and ability to engage with treatment.

Challenges in Forming the Therapeutic Alliance

The therapeutic alliance, or the cooperative relationship between therapist and client, is important to the quality and success of treatment. Intuitively, a good interpersonal relationship eases the flow of trust and information. Studies have consistently found a small relationship between therapeutic alliance and treatment outcome (Doukas et al., 2014). For people with PTSD, the strength of the therapeutic alliance is one predictor of successful treatment (Cloitre et al., 2004). However, a strong therapeutic alliance is not just a precursor for good treatment but is actually an important part of treatment (Amoroso & Workman, 2016). Since reliving trauma, avoiding triggers, and experiencing hyperarousal may interfere with the personal and professional relationships of people with PTSD, treatment for PTSD may include developing a reliable network of social support; the therapeutic alliance can be a model for supportive, open, and accepting interpersonal relationships (Amoroso, 2015; Charuvastra & Cloitre, 2008; Eftekhari et al., 2013; Mithoefer et al., 2011). MDMA's strong prosocial and feel-good effects may contribute to an especially strong interpersonal bond and trust between client and therapist (Corey et al., 2016; Hysek et al., 2014; Wardle & de Wit, 2014). This interpersonal trust between client and therapist may lead to clients' openness, and those two qualities contribute to a strong therapeutic alliance and effective psychotherapy (Charuvastra & Cloitre, 2008; Corey et al., 2016; Oehen et al., 2013; Wardle & de Wit, 2014). A drug such as MDMA that helps clients connect with therapists may make therapy more effective.

Trust

Many people who suffer from PTSD struggle to form trust in interpersonal relationships (Amoroso & Workman, 2016; Charuvastra & Cloitre, 2008; Doukas et al., 2014). Often, this

difficulty has roots in the type of trauma experienced. Charuvastra and Cloitre (2008) note that PTSD may be more likely to develop or become severe in a person who has suffered trauma at the hands of another person rather than an accidental event. Data from the National Comorbidity Survey show that both men and women most often report a human-initiated action—such as sexual assault, childhood neglect, abuse, or threat of injury with a weapon—as their most distressing trauma (Charuvastra & Cloitre, 2008). Thus, the nature of a client’s trauma may diminish the trust he or she places in other people, including his or her therapist, who may be a figure of authority or power in the client’s perspective (Charuvastra & Cloitre, 2008; Doukas et al., 2014). In addition, someone who suffers from PTSD may try several types of therapy and medications without experiencing significant relief (Oehen et al., 2013). Repeated failure of treatment may lead a client to feel discouraged and hopeless, as evidenced by high treatment dropout and suicidality rates among people with chronic and treatment-resistant PTSD (Amoroso, 2015; Amoroso & Workman, 2016; Mithoefer et al., 2011; Oehen et al., 2013). Thus, some people with PTSD may not believe that the therapy process or therapist can help them.

MDMA may help clients feel trust not only for their therapists but also for the therapy process. Wardle and de Wit (2014) observed that people who take MDMA before social interaction feel more comfortable with and understood by their partners. In their study, after a brief semi-structured social interaction, participants rated the regard, empathy, and congruence that they experienced. MDMA users reported a perception that their conversation partners had higher regard and empathy for them. Oehen, Traber, Widner, and Schnyder (2013) reported a decrease in defensiveness and isolation with an increase in empathy, openness, trust, and connection during MDMA-assisted psychotherapy. These temporary but pronounced changes in affect demonstrate interpersonal trust as a result of MDMA (Hysek et al., 2014; Mithoefer et al.,

2013; Oehen et al., 2013; Wardle & de Wit, 2014). Feeling relaxed, heard, and connected encourages clients to engage with their therapists, which in turn leads clients to feel relaxed, heard, and connected. Meaningful interaction between clients and therapists build strong therapeutic alliances, which sharply increases the likelihood of a positive therapy outcome.

Trust between client and therapist in MDMA-assisted psychotherapy may make it more effective and increase treatment adherence (Doukas et al., 2014). Although this is true for any type of therapy, MDMA's unique combination of increased serotonin and oxytocin (Mithoefer et al., 2013; Wardle & de Wit, 2014) recommend MDMA as an effective and immediate way to bolster trust in the therapy process and the therapist (Corey et al., 2016; Oehen et al., 2013). MDMA in conjunction with psychotherapy may provide hope for future positive relationships and relief from discouragement in pursuing therapy (Charuvastra & Cloitre, 2008). One of MDMA's most important effects in the therapeutic setting is increased trust in the therapist and in the therapy process itself. Trust allows clients to open up, find acceptance, and experience healing.

Openness

Just as MDMA may increase trust between client and therapist, it may also increase clients' openness—or willingness to access and discuss vulnerable memories and feelings—in therapy sessions. Some of the studies reviewed here have noted a change in clients' speech patterns after administration of MDMA (Corey et al., 2016; Wardle & de Wit, 2014). Clients who take MDMA before a therapy session use positive words more often (Wardle & de Wit, 2014) and speak more about their sense of self, others' emotions, and physical touch during the session (Corey et al., 2016). Changes in what a client says in therapy signal increased openness, which can lead to more effective treatment by allowing clients and therapists to identify, discuss, and

resolve significant problems that might otherwise remain hidden (Corey et al., 2016; Mithoefer et al., 2011; Oehen et al., 2013). Indeed, Corey, Pisano, and Halpern (2016) reported a correlation between the frequency of such positive, prosocial, and self-reflective speech and improvement of symptoms. Patterns of speech reveal that clients experience less resistance and more tolerance for vulnerability during MDMA-assisted sessions.

In addition, some researchers have recognized a relationship between low Openness (O) and high Neuroticism (N), as defined by the NEO Personality Inventory, and PTSD symptoms and/or PTSD diagnosis (Wagner et al., 2017), suggesting that innate personality traits may either contribute to or be affected by the development of PTSD. High N may manifest as a tendency toward above-average anxiety, guilt, anger, envy, and dysphoria. Low O may manifest as traditional, pragmatic, or rigid patterns of thought or behavior, whereas high O often correlates with sensitivity to the inner feelings of oneself and others, as well as a disposition to self-examination (Wagner et al., 2017). Obviously, a constellation of low N and high O seems most helpful for the treatment of any psychological disorder, not just PTSD. Therefore, MDMA's ability to achieve such a constellation can be a valuable contribution in drug-assisted therapy, especially in the treatment of PTSD. Wagner et al. (2017) found that MDMA-assisted psychotherapy correlated with greater reductions in PTSD symptoms and potential long-term reversal of low O score and high N score than in the placebo. This finding suggests that MDMA-assisted psychotherapy not only encourages cooperation during the therapy process but may also contribute to enduring positive changes in personality.

Interruptions in Fear Memory Extinction

Fear memory extinction is the main function of exposure therapy for PTSD. The goal is to override a high arousal response to a traumatic or fearful memory by pairing that memory with

a low arousal state. As previously discussed, MDMA's prosocial influence encourages clients to speak openly about their traumas (Buoso et al., 2008; Carhart-Harris et al., 2014; Corey et al., 2016; Hysek et al., 2014; Wardle & de Wit, 2014). After MDMA administration, clients may exhibit less avoidance of traumatic memories (Corey et al., 2016; Oehen et al., 2013). MDMA also tends to dampen arousal, so clients may experience exposure therapy with a wider window of tolerance (Mithoefer et al., 2011; Oehen et al., 2013). Oehen et al. (2013) noted that clients who took MDMA before psychotherapy were more willing to explore and dwell on traumatic memory. This same study also detailed increased client engagement with the experience and meaning of traumatic memory. In addition, clients show greater ability to recognize, feel, and accept feelings (Corey et al., 2016; Oehen et al., 2013). Thus, MDMA enhances fear memory extinction by increasing access to emotional memories and allowing undisturbed memory recall while keeping the client in a low arousal state (Buoso et al., 2008; Carhart-Harris et al., 2014; Corey et al., 2016; Mithoefer et al., 2013; Oehen et al., 2013; Wardle & de Wit, 2014). MDMA-assisted psychotherapy exhibits superiority to unassisted exposure therapy in increased self-disclosure and heightened tolerance (Mithoefer et al., 2011; Oehen et al., 2013). MDMA beautifully combines arousal management with introspection to enable clients to process and learn from their traumatic memories.

A theoretical benefit of MDMA is enhanced recall for clients (Carhart-Harris et al., 2014; Corey et al., 2016; Mithoefer et al., 2011; Oehen et al., 2013). Memory recall during exposure therapy may feel tedious and repetitive, if not overwhelming, but practicing fear memory extinction with a memory that feels as real as possible may be helpful for lessening the effects of certain PTSD symptoms, like flashbacks. MDMA helps clients immerse themselves deeply in traumatic memories (Amoroso, 2015; Amoroso & Workman, 2016; Carhart-Harris et al., 2014;

Mithoefer et al., 2011; Oehen et al., 2016). Carhart-Harris et al. (2014) reported that MDMA affects the vividness, intensity, and emotional valence of autobiographical memories. Specifically, MDMA decreased the emotional impact of negative memories but maintained the intensity and vividness—that is, emotional potency was affected, but cognitive engagement was not (Carhart-Harris et al., 2014; Hysek et al., 2014). Wardle and de Wit (2014) found similar effects in another study of healthy participants. In contrast with other potential drug adjuncts to psychotherapy—including other stimulants and selective serotonin reuptake inhibitors (SSRIs)—MDMA increases the impact and frequency of positive emotion while having the opposite effect on negative emotion (Wardle & de Wit, 2014). This combination of effects matches the needs of clients with PTSD who undergo exposure therapy, allowing them to maintain focus on memory recall and explore traumatic memories without emotional or physiological hyperarousal.

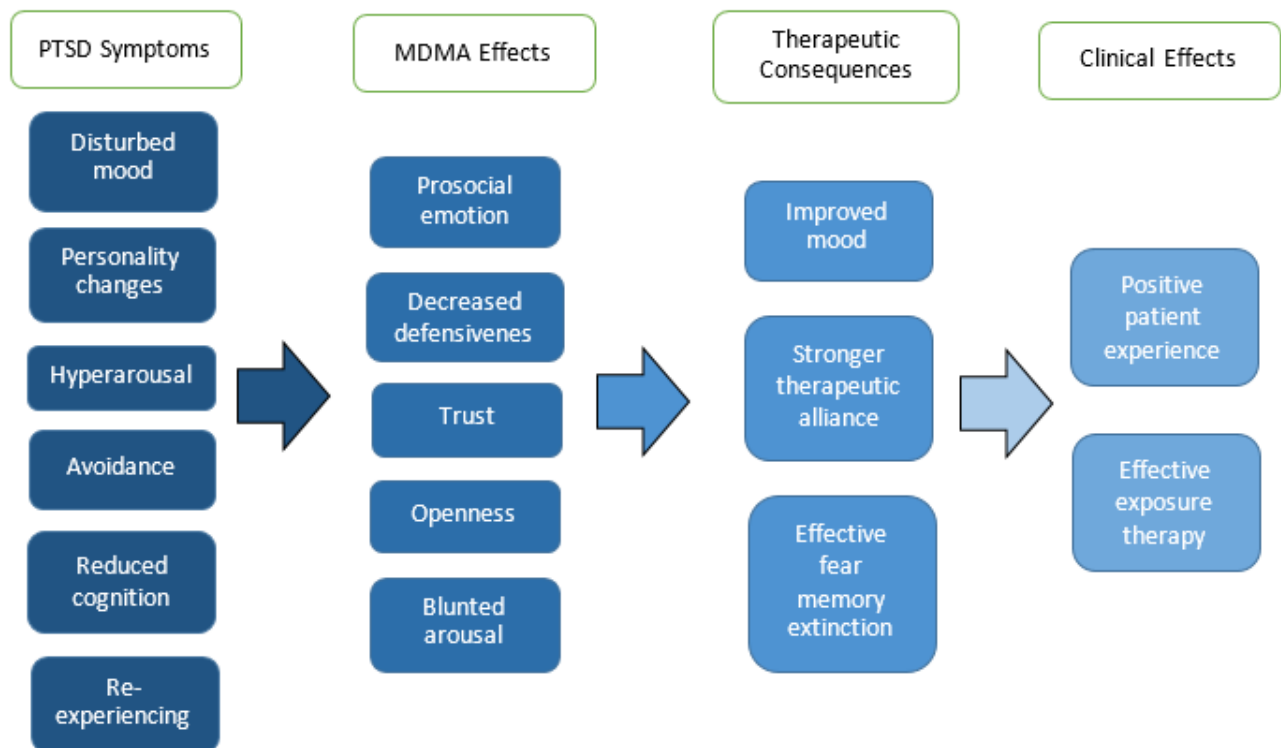


Figure 1 MDMA's psychological effects improve mood, strengthen the therapeutic alliance, and enhance fear memory extinction, leading to a positive experience for the client and to therapy that is more effective.

From a neurobiological perspective, MDMA has effects that are antithetical to the activations associated with PTSD symptoms (Amoroso, 2015; Carhart-Harris et al., 2014; Milad et al., 2009; Mithoefer et al., 2011; Oehen et al., 2013; Wicking et al., 2016). In PTSD, physiological changes in the brain support the retention rather than extinction of a traumatic memory (Milad et al., 2009; Wicking et al., 2016). Brain imaging reveals patterns of activation and deactivation in certain brain regions when people with PTSD experience anxiety and fear associated with their traumatic memories: heightened activation in the amygdala, deactivation of the anterior cingulate cortex, and deactivation of the ventromedial prefrontal cortex (Amoroso, 2015; Carhart-Harris et al., 2014; Milad et al., 2009; Mithoefer et al., 2011; Oehen et al., 2013; Wicking et al., 2016). The hippocampus also seems to be implicated in emotion and memory (Amoroso, 2015; Carhart-Harris et al., 2014; Milad et al., 2009; Mithoefer et al., 2011; Oehen et al., 2013; Wicking et al., 2016). Some studies of PTSD symptoms describe decreased hippocampal volume and activity in clients with PTSD (Carhart-Harris et al., 2014; Mithoefer et al., 2011; Wicking et al., 2016). The brain activation patterns in people with PTSD make forgetting a traumatic memory and suppressing fear responses especially difficult.

Brain-imaging studies show that the opposite activations occur when people take MDMA (Amoroso, 2015; Carhart-Harris et al., 2014; Mithoefer et al., 2011; Wicking et al., 2016; Wardle & de Wit, 2014). Several studies found decreased activity in the amygdala and increased activity in the frontal cortex (Carhart-Harris et al., 2014; Hysek et al., 2014; Mithoefer et al., 2011). The same studies that found decreased hippocampal volume and activity in clients with PTSD also found increased hippocampal activity under MDMA (Carhart-Harris et al., 2014; Mithoefer et al., 2011; Wicking et al., 2016). In addition to these patterns of brain activation/deactivation, typical neurochemical reactions to MDMA may promote clients' comfort and openness.

Research suggests that neurotransmitters and hormones like serotonin, oxytocin, norepinephrine, and dopamine are likely implicated in the calming and prosocial effects of MDMA (Carhart-Harris et al., 2014; Hysek et al., 2014; Oehen et al., 2013; Young et al., 2017). Although other drugs may stimulate or deactivate certain regions of the brain implicated in PTSD, the constellation of activation/deactivation and neurochemical effects unique to MDMA distinguishes it as an especially fitting adjunct to exposure therapy for PTSD.

Objections

Some concerns about MDMA-assisted psychotherapy include the risk of acute physiological effects, subsequent abuse, aggressive behavior, misattribution of therapy gains to the drug, or relapse after experimental sessions (Parrott, 2014; Reid et al., 2007; Thal & Lommen, 2018). The physiological effects of MDMA are wide ranging. Because MDMA is a potent stimulant and acts on the central nervous system, users will experience an altered state no matter the context in which they take the drug. Indeed, some participants reported physiological effects associated with the drug, such as nausea, fatigue, decreased appetite, and others (Mithoefer et al., 2011). However, the placebo group reported many of the same symptoms. Thus, more research will need to examine the negative side effects of MDMA itself, independent of normal fluctuations in mood and energy levels and/or placebo effects. Furthermore, MDMA's physiological effects can be managed by creating a treatment paradigm that allows for extended pre- and post-treatment observation by medical staff.

One of the psychological symptoms reported by participants who received MDMA-assisted psychotherapy for PTSD was anxiety. This raises an interesting question about the potential dangers of MDMA. Stimulants like MDMA seem to come with both a high and a subsequent low. That low can be controlled by limiting the dosage and controlling the setting, but

a client may still report a lower mood or more anxiety after treatment, even if those symptoms are only experienced in comparison with the drug state. However, this question requires much more research, because psychological distress is inherent in studies of MDMA for PTSD. On the severe end of psychological distress, MDMA has not been associated with suicidality, unlike one drug (paroxetine) currently used in the treatment of PTSD (Thal & Lommen, 2018). These considerations show that there is potential for negative side effects from administering MDMA to clients, but more research into the origin, control, treatment, and avoidance of the side effects might assuage concerns about dangers to physical and mental health.

Many people with PTSD already take medication for anxiety, depression, or disturbed sleep, but MDMA offers a different route in that it may *enhance* therapy, not just complement it as a symptom troubleshooter (Lancaster et al., 2016). Some studies reviewed here assessed risk for future substance abuse, but none found significant risk (Buoso et al., 2008; Mithoefer et al., 2011; Wardle & de Wit, 2014). One team conducted a long-term follow up and found that none of the participants of their study two years earlier had gone on to use MDMA recreationally, although one participant unsuccessfully attempted to recreate MDMA-assisted psychotherapy with a friend before discontinuing illicit use of the drug (Mithoefer et al., 2013). This study is both encouraging and concerning. Although none of the participants became recreational users, the fact that one accessed and used MDMA after treatment illustrates that there is still potential for unauthorized experimentation and/or abuse. As with most pharmacological interventions, careful administration, monitoring, and follow-up are essential.

Another concern about administering MDMA is behavioral effects. MDMA use can alter a user's behavior, and some clinicians and researchers have indicated the possibility of disinhibited and/or aggressive behavior. One study reviewed here offers a response, suggesting

that aggressive behavior associated with long-term abuse of MDMA is correlated with high dosage, polydrug use, and the context in which MDMA is taken (Reid et al., 2007). Context plays an important role in drug effects, and the street drug Ecstasy will naturally be associated with less careful usage than in the therapeutic setting. Ideally, the small, pure doses of MDMA involved in drug-assisted psychotherapy limit risk for such adverse behavioral effects. Clinical trials of MDMA-assisted psychotherapy carefully monitor participants in controlled contexts (Mithoefer et al., 2011; Oehen et al., 2013). If MDMA-assisted psychotherapy were to become available for clients, it must be conducted in clinical settings as carefully controlled as the settings of drug trials. As always, more research is needed to eliminate confounds and understand whether aggressive behavior is associated with MDMA administration in the therapeutic context rather than recreational use or abuse.

A common concern surrounding new treatments is long-term effectiveness. Relapse is common among people with PTSD, especially following pharmacological intervention only (Lancaster et al., 2016). Symptoms usually decrease somewhat following cognitive interventions, because clients learn to manage some of the symptoms rather than avoid them or suffer them. Because MDMA is an adjunct to psychotherapy used to enhance session effectiveness rather than mask symptoms, it should not show the same drop-off in symptom improvement over time. Indeed, some evidence suggests that reductions in symptoms associated with MDMA-assisted psychotherapy may prove to be long-lasting (Carhart-Harris et al., 2014; Mithoefer et al., 2013; Oehen et al., 2013). More extensive trials and rigorous follow-up will help determine if MDMA-assisted psychotherapy is more effective in the long term than the frontline treatments currently in use.

MDMA-assisted psychotherapy is limited, just like the standard therapies, in reaching the

people who might benefit. It might actually be harder to connect future locations of MDMA-assisted psychotherapy with the people who need it because of MDMA's Schedule I drug status (Giummarra et al., 2018). An additional concern is that clients might attribute improvement to the drug and disregard tools they learn for managing symptoms; however, large studies that include follow-up suggest that this is not the case (Mithoefer et al., 2013; Oehen et al., 2013; Thal & Lommen, 2018). Although drug-assisted therapy may involve some risk by nature, research reviewed here suggests that MDMA-assisted psychotherapy has produced varied benefits and few risks.

Conclusion

MDMA-assisted psychotherapy warrants much more attention and research. Future research must (1) examine the physiological, psychological, and behavioral side effects of MDMA use, (2) compare recreational use with use in the therapeutic setting, and (3) consider the most effective treatment paradigm in terms of cost, risk-to-benefit ratio, access to clients who need it, and safe and controlled drug exposure. Other directions for future research include the effects of MDMA-assisted psychotherapy within and between specific gender, race, and age groups; people with subtypes or unusual causes of PTSD; and people with varied psychological disorders. For now, prevalence of PTSD is notably high in military populations, and society may become increasingly responsible for the proper care of veterans in the wake of recent international conflict (Amoroso & Workman, 2016; Eftekhari et al., 2013; Mithoefer et al., 2011). PTSD can be chronic and devastating (Eftekhari et al., 2013; Mithoefer et al., 2011; Oehen et al., 2013), and treatment is often expensive, time-consuming, and tiring (Amoroso, 2015; Mithoefer et al., 2011; Oehen et al., 2013). The community responsible for treating people with PTSD would benefit from improving treatments or trying new treatments (Giummarra et al.,

2018). Cognitive therapies offer hope, but even the frontline treatments are not always effective; it seems prudent to continue to strive for even better outcomes. PTSD can be very challenging for both clients and therapists, and lack of progress may lead to burnout on both sides. In addition, insurance companies increasingly call for fast, effective treatment (K. Malm, personal communication, May 4, 2018). If MDMA-assisted psychotherapy proves reliable and low-risk for clients, it may become an efficient and effective therapy for PTSD.

The feel-good effects of MDMA set the stage for effective therapy. Studies of MDMA-assisted psychotherapy show increased trust and openness in the therapeutic context as well as reductions in PTSD symptoms (Amoroso & Workman, 2016; Corey et al., 2016; Mithoefer et al., 2011; Mithoefer et al., 2013; Oehen et al., 2013; Wardle & de Wit, 2014). During MDMA-assisted psychotherapy sessions, clients feel relaxed and safe, and they freely and calmly explore their traumatic memories (Mithoefer et al., 2011; Oehen et al., 2013). MDMA's combined physiological and psychological effects facilitate reprocessing of traumatic memories and extinction of fear responses (Amoroso, 2015; Hysek et al., 2014; Oehen et al., 2013; Wardle & de Wit, 2014). Furthermore, long-term follow-up research indicates limited risk for negative side effects when MDMA is administered in controlled therapeutic settings. Because of MDMA's potency and status as a Schedule I drug, care must be taken in planning, conducting, presenting, and interpreting research surrounding the controversial topic. Researchers and clinicians must account for many confounds before making any firm recommendations about MDMA-assisted psychotherapy, but preliminary research seems hopeful. MDMA's unique pharmacological and psychological effects might make it an excellent potential adjunct to psychotherapy and especially well-suited for treatment of PTSD (Amoroso, 2015; Buoso et al., 2008; Young et al., 2017; Wardle & de Wit, 2014). MDMA-assisted psychotherapy could become a solution to one

of the most devastating and debilitating chronic psychological disorders of our day.

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