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# MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder: A Review of the Literature

Erin Solomon  
erin.solomon1@gmail.com

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MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder: A Review of the Literature

Effective psychotherapy may hinge on patients' 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 most patients, psychotherapy involves some 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). In some patients, however, arousal quickly rises above psychological control and triggers sympathetic nervous system arousal (Doukas et al., 2014). This kind of arousal is common among people with Posttraumatic Stress Disorder (PTSD) and often leads patients to avoid the triggering thought or emotion (Amoroso & Workman, 2016).

The cycle of accessing emotionally charged content, experiencing arousal, and promptly practicing avoidance may render psychotherapy impossible and frustrate patients (Amoroso & Workman, 2016). Other patients may attempt to remain somewhat calm in order to process triggering content, but the experience may be more painful than helpful (Amoroso & Workman, 2016; Eftekhari et al., 2013). Between the lower threshold for arousal and upper threshold for panic 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 the window of tolerance (Amoroso & Workman, 2016; Buoso, Doblin, Farré, Alcázar, Gómez-Jarabo, 2008; Mithoefer et al., 2011). This hyperarousal complicates therapy, because patients 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).

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One of the most popular treatments for PTSD is exposure therapy, in which a patient recalls a trauma in the therapeutic setting (Amoroso & Workman, 2016; Oehen et al., 2013; Eftekhari et al., 2013). While recalling a traumatic experience in great detail, a patient 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 feeling of a patient'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). This treatment alone is effective for many people with PTSD but not all; sometimes, recall triggers such a high level of arousal that the arousal itself distracts from any intervention (Amoroso & Workman, 2016; Mithoefer et al., 2011). This discomfort may lead some patients to quit treatment in order to avoid the experiences involved in treatment altogether (Amoroso & Workman, 2016; Oehen et al., 2013; Cloitre et al., 2004; Eftekhari et al., 2013). In other cases, even patients who seek 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 solution to the difficulties with exposure therapy for people with PTSD is 3,4-methylenedioxymethamphetamine (MDMA). MDMA is a psychedelic that produces feelings of empathy, intimacy, affection, and trust (Hysek et al., 2014; Wardle & de Wit, 2014). The unique feel-good 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). In addition, MDMA can strengthen interpersonal relationships, including the alliance between

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therapist and patient (Corey et al., 2016; Hysek et al., 2014; Wardle & de Wit, 2014). Feeling unafraid and close to one's therapist primes a patient for re-processing of traumatic memories (Bouso et al., 2008; Mithoefer et al., 2011). Recalling emotional memories while under the comforting influence of MDMA weakens the memory's power to induce fear (Bouso et al., 2008; Carhart-Harris et al., 2014; Mithoefer et al., 2011; Oehen et al., 2013). Thus, MDMA-assisted psychotherapy may promote especially effective and durable fear memory extinction in exposure therapy (Mithoefer et al., 2013). The effects of MDMA distinguish it as a potentially efficacious drug adjunct for psychotherapy, especially in the treatment of PTSD (Carhart-Harris et al., 2014; Mithoefer et al., 2011).

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 (Bouso et al., 2008; Carhart-Harris et al., 2014; Corey et al., 2016; Mithoefer et al., 2011; Mithoefer et al., 2013). The difference between harmful and helpful effects of the drug lies in controlled dosage and pairing of drug use with psychotherapy (Bouso et al., 2008; Mithoefer et al., 2011). Given the increasing prevalence of PTSD, especially among soldiers (Amoroso & Workman, 2016; Mithoefer et al., 2011) and the impairment associated with the disorder, more efficient and effective treatment will serve many people, both those who suffer from the disorder and the people surrounding them. However, much more research is needed. Partly due to abuse of the drug among recreational users, concerns about post-treatment substance abuse abound. Some researchers have warned against aggressive behavior, depression, and other side effects of long-term MDMA abuse (Parrott, 2014; Reid, Elifson, & Sterk, 2007). Although recreational abuse of MDMA can have adverse effects, limited

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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 with forming an effective therapeutic alliance, and interruptions in fear memory extinction caused by hyperarousal. Finally, this review will offer evidence for MDMA-assisted psychotherapy's suitability as a solution to the aforementioned difficulties and argue against objections to this therapy.

### **Mood Alterations**

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). PTSD symptomatology is associated with high rates of functional impairment and disability (Eftekhari et al., 2013; Mithoefer et al., 2011; Oehen et al., 2013). Furthermore, even the most commonly practiced psychotherapies can be emotionally exhausting yet largely ineffective (Amoroso, 2015; Mithoefer et al., 2011; Oehen et al., 2013). Associating therapy with a negative feeling—like the panic, fear, and helplessness involved in many traumatic memories—may lead some patients to discontinue treatment and suffer chronic PTSD (Amoroso & Workman, 2016; Cloitre et al., 2004; Oehen et al., 2013; Eftekhari et al., 2013). Even when patients do attend therapy, they may feel distressed by the very exposure that should help them,

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and they often struggle to engage with therapy (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 also inhibits effective psychotherapy (Cloitre et al., 2004).

MDMA offers hopes in dealing with both issues: resistance and hyperarousal during therapy as well as decreased mood and therapy-related anxiety outside of therapy (Amoroso & Workman, 2016; Hysek et al., 2014; Mithoefer et al., 2011; Oehen et al., 2013; Wardle & de Wit, 2014). Both patients and recreational users experience a calm, relaxed mood under MDMA (Hysek et al., 2014; Reid et al., 2007; Wardle & de Wit, 2014). This mood may enhance the process of exposure therapy by producing and maintaining positive emotions (Hysek et al., 2014; Wardle & de Wit, 2014). In addition, after taking MDMA, study participants react more quickly to positive stimuli and less quickly to negative stimuli (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 found that it seems to encourage openness and self-disclosure (Carhart-Harris et al., 2014; Corey et al., 2016; Hysek et al., 2014; Wardle & de Wit, 2014). Adding the drug to psychotherapy blunts arousal and allows patients to explore their traumatic memories to greater breadth and depth (Carhart-Harris et al., 2014; Wardle & de Wit, 2014). Furthermore, the amphetamine-like effects of MDMA also allow a patient to continue therapy for longer than he or she could normally tolerate it (Amoroso, 2015). A positive treatment experience may offer hope to patients whose lives were previously dominated by despair and may encourage patients to return for future treatment (Amoroso & Workman, 2016). Thus, MDMA-assisted psychotherapy may reduce not only resistance and hyperarousal but also negative mood changes and therapy-related anxiety.

### **The Therapeutic Alliance**

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The therapeutic alliance is one of the strongest predictors of successful treatment for people with PTSD (Cloitre et al., 2004). However, a strong therapeutic alliance is not just a precursor for good treatment but actually an important part of treatment (Amoroso & Workman, 2016). Re-experiencing, avoidance, and hyperarousal may interfere with the personal and professional relationships of people with PTSD (Amoroso, 2015; Eftekhari et al., 2013; Mithoefer et al., 2011). Treatment for PTSD may include developing a reliable network of social support, and the therapeutic alliance can be a model for supportive, open, and accepting interpersonal relationships (Charuvastra & Cloitre, 2008). Due to MDMA's strong prosocial and feel-good effects, it may contribute to an especially strong interpersonal bond within the therapeutic setting (Corey et al., 2016; Hysek et al., 2014; Wardle & de Wit, 2014). In turn, MDMA-assisted psychotherapy may flourish because of interpersonal trust. Trust may lead to 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).

### **Trust**

Many people who suffer from PTSD struggle to form interpersonal bonds (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 by accident. 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 or abuse, or threat of injury with a weapon—as their most distressing trauma (Charuvastra & Cloitre, 2008). Thus, the nature of a patient's trauma may diminish the trust he or

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she places in other people, including his or her therapist, who inherently takes a position of authority and power (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 patient 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).

MDMA may help patients 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 partner. In this same study, MDMA users also more often reported that their conversation partner had high regard 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 evidence interpersonal trust as a result of MDMA (Hysek et al., 2014; Mithoefer et al., 2013; Oehen et al., 2013; Wardle & de Wit, 2014).

Trust between patient 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 both one's therapy and therapist (Corey et al., 2016; Oehen et al., 2013). MDMA in conjunction with psychotherapy may provide hope for future positive relationships and relief

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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 therapy itself.

### **Openness**

Just as MDMA may increase trust between patient and therapist, it may also increase patients' openness in sessions. Some of the studies reviewed here have noted a change in patients' speech patterns after administration of MDMA (Corey et al., 2016; Wardle & de Wit, 2014). Patients who take MDMA before a therapy session speak more about their sense of self, others' emotions, and physical touch during the session (Corey et al., 2016). During MDMA-assisted psychotherapy, patients often use positive words (Wardle & de Wit, 2014). Corey, Pisano, and Halpern (2016) reported a correlation between the frequency of such speech and improvement of symptoms. Changes in what a patient says in therapy signal increased openness, and increased openness can lead to more effective treatment (Corey et al., 2016; Mithoefer et al., 2011; Oehen et al., 2013).

In addition, some researchers have recognized a relationship between low Openness and high Neuroticism, as defined by the NEO Personality Inventory, and PTSD symptoms and/or diagnosis (Wagner et al., 2017), suggesting that innate personality traits may either contribute to or be affected by the development of PTSD. Furthermore, Wagner et al. (2017) found that MDMA-assisted psychotherapy correlated with greater reductions in PTSD symptoms and reversal of low Openness score and high Neuroticism score than did placebo plus treatment. This finding suggests that MDMA-assisted psychotherapy not only encourages honesty during therapy but also contributes to enduring, positive changes in personality (Wagner et al., 2017).

### **Fear Memory Extinction**

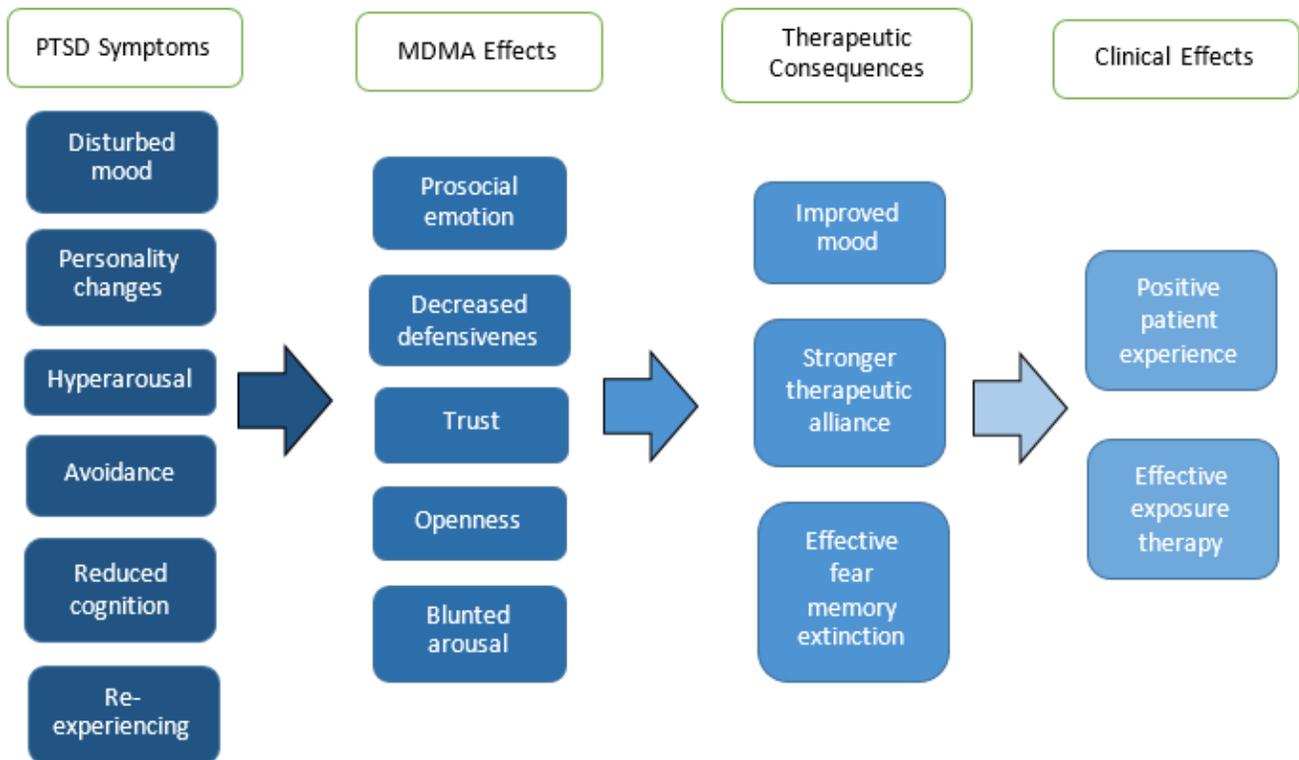
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MDMA enhances fear memory extinction by increasing access to emotional memories and allowing undisturbed memory recall (Buoso et al., 2008; Carhart-Harris et al., 2014; Corey et al., 2016; Mithoefer et al., 2013; Oehen et al., 2013; Wardle & de Wit, 2014). As previously discussed, MDMA's prosocial influence encourages patients 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, patients may exhibit less avoidance of traumatic memories (Corey et al., 2016; Oehen et al., 2013). MDMA also tends to dampen arousal, so patients may experience exposure therapy with a wider window of tolerance (Mithoefer et al., 2011; Oehen et al., 2013). Oehen et al. (2013) noted that patients who took MDMA before psychotherapy were more willing to explore and dwell on traumatic memory. This same study also detailed increased patient engagement with the experience and meaning of traumatic memory. In addition, patients show greater ability to recognize, feel, and accept feelings (Corey et al., 2016; Oehen et al., 2013). Therefore, 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 also enhances the experience of recall for patients (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 MDMA helps patients 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

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but not cognitive engagement (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 patients with PTSD who undergo exposure therapy, allowing them to maintain focus on memory recall and explore traumatic memories without emotional or physiological hyperarousal (Mithoefer et al., 2011).



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

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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 patients with PTSD (Carhart-Harris et al., 2014; Mithoefer et al., 2011; Wicking et al., 2016). These findings suggest that the brain activation patterns in people with PTSD make forgetting a traumatic memory and suppressing fear responses especially difficult (Milad et al., 2009).

Brain-imaging studies show that the opposite occurs 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 patients with PTSD also indicate 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

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activation/deactivation, typical neurochemical reactions to MDMA may promote patients' 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). While 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 (Amoroso, 2015; Buoso et al., 2008; Carhart-Harris et al., 2014; Corey et al., 2016; Mithoefer et al., 2011; Oehen et al., 2013; Wardle & de Wit, 2014).

### **Objections**

Some concerns about MDMA-assisted psychotherapy include the risk of subsequent substance abuse, aggressive behavior, or relapse after experimental sessions (Parrott, 2014; Reid et al., 2007). 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 use of the drug (Mithoefer et al., 2013). Another study suggests 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). The small, pure doses of MDMA involved in drug-assisted psychotherapy limit risk for such adverse effects, and clinical trials of MDMA-assisted psychotherapy carefully monitor participants in controlled contexts (Mithoefer et al., 2011; Oehen et al., 2013). Finally, although relapse is common among people with PTSD, some

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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).

### **Conclusion**

MDMA-assisted psychotherapy warrants much more attention and research, especially for the treatment of PTSD. Prevalence of PTSD is notably high in military populations, and society will 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). Treatment is often expensive, time-consuming, and not always effective (Amoroso, 2015; Mithoefer et al., 2011; Oehen et al., 2013). PTSD can be very challenging for both patients and therapists, and lack of progress may lead to burnout on both sides. In addition, insurance companies increasingly call for fast, effective treatment. If MDMA-assisted psychotherapy proves reliable and low-risk for patients, it may become one of the most efficient and effective therapies for PTSD (Carhart-Harris et al., 2014; Mithoefer et al., 2011; Mithoefer et al., 2013).

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). The feel-good effects of the drug set the stage for therapy. During MDMA-assisted psychotherapy sessions, patients 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

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extinction of fear responses (Amoroso, 2015; Hysek et al., 2014; Oehen et al., 2013; Wardle & de Wit, 2014). In conclusion, MDMA's unique pharmacological and psychological effects 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).

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