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Legalizing MDMA–Assisted Psychotherapy for the Treatment of Trauma–Related Mental Health Disorders

3, 4–methylenedioxymethamphetamine, or MDMA as it is commonly known, is classified as a "Schedule 1" substance in Canada and the United States. For decades, the compound has been shrouded by the stigma of being a dangerous party drug thought to kill brain cells and be severely addictive. However, when it was originally discovered, it was experimentally used in clinical settings as an adjunct to therapy. This idea is now resurfacing as researchers are turning back to MDMA as an innovative way to treat trauma-related mental health disorders like post-traumatic stress disorder. Considering the limitations of existing treatments for trauma-related disorders, MDMA's pharmacological and psychological effects, and the growing body of methodologically sound research on MDMA-assisted psychotherapy, legalizing this type of therapy could provide much-needed relief to people struggling with the severe, painful, lifelong effects of trauma and related psychological disorders.

Keywords: 3, 4–methylenedioxymethamphetamine (MDMA), MDMA-assisted psychotherapy, trauma, treatment-resistant, post-traumatic stress disorder (PTSD)

In Canada, the lifetime prevalence of post-traumatic stress disorder (PTSD) was once estimated at 9.2%, with the current PTSD rate being 2.4% as of 2008 (Ameringen et al., 2008). In fact, trauma itself has been identified as a public health issue with effects that cascade from the individual through to their relationships, the community, and even society (Magruder et al., 2017). Post-traumatic stress disorder is one of the most common and severe instances of trauma, causing high rates of disability and impaired daily functioning. In the United States, missed days at work due to PTSD resulted in losses in productivity once estimated to be over $3 billion dollars (Kessler, 2000). There is even some evidence that substance use disorders may also be strongly related to PTSD (McDevitt-Murphy, 2010). Although reasonably effective pharmacotherapies and psychotherapies are being used to currently treat this disease, recent meta-analyses reiterate the need for more effective treatments, especially for

treatment-resistant populations (Foa et al., 2013; Puetz et al., 2015; Watkins et al., 2018). In response to this critical need, certain researchers are turning to more controversial methods to treat trauma and its related disorders. 3,4-Methylenedioxy methamphetamine (MDMA)-assisted psychotherapy is one of these methods used to treat PTSD and based on the results of studies testing this approach, additional studies examining this new therapeutic intervention should be funded and supported by governments and academic institutions. Considering the shortcomings of current treatments, MDMA's documented physiological and psychological effects, and the results of studies measuring the efficacy of MDMA-assisted psychotherapy, MDMA-assisted psychotherapy is emerging as a revolutionary treatment for trauma that should be legalized for clinical use.

MDMA, or as it is colloquially referred to, "Molly" or "Ecstasy," is classified as a "Schedule 1" substance in Canada and the United States (Ameringen et al., 2008; Danforth et al., 2016). For decades, the compound has been shrouded by the stigma of being a dangerous party drug that can cause neurotoxicity (Danforth et al., 2016). However, when it was originally discovered, it was experimentally used in clinical settings as an adjunct to therapy (Greer & Tolbert, 1986). This approach is now resurfacing as researchers are reconsidering MDMA as an innovative way to treat trauma-related mental health disorders like PTSD (Danforth et al., 2018; Mithoefer et al., 2011; Oehen et al., 2013; Ot'alora G et al., 2018). Alexander Shulgin, a chemist, was the first to report the psychological effects of MDMA as he explored its ability to induce controlled altered states of consciousness (Amoroso, 2015; Greer & Tolbert, 1986). After this, Dr. George Greer and Requa Tolbert were the first people to study MDMA and administer it in a clinical setting (Greer & Tolbert, 1986). Before this, throughout the mid-1970s, MDMA was legally provided by mental health professionals to thousands of people as a complement to therapy. Although positive effects were reported anecdotally, no methodologically sound research was published (Danforth et al., 2016). Amid mounting concern about the abuse potential of MDMA and the ongoing "War on Drugs" sparked by President Nixon in the United States, MDMA was labeled as a "Schedule 1" substance (Cutcliffe, 2014). The studies and literature in the decades to follow largely focused on whether the use of MDMA could result in neurotoxicity and brain damage (Danforth et al., 2016).

Although the stigma of its street reputation touted MDMA as a dangerous, addictive drug, all subjects in Greer and Tolbert (1986) reported some benefit from the experience. The majority of subjects reported a variety of cognitive improvements, including a more open worldview, insight into one's personal patterns as psychological issues, and even an enhanced ability for self-examination. The methodology from Greer and Tolbert (1986) differed from other studies as the dosage was controlled and used in conjunction with psychotherapy. Decades later, studies have begun to build on this model by administering MDMA as an adjunct to psychotherapy for small samples of people suffering from various levels of trauma;

with results indicating lasting and significant improvement in the subjects (Bouso et al., 2008; Mithoefer, 2011). This begs the question of whether this compound should be legalized to help those suffering from PTSD and other trauma-related diseases. Based on the limitations of current treatments, the indications that MDMA is physiologically and psychologically tailored to treat trauma, and the growing body of sound research demonstrating high efficacy rates for MDMA-assisted psychotherapy, legalizing this innovative intervention could be a positive step in alleviating the suffering of people struggling with severe trauma-related mental health issues.

Currently, PTSD is treated using both pharmacological and psychological approaches. The most common pharmacotherapies used to treat PTSD involve selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (Puetz et al., 2015). These are prescribed to treat the resulting anxious and depressive symptoms that normally accompany PTSD (Hutchison & Bressi, 2020). Meta-analyses have found that although these medications do produce a statistically significant change in PTSD symptoms with a modest effect size, some studies in contrast indicate that psychotherapies, such as exposure therapy, had higher efficacy (Foa et al., 2013). While these pharmacotherapies are somewhat effective, reviews of relevant literature still call for more research into pharmacological interventions for treatment-resistant PTSD, particularly those that can address cognitive symptoms, such as avoidance and intrusive, upsetting memories (Foa et al., 2013; Puetz et al., 2015). Therefore, the modest and selective improvement in symptoms with pharmacotherapy, along with the inability to treat the root cause of the disorder, leaves a gap in the PTSD therapeutic milieu that some psychological treatments attempt to address.

The most well-known psychological treatments for PTSD are cognitive behavioural therapy (CBT), Eye-Movement Desensitization and Reprocessing (EMDR) therapy, and psychodynamic therapy (Foa et al., 2013). Reviews of accepted psychotherapies to treat PTSD have found that trauma-focused methods like cognitive processing therapy and prolonged exposure therapy are most effective (Paintain & Cassidy, 2018; Steenkamp et al., 2015; Tran & Gregor, 2016). Both of these psychotherapeutic modalities are built around the concept of exposure therapy (Steenkamp et al., 2015). This component of therapy involves provoking and eliminating involuntary, overactive fear responses. This is achieved by guiding patients through re-experiencing the traumatic event in some way within the therapeutic setting, so that they may learn to re-process the feelings, emotions, and triggers associated with the event (Foa et al., 2013; Steenkamp et al., 2015). Re-exposure to the traumatic memory can be evoked in a few different ways; however, regardless of the method, the patient must be emotionally engaged enough to stimulate the activation of their autonomic fear response without overwhelming them with the anxiety of reliving the experience (Foa et al., 2013; Mithoefer et al., 2011). Those who suffer from PTSD are often susceptible to states of emotional numbness

and extreme anxiety, with very little space between thresholds in either direction. This space has been referred to as the optimal arousal zone or "Window of Tolerance" (Corrigan et al., 2011). However, studies and reviews have shown that the anxiety induced from exposure and the fear of re-traumatization often leads to high rates of dropout and deters clinicians from using it in their practices (Paintain & Cassidy, 2018; Zoellner et al., 2011). This is where MDMA may find its role in the PTSD therapeutic milieu. The emerging research on MDMA is starting to convincingly exhibit how this stigmatized compound can reshape the way we process trauma and the mechanisms by which this works. With an understanding of the shortcomings of pharmacological treatments and the challenges involved with best-practice psychological treatments, analyzing the known physiological and psychological effects of MDMA can illustrate how MDMA will address these limitations.

Studies seeking to unveil the physiological and psychological mechanisms of action of MDMA have begun to outline how MDMA is tailored for use in the treatment of trauma-related disorders like PTSD. MDMA has been found to stimulate increased levels of oxytocin (Hysek et al., 2014), which is a compound that has a rich evolutionary history of being associated with pair-bonding, attachment, and pro-social feelings and behaviour in humans and other mammals (Danforth et al., 2016; MacDonald & MacDonald, 2010). Oxytocin and MDMA are also both associated with reducing activation and stimulation of the part of the brain that is responsible for modulating the brain's response to fear-inducing stimuli, and our interpretation of negative emotions in others (Gamma, 2000; Hysek et al., 2014; MacDonald & MacDonald, 2010). These studies show how MDMA and its stimulation of oxytocin might address gaps in current treatment plans by helping to create a strong and healthy therapeutic relationship between the client and therapist, while also facilitating intense emotional engagement in the client as they attempt to address traumatic events in the therapeutic context.

The psychological effects of MDMA may be the best indication of how MDMA could be useful in treating trauma. Early studies on MDMA indicated that it increased emotional engagement, self-acceptance and self-confidence, enhanced one's ability for honest self-reflection and communication, while also increasing feelings of closeness and connection to others (Greer & Tolbert, 1986). Its ability to increase sensory awareness may even be beneficial in allowing the patient to re-experience the traumatic event more authentically during exposure, as such memories often involve vivid sensory information. In another study, participants on MDMA were asked to remember their best and worst memories while functional magnetic resonance imaging (fMRI) was used to detect unique changes in blood flow in the brain (Carhart-Harris et al., 2014). These researchers discovered that the participants found their worst memories more tolerable and their best memories even more pleasurable and vivid (Carhart-Harris et al., 2014). All of these effects are extremely valuable in fostering a strong relationship between the therapist and patient, with the

potential of widening the optimal arousal zone for inducing exposure and reprocessing traumatic memories. These reported effects of MDMA, along with increased interest in this compound's utility to treat trauma, have spurred researchers to conduct studies that can demonstrate the efficacy of MDMA-assisted psychotherapy as a treatment for PTSD.

The legalization of a drug for clinical purposes is based upon empirically proven data that confirms the safety and efficacy of a particular treatment. Studies addressing these concerns for MDMA-assisted psychotherapy are showing to be very promising, with results that are demonstrating reductions in symptoms that are relatively greater than those reported by meta-analyses for current treatments of PTSD (Mithoefer et al., 2018; Puetz et al., 2015; Tran & Gregor, 2016). One of the first studies to report such findings was a randomized, double-blind, control trial on subjects that had chronic, treatment-resistant PTSD (Mithoefer et al., 2011). After just one session of MDMA-assisted psychotherapy, mean scores on the Clinician-Administered PTSD Scale (CAPS-IV) for the experimental group were reduced from 79.2 to 37.0, compared to a five-point reduction to 74.1 for the placebo group (Mithoefer et al., 2011). These benefits were strengthened by the second session and sustained until the 2-month follow up, with 10 of the 12 people in the experimental group not even meeting the CAPS-IV threshold for a PTSD diagnosis (Mithoefer et al., 2011). This is quite significant as the participants, on average, had been suffering from PTSD for 19 years and had been resistant to the normal forms of treatment. Additionally, attention, information processing, memory, language, and visuo-spatial abilities were assessed before the experimental sessions and at the 2-month follow up, and there were no signs of any functional cognitive impairment (Mithoefer et al., 2011). To determine the lasting effect of these results, a long-term follow-up of this study was conducted approximately three years after the 2-month follow-up sessions were originally completed (Mithoefer et al., 2013). After the 3-year period, 14 of the 16 formerly treatment-resistant subjects maintained significant decreases in the CAPS-IV score (Mithoefer et al., 2013). This study, although conducted with self-reported measures, also confirmed that there were no persisting functional cognitive impairments, nor were there attempts to find MDMA outside the clinical setting (Mithoefer et al., 2013).

Based on promising safety and efficacy results from the previous studies (Mithoefer et al., 2011; 2013), Phase 2 randomized, controlled, double-blind, dose-response studies trials were granted approval in the United States; a critical stage in new drug legalization (Hutchison & Bressi, 2020). One such study compared groups that received three different doses of MDMA (Ot'alora G et al., 2018). Two active-dose groups each received doses of either 100 mg or 125 mg of MDMA, while one comparator group received a 40 mg dose, which was considered to produce enough drug effect to be an appropriate blind without having a significant effect on the CAPS-IV score (Ot'alora G et al., 2018). Results of the CAPS-IV scores, one month after the second active dose, did appear to be dose-respondent with very small changes

detected in the 40 mg group compared to the 100 mg and 125 mg active dose groups (Ot'alora G et al., 2018). More significantly, 12 months later, 19 of 25 participants did not meet the CAPS-IV score criteria for a PTSD (Ot'alora G et al., 2018). These findings are important as the participants had been suffering from PTSD for an average of 29.4 years and had been resistant to currently accepted treatments including, but not limited to, CBT, EMDR, and pharmacotherapy. Mithoefer et al. (2018) also published the results of a Phase 2 trial with slightly different dose groups, with the active control being given 30 mg of MDMA and the experimental groups receiving either 75 mg or 125 mg. After the two blinded sessions of MDMA-assisted psychotherapy, seven of seven subjects in the 75 mg group, and eight of 12 in the 125 mg group did not meet the criteria for a diagnosis of PTSD (Mithoefer et al., 2018). One year later, 16 of the 24 who completed follow-up assessments were no longer diagnosable with PTSD (Mithoefer et al., 2018). This prolonged improvement in symptoms again highlights a key finding considering participants were first responders and veterans who had been unresponsive to multiple different treatment combinations (Mithoefer et al., 2018). These results have spurred clinicians and lawmakers alike to see the possible benefits of this therapy for people suffering from severe and chronic bouts of PTSD. This was further exemplified when the Food and Drug Administration (FDA) recently granted MDMA what is known as Breakthrough Therapy Designation in the United States (Hutchison & Bressi, 2020).

Although the United States's FDA granted MDMA Breakthrough Therapy Designation in 2017, it remains a Schedule 1 illegal substance across North America (Hutchison & Bressi, 2020). Ever since its placement in this category by the United States's Drug Enforcement Agency in 1986, the greatest concerns among scientists and researchers regarding MDMA have been that it can cause neurotoxicity in the brain and had a high potential for abuse (Danforth et al., 2016). MDMA's reputation as a party drug commonly used at raves and in other uncontrolled situations perpetuated these views and informed much of the ongoing literature at the time. Many of the studies that support these notions use animal subjects such as rats and monkeys and employ continuous, binge administration of MDMA over many days or even a couple of weeks (Cadoni et al., 2017; Danforth et al., 2016; Ricaurte et al., 2002). The doses given were also much higher than the equivalent human doses and were sometimes administered intravenously, which greatly alters the nature of the drug effects, and is generally never done in human cases (Amoroso, 2015; Danforth et al., 2016). In fact, the authors of one of the more influential studies claiming to have found evidence for persistent MDMA-related neurotoxic effects in squirrel monkeys retracted the article and its results a few years later, citing that they had mistakenly been administering methamphetamine to the monkeys and not MDMA (Ricaurte et al., 2003).

Another common criticism of legalizing MDMA for any kind of therapeutic use is its abuse potential, with studies upholding this claim often drawing from

recreational Ecstasy users who reported to health professionals or other substance use disorder (SUD) programs (Cottler et al., 2001; Danforth et al., 2016; Jerome et al., 2013; Parrott, 2013). Sampling from recreational users who reported substance abuse issues introduces several confounding variables, including varying and extreme dosages, multiple substance use or "stacking," and dangerous environmental conditions (Danforth et al, 2016). On the contrary, of all participants in the studies that used MDMA as a clinical adjunct to psychotherapy, only three reported MDMA use after the experimental sessions and each only one time (Mithoefer et al., 2018, 2013; Oehen et al., 2013; Ot'alora G et al., 2018). One of these studies followed up at 2-, 6-, and 12-month intervals with urine drug tests and confirmed that no participants sought out and used MDMA after the subject treatment (Oehen et al., 2013). In some reports of MDMA-assisted psychotherapy and its effects, subjects reported a reduced desire for other substances like alcohol, marijuana, or coffee (Bouso et al., 2008; Greer & Tolbert, 1986). Considering its ability to address trauma, MDMA-assisted psychotherapy has actually been considered to treat the root causes of substance abuse (Jerome et al., 2013). Regardless—bearing in mind the relatively mild to moderate abuse liability for MDMA, its availability as a street drug, and the high rate at which PTSD and SUD comorbidly occur—it should only be administered to those who are not currently struggling with substance use issues (Hutchison & Bressi, 2020). Accordingly, all studies testing the effectiveness of MDMA-assisted psychotherapy took this into consideration, excluding any subjects who had active substance abuse issues within 60 days of the treatments (Hutchison & Bressi, 2020). Ot'alora G et al. (2018) postulated that the process of remembering and reflecting on traumatic events in one's past creates an experience that is not completely devoid of unpleasant feelings like anxiety, sadness, or depression, which in turn, may reduce the likelihood of subjects seeking MDMA outside of the clinical setting (Ot'alora G et al., 2018).

For decades MDMA was relegated to the peripheries of society as a party drug thought to kill brain cells and to be severely addictive. As such, the potential therapeutic benefits sensed by a few forward-thinking scientists when MDMA was first discovered were stifled by a stigma that persists to this day. However, over time, studies addressing these concerns have shown that this socially conditioned fear was based on information with questionable validity (Danforth et al., 2018). Lately, more researchers are interested in conducting methodologically sound experiments that are aimed at shedding light on the way MDMA works in the body and mind (Bedi et al., 2009; Carhart-Harris et al., 2014; Hysek et al., 2014; Kuypers et al., 2017). Furthermore, results of studies exploring the power of MDMA-assisted psychotherapy to treat PTSD are proving so efficacious that it now has Breakthrough Therapy status in the United States (Hutchison & Bressi, 2020). Phase 3 trials attempting to replicate benefits on a larger scale are in the process of being completed, which is a critical step in new therapeutic drug discovery (Hutchison & Bressi, 2020). If these trials are

successful, they will provide a strong case for the legalization of this therapy for PTSD. MDMA is a compound that, when applied appropriately, has the potential to dramatically help many people struggling with the severe, painful, lifelong effects of trauma and related psychological disorders. Legalizing MDMA as an adjunct to psychotherapy would be the first revolutionary step in learning more about how this misunderstood compound could be applied to reduce the suffering of so many.

REFERENCES

Ameringen, M. V., Mancini, C., Patterson, B., & Boyle, M. H. (2008). Post-traumatic stress disorder in Canada. *CNS Neuroscience & Therapeutics*, 14(3), 171–181. https://doi.org/10.1111/j.1755-5949.2008.00049.x

Amoroso, T. (2015). The psychopharmacology of ±3,4 methylenedioxymeth-amphetamine and its role in the treatment of posttraumatic stress disorder. *Journal of Psychoactive Drugs*, 47(5), 337–344. https://doi.org/10.1080/02791072.2015.1094156

Bedi, G., Phan, K. L., Angstadt, M., & de Wit, H. (2009). Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology*, 207(1), 73–83. http://dx.doi.org/10.1007/s00213-009-1635-z

Bouso, J. C., Doblin, R., Farré, M., Alcázar, M. Á., & Gómez-Jarabo, G. (2008). MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder. *Journal of Psychoactive Drugs*, 40(3), 225–236. https://doi.org/10.1080/02791072.2008.10400637

Cadoni, C., Pisanu, A., Simola, N., Frau, L., Porceddu, P. F., Corongiu, S., Dessì, C., Sil, A., Plumitallo, A., Wardas, J., & Di Chiara, G. (2017). Widespread reduction of dopamine cell bodies and terminals in adult rats exposed to a low dose regimen of MDMA during adolescence. *Neuropharmacology*, 123, 385–394. https://doi.org/10.1016/j.neuropharm.2017.06.008

Carhart-Harris, R. L., Wall, M. B., Erritzoe, D., Kaelen, M., Ferguson, B., De Meer, I., Tanner, M., Bloomfield, M., Williams, T. M., Bolstridge, M., Stewart, L., Morgan, C. J., Newbould, R. D., Feilding, A., Curran, H. V., & Nutt, D. J. (2014). The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. *The International Journal of Neuropsychopharmacology*, 17(4), 527–540. https://doi.org/10.1017/S1461145713001405

Corrigan, F. M., Fisher, J. J., & Nutt, D. J. (2011). Autonomic dysregulation and the Window of Tolerance model of the effects of complex emotional trauma. *Journal of Psychopharmacology*, 25(1), 17–25. https://doi.org/10.1177/0269881109354930

Cottler, L. B., Womack, S. B., Compton, W. M., & Ben-Abdallah, A. (2001). Ecstasy abuse and dependence among adolescents and young adults: applicability and reliability of DSM-IV criteria. *Human Psychopharmacology: Clinical and Experimental*, 16(8), 599–606. https://doi.org/10.1002/hup.343

Cutcliffe, J. R., & Saadeh, B. (2014). Grounded in evidence or a puritanical legacy: A critique of twenty-first-century US drug policy. *Mental Health and Substance Use*, 7(3), 195–206. http://dx.doi.org/10.1080/17523281.2013.826271

Danforth, A. L., Grob, C. S., Struble, C., Feduccia, A. A., Walker, N., Jerome, L., Yazar-Klosinski, B., & Emerson, A. (2018). Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: A randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology*, 235, 3137–3148. https://doi.org/10.1007/s00213-018-5010-9

Danforth, A. L., Struble, C. M., Yazar-Klosinski, B., & Grob, C. S. (2016). MDMA-assisted therapy: A new treatment model for social anxiety in autistic adults. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 64, 237–249. https://doi.org/10.1016/j.pnpbp.2015.03.011

Foa, E. B., Gillihan, S. J., & Bryant, R. A. (2013). Challenges and successes in dissemination of evidence-based treatments for posttraumatic stress: Lessons learned from prolonged exposure therapy for PTSD. *Psychological Science in the Public Interest*, 14(2), 65–111. https://doi.org/10.1177/1529100612468841

Gamma, A. (2000). 3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [H215O]-PET in healthy humans. *Neuropsychopharmacology*, 23(4), 388–395. https://doi.org/10.1016/S0893-133X(00)00130-5

Greer, G., & Tolbert, R. (1986). Subjective reports of the effects of MDMA in a clinical setting. *Journal of Psychoactive Drugs*, 18(4), 319–327. http://dx.doi.org/10.1080/02791072.1986.10472364

Hutchison, C. A., & Bressi, S. K. (2018). MDMA-assisted psychotherapy for posttraumatic stress disorder: Implications for social work practice and research. *Clinical Social Work Journal*, 48, 421–430. https://doi.org/10.1007 /s10615-018-0676-3

Hysek, C. M., Schmid, Y., Simmler, L. D., Domes, G., Heinrichs, M., Eisenegger, C., Preller, K. H., Quednow, B. B., & Liechti, M. E. (2014). MDMA enhances emotional empathy and prosocial behavior. *Social Cognitive and Affective Neuroscience*, 9(11), 1645–1652. https://doi.org/10.1093/scan/nst161

Jerome, L., Schuster, S., & Yazar-Klosinski, B. B. (2013). Can MDMA play a role in the treatment of substance abuse? *Current Drug Abuse Reviews*, 6(1), 54–62. https://doi.org/10.2174/18744737112059990005

Kessler, R. C. (2000). Posttraumatic stress disorder: The burden to the individual and to society. *The Journal of Clinical Psychiatry*, 61(Suppl 5), 4–12.

Kuypers, K. P., Dolder, P. C., Ramaekers, J. G., & Liechti, M. E. (2017). Multifaceted empathy of healthy volunteers after single doses of MDMA: A pooled sample of placebo-controlled studies. *Journal of Psychopharmacology*, 31(5), 589–598. https://doi.org/10.1177/0269881117699617

MacDonald, K., & MacDonald, T. M. (2010). The peptide that binds: A systematic review of oxytocin and its prosocial effects in humans. *Harvard Review of Psychiatry*, 18(1), 1–21. https://doi.org/10.3109/10673220903523615

Magruder, K. M., McLaughlin, K. A., & Borbon, D. L. E. (2017). Trauma is a public health issue. *European Journal of Psychotraumatology*, 8(1). https://doi.org/10.1080/20008198.2017.1375338

McDevitt-Murphy, M. E., Murphy, J. G., Monahan, C. M., Flood, A. M., & Weathers, F. W. (2010). Unique patterns of substance misuse associated with PTSD, depression, and social phobia. *Journal of Dual Diagnosis*, 6(2), 94–110. https://doi.org/10.1080/15504261003701445

Mithoefer, M. C., Mithoefer, A. T., Feduccia, A. A., Jerome, L., Wagner, M., Wymer, J., Holland, J., Hamilton, S., Yazar-Klosinski, B., Emerson, A., & Doblin, R. (2018). 3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: A randomised, double-blind, dose-response, phase 2 clinical trial. *The Lancet Psychiatry*, 5(6), 486–497. https://doi.org/10.1016/S2215-0366(18)30135-4

Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., & Doblin, R. (2011). The safety and efficacy of ±3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: The first randomized controlled pilot study. *Journal of Psychopharmacology*, 25(4), 439–452. https://doi.org/10.1177/0269881110378371

Mithoefer, M. C., Wagner, M. T., Mithoefer, A. T., Jerome, L., Martin, S. F., Yazar-Klosinski, B., Michel, Y., Brewerton, T. D., & Doblin, R. (2013). Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: A prospective long-term follow-up study. *Journal of Psychopharmacology*, 27(1), 28–39. https://doi.org/10.1177/0269881112456611

Oehen, P., Traber, R., Widmer, V., & Schnyder, U. (2013). A randomized, controlled pilot study of MDMA (±3,4-methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *Journal of Psychopharmacology*, 27(1), 40–52. https://doi.org/10.1177/0269881112464827

Ot'alora G, M., Grigsby, J., Poulter, B., Van Derveer, J. W., Giron, S. G., Jerome, L., Feduccia, A. A., Hamilton, S., Yazar-Klosinski, B., Emerson, A., Mithoefer, M. C., & Doblin, R. (2018). 3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A

randomized phase 2 controlled trial. *Journal of Psychopharmacology*, 32(12), 1295–1307. https://doi.org/10.1177/0269881118806297

Paintain, E., & Cassidy, S. (2018). First-line therapy for post-traumatic stress disorder: A systematic review of cognitive behavioural therapy and psychodynamic approaches. *Counselling and Psychotherapy Research*, 18(3), 237–250. https://doi.org/10.1002/capr.12174

Parrott, A. C. (2013). Human psychobiology of MDMA or 'Ecstasy': An overview of 25 years of empirical research. *Human Psychopharmacology: Clinical and Experimental*, 28(4), 289–307. https://doi.org/10.1002/hup.2318

Puetz, T. W., Youngstedt, S. D., & Herring, M. P. (2015). Effects of pharmacotherapy on combat-related PTSD, anxiety, and depression: A systematic review and meta-regression analysis. *PLOS ONE*, 10(5), e0126529. https://doi.org/10.1371/journal.pone.0126529

Ricaurte, G. A., Yuan, J., Hatzidimitriou, G., Cord, B. J., & McCann, U. D. (2002). Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("Ecstasy"). *Science*, 297(5590), 2260–2263. https://doi.org/10.1126/science.1074501

Ricaurte, G. A., Yuan, J., Hatzidimitriou, G., Cord, B. J., & McCann, U. D. (2003). Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("ecstasy"): Retraction. *Science*, 301(5639), 1479. http://doi.org/10.1126/science.301.5639.1479b

Steenkamp, M. M., Litz, B. T., Hoge, C. W., & Marmar, C. R. (2015). Psychotherapy for military-related PTSD: A review of randomized clinical trials. *JAMA*, 314(5), 489–500. https://doi.org/10.1001/jama.2015.8370

Tran, U. S., & Gregor, B. (2016). The relative efficacy of bona fide psychotherapies for post-traumatic stress disorder: A meta-analytical evaluation of randomized controlled trials. *BMC Psychiatry*, 16(266). https://doi.org/10.1186/s12888-016-0979-2

Watkins, L. E., Sprang, K. R., & Rothbaum, B. O. (2018). Treating PTSD: A review of evidence-based psychotherapy interventions. *Frontiers in Behavioral Neuroscience*, 12(258). https://doi.org/10.3389/fnbeh.2018.00258

Zoellner, L. A., Feeny, N. C., Bittinger, J. N., Bedard-Gilligan, M. A., Slagle, D. M., Post, L. M., & Chen, J. A. (2011). Teaching trauma-focused exposure therapy for PTSD: Critical clinical lessons for novice exposure therapists. *Psychological Trauma: Theory, Research, Practice, and Policy*, 3(3), 300–308. https://doi.org/10.1037/a0024642