REVIEW ARTICLE

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MDMA to Treat PTSD in Adults

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ABSTRACT *~ Post-traumatic stress disorder (PTSD) has become one of the most common psychiatric diagnosis in the United States specifically within the veteran population. The current treatment options for this debilitating diagnosis include trauma-focused psychotherapies along with selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI).[1] MDMA has recently been shown as a novel therapeutic agent with promisingly results in the treatment of PTSD. MDMA is a psychoactive compound traditionally categorized as a psychedelic amphetamine that deemed a Schedule I controlled substance in the 1980s. Prior to its status as a controlled substance, it was used by psychotherapists for an array of psychiatric issues. In more recent times, MDMA has resurfaced as a potential therapy for PTSD and the data produced from randomized, controlled trials back the desire for MDMA to be utilized as an effective pharmacologic therapy in conjunction with psychotherapy.[2]* Psychopharmacology Bulletin. *2021;51(3):125–149.*

Introduction

PTSD Defined & Current Treatment Options

Post-traumatic stress disorder (PTSD), as defined by the DSM-5, is a mental health disorder that emerges from exposure to a traumatic event, particularly: actual or threatened death, serious injury, and/or sexual violence. PTSD is characterized

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by recurring and distressing symptoms, which last a minimum of one month following the traumatic episode. PTSD symptoms include dissociative reactions, distressing dreams, perpetual avoidance of trauma-related stimuli, psychological distress, negative adaptations in cognition and mood, and evident variation in arousal and reactivity.

The American Psychiatric Association (APA) recommends trauma-focused psychotherapies (e.g., cognitive processing therapy and prolonged exposure therapy) as the first means of treatment for PTSD—along with selective serotonin reuptake inhibitors (SSRIs) (e.g., paroxetine & sertraline) as the first line of pharmacologic intervention. The selective-norepinephrine reuptake inhibitor (SNRI), venlafaxine, has also been used with comparable effect to SSRIs. In terms of efficacy, however, only 20–30% of PTSD patients maintained a meaningful clinical response after using this class of treatment.[1,3,4] Other treatment options include α-1-adrenoreceptor antagonists, benzodiazepines, and neurostimulation; however, the efficacy of these treatment options remains uncertain.[5]

(±)-MDMA Basic Drug Info

(±)-3,4-Methylenedioxymethamphetamine ((±)-MDMA) is a psychoactive compound traditionally categorized as a psychedelic amphetamine; this is due to its chemical relation with various psychostimulants (e.g., amphetamine) and hallucinogens (e.g., mescaline).[6] While the subjective effects of (±)-MDMA are reminiscent of these psychoactive compounds, the nature of its phenomenology was deemed sufficiently unique to warrant a new classification as an *entactogen*: a term coined by David Nichols meaning, "to touch within".[7]

(±)-MDMA is available as a tablet, capsule, powder, or liquid and can be administered orally or intravenously, though the compound is typically administered orally in the hydrochloride salt form to humans.[8] (±)-MDMA is generally administered to humans in doses ranging from 75–150 mg, which yield subjective effects that persist for 4–6 hours after oral administration.[9–12] These effects include: increased prosocial behavior, decreased aggression, lowered social inhibition, enhanced response to the positive emotions of others, increased alertness, and positive mood.[13–15]

(±)-MDMA History & Novel Applications

(±)-MDMA was first synthesized in 1912 by the German pharmaceutical company Merck.[16] While medical literature traditionally

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supposed that Merck synthesized (±)-MDMA in order to develop an appetite suppressant,[17,18] an analysis of the original documents in Merck's historical archive proved that the drug was envisioned as a precursor in the synthesis of a novel hemostatic agent.[19] The first pharmacological test using (±)-MDMA was not executed until decades later,[19] with the first formal animal study using (±)-MDMA—sponsored by the U.S. army—taking place secretly in 1953; however, this covert study was not actually published until 1973.[20,21] During the 1970s, the psychoactive effects of (±)-MDMA gained increased attention with the commencement of the first (±)-MDMA studies in humans—after which several psychotherapists adopted its use as an adjunct to psychotherapy.[16,22,23] However, this practice was quickly halted in 1985 after the recreational use of (±)-MDMA increased radically, and growing evidence indicated that MDA, a compound structurally associated with (±)-MDMA, was neurotoxic and potentially lethal.[24,25] With insubstantial data regarding the safety of (±)-MDMA and the surging use of ecstasy throughout large cities in the mid-west, senators urged the DEA to place (±)-MDMA on the list of controlled substances in 1985; this action was largely due to (±)-MDMA's chemical similarity to MDA.[24] Despite mounting backlash from the scientific community, (±)-MDMA was permanently assigned schedule I status in 1988, effectively pausing research on the compound's potential therapeutic use.[6]

While contemporary research has since revealed that (±)-MDMA is less toxic than its counterpart MDA, (±)-MDMA's toxicity is still under question—as its use in non-medical settings has been linked to fatalities resulting from hepatic toxicity,[26,27] cardiovascular toxicity,[28] cerebral toxicity resulting from hyponatremia,[29,30] hyperpyrexia,[17] and serotonin syndrome.[31] To clarify, most cases of serious toxicity have involved extreme dosing (i.e., blood levels of (±)-MDMA much higher than the standard recreational or therapeutic dose), drug cutting (i.e., (±)-MDMA is cut with another risky substance), or hazardous settinge.[17] That being said, there have been zero deaths or severely harmful events in any of the medical (±)-MDMA studies conducted since research originated in the 1980s.[32]

Despite (±) MDMA's controversial history, contemporary clinical research trumpets the promise of (±)-MDMA-assisted psychotherapy's in treating a myriad of psychiatric disorders.[2] Preliminary research has already revealed that (±)-MDMA-assisted psychotherapy is effective in treating PTSD, as well as social anxiety in autistic adults—affording those currently suffering a reasonable hope in its potential therapeutic capacity.[33–35]

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Epidemiology, Pathophysiology, Diagnosis, Risk Factors, Presentations of PTSD, and Suicidality

Epidemiology

In the United States, the lifetime prevalence of PTSD was found to be between 6.1% and 6.8%, of whom more than 59.4% sought treatment on average 4.5 years following the onset of the disorder.[36,37] In the United States, PTSD is approximately twice as prevalent in women as men.[38]

Pathophysiology

Although PTSD, and its causal pathophysiology, has been the subject of expansive research for several decades, a precise etiology remains unclear. This is due, in part, to the wide array of neurobiological systems involved and the complex interplay of these systems. There is significant evidence for the importance of noradrenergic dysregulation in the pathophysiology of PTSD. Unbalanced and altered expression of central α_1 and α_2 adrenergic receptors and the role these receptors play in the regulation of major stress-response systems, such as the amygdala and locus ceruleus, present one mechanism for clinical manifestations of PTSD, as well as providing targets for pharmacotherapy.[39,40] Dysregulation of serotonin, particularly central serotonin receptors, is also a potential contributor to PTSD. Serotonin plays a key modulatory role in the regulation of fear and stress loci throughout the brain, including the amygdala and hippocampus. In fact, studies selectively stimulating various serotonin receptors (5-HTs) have shown successfully replicated symptoms in adults with known PTSD and produced PTSD-like symptoms in animal studies.[41,42] Perhaps unsurprisingly, given its regulation of major connections between the amygdala and prefrontal cortex as well as its role in fear and memory, there is also mounting evidence of the glutamatergic system dysregulation in PTSD. Increased hippocampal NMDA receptor density demonstrated in animal models of PTSD and elevated glutamate levels in patients with PTSD following a recent traumatic event provide a basis for the role of glutamatergic dysregulation in the dissociative symptoms of PTSD.[43–45]

Diagnosis

First introduced into the third edition of the Diagnostic and Statistical Manual of Mental Disorders third edition (DSM-III) in 1980, the diagnostic criteria for PTSD have most recently been updated in the DSM-V. The current diagnostic criteria are as follows:[46]

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TABLE 1

DSM-5 Diagnostic Criteria for PTSD

Criterion 1: Exposure to a traumatic event

- Directly experiencing the traumatic event(s)
- Witnessing, in person, the event(s) as it occurred to others
- Learning that the traumatic event(s) occurred to a close family member or friend
- Experiencing repeated or extreme exposure to aversive details of the traumatic event(s); this does not apply to exposure through media such as television, movies or pictures

Criterion 2: Persistent re-experiencing of the event in *one* of several ways:

- Thoughts or perception
- Images
- Dreams
- Illusions or hallucinations
- Dissociative flashback episodes
- Intense psychological distress or reactivity to cues that symbolize some aspect of the event

Criterion 3: Avoidance of stimuli associated with the trauma and numbing of general responsiveness, as determined by the presence of *one* or both of the following:

- Avoidance of thoughts, feelings or conversations associated with the event
- Avoidance of people, places or activities that may trigger recollections of the event

Criterion 4: At least *two* symptoms of negative alterations in cognitions and mood associated with the trauma:

- Inability to remember an important aspect of the event(s)
- Persistent and exaggerated negative beliefs about oneself, others or the world
- Persistent, distorted cognitions about the cause or consequences of the event(s)
- Persistent negative emotional state
- Markedly diminished interest or participation in significant activities
- Feelings of detachment or estrangement from others
- Persistent inability to experience positive emotions

Criterion 5: Marked alterations in arousal and reactivity, as evidenced by at least *two* of the following:

- Irritable behaviour and angry outbursts
- Reckless or self-destructive behaviour
- Hypervigilance
- Exaggerated startle response
- Concentration problems
- Sleep disturbance

Criterion 6: The duration of symptoms is more than 1 month
Criterion 7: The disturbance causes clinically significant distress or impairment in functioning
Criterion 8: The disturbance is not attributable to the physiological effects of a substance or other medical condition

Note: Unlike adults, children re-experience the event through repetitive play rather than through perception.

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Risk factors

There are significant demographic correlates predisposing individuals to PTSD. In the United States, demographic risk factors include being female, Caucasians, and American Indians/Alaska Natives, previously married, and of low socioeconomic and educational status.[36] Exposure to a traumatic event being the first criterion for the diagnosis of PTSD, several subsets of traumatic exposures most commonly precede the diagnosis. These subsets vary by study, but common categories include assaultive violence to the individual, unintentional traumatic injury, witnessed atrocities, or traumatic events experienced by a loved one.[47] Compared to civilians, military personnel, particularly those returning from active combat zones, are at significantly greater risk of developing PTSD. This is a well-documented commonality among combat veterans across generations, wars, and conflicts since the establishment of PTSD as a diagnosis.[48–50] Compared to men, trauma related to rape, sexual assault, or otherwise, non-consensual sexual events were significantly more likely to have been experienced by women diagnosed with PTSD.[36] Concurrent substance use disorder (SUD), the majority of which is accounted for by alcohol abuse and dependence, is not uncommon among individuals with PTSD; additionally, individuals with a physical disability are significantly more likely than nondisabled individuals to experience comorbid PTSD and SUD.[51]

Suicidality

The risk of suicidality in PTSD patients increases with the existence of comorbid psychiatric disorders. Pagura et al. found that of U.S. patients with PTSD to be approximately 8% had attempted suicide over their lifetime, whereas the same study found that of U.S. patients with coexistent diagnoses of PTSD and bipolar disorder, more than 32% had attempted suicide.[52] Females are more likely to develop PTSD. Both the type of trauma and the number of traumatic events experienced by individuals with PTSD has been found to be significantly associated with suicidality. LeBouthillier et al. found the traumatic exposures associated with the highest rates of suicidal ideation and suicide attempts are childhood maltreatment, assaultive violence, and traumas sustained in military service; additionally, each additional trauma greatly increased the rates of both suicidal ideation and suicide attempts.[53]

Treatment of PTSD in Adults

While the clinical practice guidelines of both the American Psychological Association (APA) and U.S. Department of Veterans

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Affairs (V.A.) issue strong recommendations for the use of trauma-focused psychotherapy over pharmacologic interventions, pharmacotherapy is recommended for individuals for whom psychotherapy is either not available or not preferred.[54,55] Pharmacotherapy for PTSD targets a reduction in the severity of symptoms and increased time between experiencing symptoms.

SSRI/SNRI

Serotonin reuptake inhibitors, both selective serotonin (SSRI) and serotonin-norepinephrine (SNRI), received strong recommendations from the V.A. as well as conditional recommendations from the APA. Specifically, SSRIs fluoxetine, paroxetine, and sertraline and SNRI venlafaxine are widely used as monotherapy for the treatment of PTSD.[54] Side effects are common with SSRI use and cover a broad spectrum of undesirable effects. While sexual dysfunction, drowsiness, and weight gain are among the most commonly reported, SSRIs have also been associated with significant QTc prolongation; however, this cardiac effect has not been shown with fluoxetine or paroxetine.[56,57] According to a review of 51 randomized controlled trials, 31 of which evaluated SSRI or SNRI monotherapy, fluoxetine, paroxetine, and venlafaxine had a significant positive impact on PTSD symptoms; however, the effect size was not as significantly positive as found in previous analyses.[1] Of notable concern when prescribing SSRIs is serotonin syndrome. While it is more common for this potentially deadly complication to occur in the setting of multiple serotonergic medications, cases have been described involving single-agent initiation or following dosing adjustments.[58]

Second-generation Antipsychotics

Second-generation, or atypical, antipsychotics, particularly quetiapine, have proven to effective in the treatment of PSTD. A randomized, placebo-controlled trial found significant improvement of PTSD symptoms with quetiapine monotherapy.[59] However, the V.A. guidelines recommend weakly against the monotherapy and augmentation therapy utilization of quetiapine, olanzapine, and other atypical antipsychotics, with the addition of a recommendation strongly against the use of risperidone.[54] Atypical antipsychotics are well documented for their extensive side effect profiles. Weight gain and other metabolic effects are relatively common, as well as sedation and hypotension. Though to a lesser extent than first-generation antipsychotics, some atypical antipsychotics can result in prolactin elevations, extrapyramidal and anticholinergic effects, and QTc prolongation.[54,60]

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Benzodiazepines

Utilization of benzodiazepines remains prevalent in clinical practice regardless of the lack of evidence support their efficacy in the treatment of PTSD.[61] Given the risk for substance abuse related to benzodiazepine use coupled with the increased prevalence of substance abuse in patients with a PTSD diagnosis, the appropriateness of benzodiazepines in the setting of PTSD is considered questionable or strongly recommended against, and monitoring for misuse is recommended.[47,54] In addition to substance abuse, dose-dependent complications of benzodiazepines arise in the form of cognitive, cardiovascular, and respiratory depression.[62] Further, these effects have clinically significant potential to be exaggerated in elderly patients warranting additional caution.[63]

MDMA

Although it is more widely known for its popularity as an illicit "party drug", recent studies suggest 3,4-Methylenedioxymethamphetamine (MDMA) shows promise as a potential treatment option in treatment-resistant PTSD.

The Chemistry of (±)-MDMA

(±)-MDMA is a ring-substituted phenethylamine with an International Union of Pure and Applied Chemistry (IUPAC) name reading: 1-(1,3-benzodioxol-5-yl)-*N*-methylpropan-2-amine. (±)-MDMA possesses a single chiral center and freely crosses the blood-brain barrier owing to its relatively low molecular weight (193.24 g/mol) and hydrophobic nature (logP = 2.050).[64]

As mentioned, (±)-MDMA is structurally related to psychostimulants (e.g., amphetamine, methamphetamine, and methylphenidate) and hallucinogens (e.g., 2,5-dimethoxy-4-iodoamphetamine, 2,5-dimethoxy-4-bromophenethylamine, and mescaline), as it contains a phenethylamine core structure shared by these compounds.[6] Ergo, it is unsurprising that (±)-MDMA has subjective qualities similar to both hallucinogens and psychostimulants. However, the interoceptive properties of (±)-MDMA are distinct from those created by either of these well-known classes of psychoactive compounds, rendering its unique classification as an entactogen necessary.[65]

Due to its chiral center and lack of an internal mirror plane, (±)-MDMA can exist in two enantiomeric forms, denoted R(–)-(±)-MDMA and S(+)-(±)-MDMA.[64] While virtually identical, having a shared chemical composition, the mirrored structure of the two

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enantiomers results in significant, fundamental differences in the manner with which each enantiomer binds and affects metabolic enzymes. Thus, the molecules' opposite orientations in three-dimensional space can bestow legitimate differences between their pharmacokinetic, pharmacodynamic, and behavioral properties.[66] Despite this, racemic (±)-MDMA—the aggregate form of these two enantiomers—is the solution that has classically been consumed recreationally and also administered in clinical settings.[6] Future research differentiating the physical and subjective effects of R(–)-(±)-MDMA and S(+)-(±)-MDMA in humans will likely enhance the molecule's clinical utility—as was evidenced by the improved therapeutic indices of antidepressants leading to greater specificity and improved outcomes in treatment.[67,68]

Neurobiology and Metabolism

While the atomic structure of (±)-MDMA is rather simple, the molecule induces robust psychophysiological responses by attaching with great affinity to multiple effectual transporters and neuroreceptors.[6] (±)-MDMA binds to and inhibits the norepinephrine transporter (NET), dopamine transporter (DAT), and serotonin transporter (SERT) and has also been shown to prevent the packaging of dopamine and serotonin into both vesicles and synaptosomes,[69] leading to efflux of these monoamines into the synapse.[70–72] It should be noted that the majority of the behavioral effects of (±)-MDMA arise through this mechanism.[6]

Nonetheless, (±)-MDMA also binds to α-2-adrenergic, serotonin $(5\text{-HT})_2$, H1 histamine, β-adrenergic, and dopamine D1 and D2 receptors—albeit the receptor-mediated subjective effects are likely produced indirectly through the release of endogenous monoamine neurotransmitters.[6] In addition, the metabolism of (±)-MDMA also has significant hormonal effects, leading to robust increases in dehydroepiandrosterone (DHEA), vasopressin, prolactin, cortisol, and oxytocin—which is likely the result of augmented serotonergic activity.[73–76] The united amplification of these hormones and neurotransmitters orchestrate the distinctive phenomenology of the (±)-MDMA experience.

(±)-MDMA is primarily metabolized in the liver by various cytochrome P450 enzymes.[6] The major pathways for metabolism are *N*-demethylation and eradication of the methylene spacer bridging the catechol.[77] (±)-MDMA is first *N*-demethylated to MDA, and each is then metabolized via cytochrome 450 2D6 (CYP2D6) to 3,4-dihydroxymethamphetamine (HHMA) and 3,4-dihydroxyamphetamine (HHA), respectively. This is followed by methylation of the 2-hydroxy functional groups in each product via catechol-O-methyltransferase,

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producing 4-hydroxy-3-methoxy-methamphetamine (HMMA) and 4-hydroxy-3-methoxy-amphetamine (HMA).[6] HMMA acts as the principal metabolite of (±)-MDMA in humans and is excreted as the glucuronic acid conjugate in urine.[78]

Pharmacokinetics, Pharmacodynamics, and Potential Drug Interactions

When a dose of 100 mg of (±)-MDMA is administered to humans, (±)-MDMA has a half-life of 8–9 hours and yields plasma t_{max} and C_{max} values of 2.3 hours and 222.5 ng/ml, respectively.[79] However, it has been shown that (±)-MDMA exhibits nonlinear pharmacokinetics in healthy human subjects—likely the result of cytochrome P450 inhibition by (±)-MDMA[80]—implying that increasing doses of (±)-MDMA would lead to disproportionate increases in drug exposure.[6] Genetic polymorphisms in Cytochrome P450 1A2 (CYP1A2), Cytochrome P450 2C19 (CYP2C19), and Cytochrome P450 2B6 (CYP2B6) have also been shown to moderate the pharmacokinetics of (±)-MDMA in humans (e.g. (±)-MDMA—MDA conversion was found to be positively associated with higher levels of CYP2C19 and CYP2B6 activities).[81] Additionally, enantioselectivity has a distinct effect on (±)-MDMA metabolism, as S(+)-(±)-MDMA has an appreciably shorter half-life than R(–)-(±)-MDMA.[82,83]

Upon ingestion, (±)-MDMA is readily absorbed from the gastrointestinal tract and transferred to the liver to be broken down metabolically, predominantly by CYP2D6.[17] As previously mentioned, the subjective effect of (±)-MDMA is chiefly the result of increased levels of serotonin, norepinephrine, and, to a lesser degree, dopamine,[17,20] (±)-MDMA does not primarily act by directly releasing these monoamine neurotransmitters but, rather, by binding to their respective transporters and inhibiting the reuptake of these monoamines.[71,72] The upturn in the release of serotonin from its synaptic bouton is the key mechanism undergirding the unique mental effects of (±)-MDMA, whereas the increased release of norepinephrine is largely to blame for the physical effects that (±)-MDMA shares with other psychostimulants.[17]

There is an abundance of scientific literature providing insight into potentially serious (±)-MDMA drug interactions with pharmaceuticals and other substances, such as cardiovascular drugs, antipsychotics, psychostimulants, anti-dementia drugs, cough and cold preparations, alcohol, caffeine, and cannabis.[84] Perhaps most important is (±)-MDMA's interaction with antidepressants (e.g., SSRIs and, to a smaller extent, SNRIs, NRIs, and NDRIs). Experimental administration of (±)-MDMA in human subjects that have taken therapeutic doses of the

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SSRI paroxetine in the past revealed a 30% increase in (±)-MDMA plasmatic concentration, with a 40% decrease in concentrations of its primary metabolite HMMA, suggesting a pharmacodynamic and pharmacokinetic drug interaction.[85] Given that antidepressants are typically the first line of pharmacologic defense for those suffering from PTSD, careful consideration must be taken when evaluating the therapeutic potential of (±)-MDMA for these select populations.

Clinical Trials, Studies, Efficacy, Safety of MDMA in PTSD

There is limited research regarding MDMA as a treatment for PTSD in the 20th century. Our focus in this section is to summarize the recent literature on methods of its use and efficacy. Several of the studies demonstrate similar methods and techniques to MDMA-assisted psychotherapy. All of the studies reported were randomized, double-blinded control trials. Due to the nature of the MDMA, true blinding was difficult to achieve. In addition, throughout the literature review, the majority of the subjects are females creating limits on extrapolation.

One of the first trials in the 20th century planned to study 29 women randomly assigned to receive 50 to 150 mg of MDMA but was truncated due to political pressures. Four women with treatment-resistant PTSD completed treatment with the initial randomized MDMA dose (75 mg [n=1], 50 mg [n=3]), and 2 women received placebo. Each subject participated in 90-minute psychotherapy sessions. Three of the sessions occurred before the MDMA-assisted session, and three took place after. Of the three post-MDMA psychotherapy sessions, one happened the day after the MDMA treatment, with the rest occurring within a 5–7-day interval. All the post-MDMA sessions provided a side-effect questionnaire. The one MDMA-assisted psychotherapy session was a total of 6 hours with 2 hours of rest. Throughout this session, heart rate and blood pressure were assessed every 30 minutes. One of the differences between the protocol of this study and others was subjects could go home with someone instead of staying overnight at the facility. Due to the truncated study, all subjects were present for their one-month follow-up, but only one subject made it to the 6-month follow-up. Many assessments were used as outcome measures, including a sociodemographic interview and several psychopathological scales (The Severity of Symptoms Scale for PTSD [an adaptation of the PTSD Symptom Scale], The State-Trait Anxiety Inventory, Beck Depression Inventory, Hamilton Rating Scale, Modified Fear Scale, Maladjustment Scale, and the Rosenburg Self-Esteem Scale).

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Side effects were measured by the Hallucinogen Rating Scale and the UKU Scale of Secondary Effects, which rates psychological and neurological effects. Due to the limited subject size, no statistical analysis was performed, but the results were still reported. The subject who received 75 mg experienced an improvement in nearly all the outcome scales, except the Rosenburg Self-Esteem Scale and Maladjustment scale, and the greatest decrease in their Severity of Symptoms Scale for PTSD score post-treatment and at follow-up. The 75 mg subject also reported higher subjective side effects than any other group. The 50 mg subjects scored best on the Maladjustment scale; this was attributed to one subject's substantial score reduction, which affected the mean. This group also scored better on outcome scales than the placebo group. Only the MDMA groups reported mild 24-hour symptoms such as sleepiness, tension, palpitations, headache, and increased fatigability. No remarkable changes occurred in heart rate or blood pressure during the experimental session.[86] Since there was no statistical analysis from this study due to size, it is difficult to assess the significance of its results.

In a larger study, 20 subjects were screened by telephone and scored by a blinded independent rater. All subjects met diagnostic criteria for PTSD with a CAPS score ⩾50 and had a prior trial with an SSRI or SNRI and psychotherapy for 3 and 6 months, respectively. Some exclusion criteria included bipolar 1 disorder, borderline personality disorder, and current substance use disorder. Twelve subjects underwent MDMA-assisted psychotherapy, and eight were placed in the psychotherapy placebo group. The study consisted of two blinded 8-hour MDMA-assisted psychotherapy sessions. A third session was permitted for placebo subjects; although, this data was not included in the analysis. At the start of the session, study subjects were given 125 mg dose of MDMA and, if deemed safe, were provided a supplemental dose of 62.5 mg 2–2 ½ hours into the therapy. The supplemental dose was given in all but one session. Subjects stayed overnight and received one of their eight psychotherapy-only sessions the morning after each MDMA session. The last session took place two months after the second MDMA session. The primary outcome measured was the Clinical Administered PTSD Scale (CAPS), and secondary outcomes included two self-reports: the Impact of Events Scale-Revised (IES-R) and the Symptom Checklist 90-Revised. Subjects were considered to have a clinical response if their CAPS score decreased by >30%. Two neurocognitive tests measured memory, attention, processing speed, and other cognitive processes, and vitals were checked throughout MDMA-assisted therapy sessions. Using ANOVA analysis, CAPS and

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IES-R scores in both groups improved with statistical significance. However, the MDMA group exhibited a higher clinical response with 10/12 subjects no longer fitting criteria for PTSD. No difference of significance was reported in neurocognitive measures. The experimental group experienced a greater rise in blood pressure, heart rate, and temperature than the placebo group. However, both groups' vitals were restored to baseline shortly after the session. The MDMA group more frequently experienced dizziness, jaw tightness, loss of appetite, coldness, nausea, and impaired balance. Common adverse effects in both groups the days following the MDMA session were low mood, anxiety, fatigue, headache, and nausea, and mostly resolved within days. Anxiety, irritability, and loss of appetite were endorsed more frequently in the MDMA group.[87] This was the first recent study able to demonstrate the efficacy of MDMA-assisted psychotherapy as a treatment for PTSD. In a follow-up to the previously described study, the authors assessed both the experimental group and the placebo group who crossed over to receive MDMA treatment. The CAPS and IES-R scores of 19 subjects were to be assessed by the same independent rater as the first study. Eight of these subjects had received a third experimental session at the end of the prior study. Of the 19 subjects, 16 completed an additional CAPS and IES-R assessment. Scores for the 16 subjects were not significantly varied from 2-month post-treatment to long term follow up. Subjects who received three sessions did not have CAPS score that differed significantly from subjects who only underwent two sessions. Two subjects' PTSD recurred. This follow-up also provided a questionnaire with multiple questions, including perceived persistence of benefit from the MDMA-assisted treatment.[88] The follow-up study showed potential long term effects and sustainability of MDMA treatment.

Another study the same year used similar inclusion and exclusion criteria to select subjects, including a CAPS score of ⩾50 and prior psychotherapy ⩾ six months and ⩾ three months of SSRI treatment. The authors allowed comorbid diagnoses of depression, anxiety disorders, and eating disorders if there was no ongoing purging and previously established outpatient therapy to continue. Eight subjects received the full dose of 125 mg, and four were given 25 mg as a placebo dose. Similarly, the study allowed an additional dose to be given 2 hours into the session to the experimental and placebo group, 62.5 mg and 12.5, respectively. Subjects underwent 3 MDMA-assisted psychotherapy sessions, and primary outcomes were CAPS and the Posttraumatic Diagnostic Scale (PDS). Twelve psychotherapy-only sessions occurred with a timeline parallel to the studies described previously. Blood pressure, temperature,

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and heart rate were recorded before and throughout the session and averaged for each subject across their three sessions. Blood pressure and heart rate for the experimental group barely missed statistical significance when compared to placebo. Common side effects in both groups were insomnia and loss of appetite, while the experimental group reported restlessness, jaw tightness, thirst, and coldness almost exclusively. Using ANOVA analysis, the experimental group exhibited a large decrease in their CAPS score when compared to placebo across three sessions. However, the data only trended towards statistical significance and did not reach it ($p = 0.066$). When focusing on timeframes, the decrease in CAPS scores between 3 weeks after the 2nd MDMA session to 3 weeks after the 3rd session did reach statistical significance. In the crossover study for the four placebo subjects, 2 achieved a clinical response, no longer meeting criteria for PTSD. Follow-up at one year showed 5 of the 12 subjects did not meet PTSD criteria. Additionally, at follow-up, 4 of the subjects who previously were on disability or limited-work were able to return to full-time employment.[89] This study provided more information regarding not only the clinical application of MDMA-assisted psychotherapy but the practical changes that can be achieved in a subject's life.

One of two recent studies in 2018 varied slightly differently in the methods from previous studies. Inclusion criteria were set as a CAPS score ⩾50 but did not specify the length of psychotherapy or pharmacotherapy a subject had previously tried. The study had two experimental groups (125 mg or 100 mg of MDMA) and one active placebo group (40 mg MDMA). Thirteen subjects were placed in the 125 mg group, 9 in the 100 mg, and 6 in the placebo group. Two MDMA-assisted psychotherapy sessions took place one month apart. Like other studies, a half dose of MDMA was offered during the session: 62.5 mg, 50 mg, and 20 mg, respectively. Six psychotherapy sessions occurred in a similar timeline as previously discussed studies as well as phone follow-up daily the week following the MDMA session. The primary outcome was a CAPS score, and clinical response was defined the same as prior studies (>30% decrease in CAPS score). Secondary outcomes were Beck Depression Inventory (BDI), Dissociative Experiences Scale II (DES-II), and Pittsburg Sleep Quality Index (PSQI). Heart rate, blood pressure, and temperature were recorded. An increase in heart rate and systolic blood pressure reached significance and near significance, respectively. With intent to treat analysis, no statistically significant change was noted in CAPS score, but the active groups experienced the greatest decrease in the severity of their PTSD symptoms. When analyzing per protocol, statistical significance was reached for overall

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CAPS scores. The per-protocol set included all subjects who received both blinded MDMA sessions and whose CAPS scores were assessed. When comparing the experimental groups to the placebo group, the reduction in CAPS scores of the 125 mg group achieved significance, while the 100 mg group trended towards significance ($p = 0.10$). No secondary measures were significant. When the blind was finished, both experimental groups could participate in a third open-label session to assess whether a third session would be beneficial. Both the 100 mg and 125 mg had a statistically significant reduction in their CAPS scores two months after the open-label session when compared to the blinded endpoint. After the initial assessment, the placebo group were offered a crossover study and randomly assigned a dose. Primary and two secondary outcomes, BDI and DES-II, achieved statistical significance a month following the second open-label MDMA session. Unlike the initial experimental groups, a third session did not significantly affect CAPS scores. Treatment-emergent adverse events were more common in the experimental groups, and psychiatric symptoms included anxiety, depressed mood, and irritability.[35] The study showed higher doses could potentially provide a better clinical response, and more investigation is warranted into whether a third treatment session could be beneficial.

The last randomized, double-blinded control trial to date also used a CAPS score ⩾50 as inclusion criteria. Twenty-six first responders and veterans with chronic PTSD were randomized to the experimental groups (75 mg [n=7] or 125 mg [n=12]) or the active placebo group (30 mg [n=7]). Each group underwent 2 MDMA-assisted psychotherapy sessions, and the 30 mg and 75 mg group could participate in a crossover study (3 100–125 mg sessions) after the blind. The primary outcome measured was the CAPS score, and subjects from all groups were followed up at 1 year. Vital signs and side effects were recorded. One serious adverse event may have been due to the study. Both experimental groups had a significant decrease in their CAPS score compared to the 30 mg group. Post-blind, the 30 mg group in the crossover study also had a statistically significant reduction in the primary outcome, though the 75 mg subjects did not have further improvement of their symptoms. At long-term follow-up, CAPS scores for all subjects who received 100–125 mg of MDMA were significantly better than their baseline.[90] This study proposes MDMA doses as low as 75 mg could be beneficial in reducing PTSD symptoms. It also builds upon the clinical efficacy of MDMA as treatment for chronic PTSD and presents a specific patient population with positive results.

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TABLE 2

Clinical Efficacy

STUDY TYPE	AUTHOR (YEAR)	GROUPS STUDIED AND INTERVENTION	RESULTS AND FINDINGS	CONCLUSIONS
Randomized, double blinded control trial	Bouso, José Carlos; Doblin, Rick; Farré, Magí; et al (2008).[86]	6 women with treatment-resistant PTSD: 4 received one MDMA-assisted psychotherapy (75 mg [n=1], 50 mg [n=3]) + 6 psychotherapy-only sessions, and 2 women received psychotherapy only.	Due to truncated study, no statistical analysis performed. 75 mg subject had improvement in nearly all the outcome scales, and the greatest decrease in their Severity of Symptoms Scale for PTSD score post-treatment and at follow-up. The 50 mg group scored better on outcome scales than the placebo group.	Due to the small subject size and study being shut down, there are limited conclusions that can be drawn from the study. It does show further exploration is warranted into MDMA-assisted psychotherapy for treatment-resistant PTSD.
Randomized, double blinded control trial	Mithoefer, Michael C.; Wagner, Mark T.; Mithoefer, Ann T.; et al (2011).[87]	20 subjects with treatment-resistant PTSD: 12 subjects received 2 MDMA-assisted psychotherapy (125 mg) + 8 psychotherapy-only sessions, and 8 were placed in the psychotherapy placebo group.	CAPS and IES-R scores in both groups improved with statistical significance. MDMA group exhibited higher clinical response with 10/12 subjects no longer fitting criteria for PTSD.	As the first study using statistical analysis in the 20th century, it was able to demonstrate the potential efficacy of MDMA-assisted psychotherapy as a treatment for PTSD.
Long term follow-up study (17–74 months) to randomized, double blinded control trial	Mithoefer, Michael C.; Wagner, Mark T.; Mithoefer, Ann T.; et al (2013).[88]	Assessed both the experimental group and the placebo group who crossed over to receive MDMA treatment. 16 subjects completed a second assessment.	CAPs scores were not significantly varied from 2-month post-treatment to long term-follow up. Subjects who received 3 sessions did not have CAPS score that differed significantly from subjects who only underwent 2 sessions.	The follow-up study shows potential long-term effects and sustainability of MDMA treatment. It also questions whether a third treatment session is necessary to achieve clinical response.

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Randomized, double blinded control trial	Oehen, Peter; Traber, Rafael; Widmer, Verena; et al (2013).[89]	8 subjects with treatment-resistant PTSD received 3 MDMA-assisted psychotherapy sessions (125 mg) + 12 psychotherapy-only sessions, and 4 were given 3 25 mg MDMA sessions + 12 psychotherapy sessions.	The experimental group had a large decrease in their CAPS score when compared to placebo across 3 sessions but only trended towards statistically significance. Follow up at 1 year showed 5 of the 12 subjects did not met PTSD criteria and 4 of the subjects who previously were on disability or limited-work were able to return to full-time employment.	Though the clinical response was not achieved in this study, it provides more information regarding the practical life improvements that can be achieved after MDMA-assisted psychotherapy.
Randomized, double blinded control trial	Ot'alaora G, Marcela; Grigsby, Jim; Poulter, Bruce; et al (2018).[35]	28 subjects randomized into experimental groups (125 mg or 100 mg of MDMA) or active placebo group (40 mg MDMA). 13 subjects in the 125 mg group, 9 in the 100 mg, and 6 in the placebo group. Two MDMA sessions + 6 psychotherapy-only sessions	With ITT analysis, no statistically significant change was noted in CAPS score. Analyzing per protocol: the reduction in CAPS scores of the 125 mg group achieved significance while the 100 mg group trended towards significance. Third open-label session for experimental groups offered and statistically significant reduction in CAPS scores two months after the open-label session when compared to blinded endpoint.	The study suggests higher doses could potentially provide a better clinical response, and more investigation is warranted into whether a third treatment session could be beneficial.

(*Continued*)

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TABLE 2 (*Continued*)

Clinical Efficacy

STUDY TYPE	AUTHOR (YEAR)	GROUPS STUDIED AND INTERVENTION	RESULTS AND FINDINGS	CONCLUSIONS
			Placebo group offered a crossover study. Primary and two secondary outcomes achieved statistical significance a month following the second open-label MDMA session. A third session did not significantly affect CAPS scores.	
Randomized, double blinded control trial	Mithoefer, Michael C; Mithoefer, Ann T; Feduccia, Allison A; et al (2018).[90]	26 first responders or veterans with chronic PTSD were randomized to the MDMA experimental groups (75 mg [n=7] or 125 mg[n=12]) or the active placebo group (30 mg [n=7]) + psychotherapy.	75 mg and 125 mg groups had significant decrease in their CAPS score compared to the 30 mg group. Post-blind, the 30 mg group in the crossover study also had statistically significant reduction in the primary outcome. At long-term follow-up, CAPS scores for all subjects who received 100–125 mg of MDMA were significantly better than their baseline.	This study proposes MDMA doses as low as 75 mg could be beneficial in reducing PTSD symptoms. It also builds upon the clinical efficacy of MDMA as treatment for chronic PTSD and presents a specific patient population with positive results.

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TABLE 3

Safety

STUDY TYPE	AUTHOR (YEAR)	SAFETY MEASURES	RESULTS	CONCLUSIONS
Randomized, double blinded control trial	Bouso, José Carlos; Doblin, Rick; Farré, Magí; et al (2008).[86]	Heart rate, blood pressure, Hallucinogen Rating Scale and the UKU Scale of Secondary Effects, side effects	MDMA groups reported mild 24-hour symptoms such as sleepiness, tension, palpitations, headache, and increased fatigability. No remarkable changes occurred in heart rate or blood pressure during the experimental session	Due to the small subject size and no statistical analysis, there are limited conclusions that can be drawn from the study.
Randomized, double blinded control trial	Mithoefer, Michael C.; Wagner, Mark T.; Mithoefer, Ann T.; et al (2011).[87]	Blood pressure, heart rate, temperature, side effects	Experimental group had a greater rise in blood pressure, heart rate, and temperature than the placebo group. Both groups vitals restored to baseline shortly after session. MDMA group more frequently experienced dizziness, jaw tightness, loss of appetite, coldness, nausea and impaired balance. Anxiety, irritability, and loss of appetite were endorsed more frequently in the MDMA group but also experienced in the placebo group.	MDMA will likely alter vital signs during sessions but should return to baseline after administration. MDMA may cause patients symptoms but majority are self-limiting.
Randomized, double blinded control trial	Oehen, Peter; Traber, Rafael; Widmer, Verena; et al (2013).[89]	Blood pressure, heart rate, temperature, side effects	Blood pressure and heart rate for the experimental group barely missed statistical significance when compared to placebo. Common side effects in both groups were insomnia and loss of appetite; while the experimental group reported restlessness, jaw tightness, thirst, and coldness almost exclusively. No adverse events.	MDMA has the potential to be administered safely without major adverse events. When considering this study with prior ones, jaw tightness and coldness seem to be recurring symptoms for only the MDMA group.

(*Continued*)

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TABLE 3 (*Continued*)

Safety

STUDY TYPE	AUTHOR (YEAR)	SAFETY MEASURES	RESULTS	CONCLUSIONS
Randomized, double blinded control trial	Ot'alaora G, Marcela; Grigsby, Jim; Poulter, Bruce; et al (2018).[35]	Heart rate, blood pressure, and temperature, treatment emergent adverse events	Increase in heart rate and systolic blood pressure reached significance and near significance, respectively. Treatment emergent adverse events were more common in the experimental groups, and psychiatric symptoms included anxiety, depressed mood, and irritability.	Changes in most vital signs due to MDMA can be significant but return to baseline. Psychiatric symptoms are possibly more common in subjects who receive MDMA.

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Conclusion

Given the data from multiple controlled trials, MDMA-assisted psychotherapy for PTSD has strong evidence as a therapeutic agent. There is a strong correlation between decreased symptoms of PTSD and the use of MDMA-assisted psychotherapy as shown by the data presented. While the numbers of participants in these studies are relatively low, the results show promise in providing a new tool in the toolbox of psychiatric care for PTSD. Further studies are necessary to solidify MDMA's role in psychiatry and one major barrier to producing studies with increased participants is MDMA's status by the DEA as a controlled substance. ✤

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