MDMA Literature Overview

Introduction

The initial search to identify all of the health conditions in which MDMA might act as a treatment resulted in three overarching conditions: Post-traumatic stress disorder (PTSD), anxiety disorders in specific populations, and tinnitus. To compare the efficacy of current gold-standard treatments and MDMA in these identified health conditions, we reviewed primary randomized controlled trials (RCTs) investigating the use of MDMA-assisted psychotherapy, along with meta-analyses and systematic reviews. However, the only study investigating tinnitus was not an RCT, and therefore did not meet the criteria for inclusion set forth by the task force. Additionally, MDMA, in conjunction with psychotherapy, has been submitted to the Food and Drug Administration (FDA) for consideration as a new drug in the treatment of PTSD. Review of the data is ongoing, and a decision is expected by August 2024. Two phase 3 trials were submitted with supporting evidence of safety and efficacy of the treatment; phase 3 trials are required by the FDA for the submission of a new drug application. As such, these trials will receive special consideration in this report.

Post-Traumatic Stress Disorder

Six primary RCTs investigating the use of MDMA-assisted psychotherapy as a treatment for PTSD were evaluated[1-6]. Participants in all of these RCTs suffered from moderate to severe, often treatment-resistant, PTSD. Veterans and first responders were included as a specific population of interest in one trial[3]. All of these studies were associated with Lykos Therapeutics (founded by the Multidisciplinary Association for Psychedelic Studies (MAPS), and formerly called MAPS Public Benefit Corporation). Because these studies come from one group, the methods are fairly consistent across the included studies. Two of the six studies were phase 3 clinical trials[5,6], and will be reported in their own section below. The remaining phase 2 trials will also be reported in their own section as well[1-4].

Phase III Trials

Two phase three trials (called MAPP1[5] and MAPP2[6]) sponsored by Lykos Therapeutics were identified in the literature review. These trials have been submitted to the FDA and are currently under review. Both studies evaluated the short-term efficacy and safety of MDMA-assisted psychotherapy for the treatment of moderate to severe PTSD. A total of 194 individuals were included between the two trials; 99 participants received MDMA-assisted psychotherapy, while 95 participants received placebo plus the same psychotherapy. Because these trials were designed by the same entity (MAPS) the methods were the same. Each participant, regardless of treatment group, received three 90-minute preparatory therapy sessions, three 8-hour treatment sessions with two therapists and an overnight stay, and three 90-minute non-drug integrative psychotherapeutic sessions after each treatment session (for a total of nine non-drug integrative sessions). The primary endpoint of each study was 18 weeks after the beginning of the trial. In the first treatment session, individuals in the MDMA group received 80 milligrams (mg) of the drug at the beginning of the session, with an optional half-dose administered approximately two hours later. During the second and third treatment sessions, the dose was

120mg, again with an optional half-dose. The escalation of dose was optional as well, at the discretion of either the participant or the therapists.

Assessment of PTSD symptomology was the primary outcome in both trials, and was made through the Clinician-Administered PTSD Scale for the DSM-V (CAPS-V), both between and within groups. The CAPS-V is considered a gold-standard measurement scale for PTSD. Investigators also assessed clinically meaningful responses (defined as a ≥10-point reduction in CAPS-V total severity score), loss of PTSD diagnosis, and remission from the disorder (defined as the loss of the diagnosis along with a total CAPS-V score of ≤ 11).

Both studies compared the change in the respective scores from baseline to 18 weeks, and measured effect sizes (using Cohen's d). As a reminder, effect sizes are typically considered small if they are 0.2 or less, medium if they are around 0.5, large if they are 0.8, very large if they are 1.2, and huge if they are 2.0 and above (i.e., the further away from 0, the greater the effect). Both studies found that **MDMA-assisted psychotherapy resulted in statistically significant reductions of PTSD symptomology**, as compared with each study's placebo condition. Each trial also found moderate to large effect sizes of MDMA-assisted therapy when comparing between the groups (MAPP1, d=0.91; MAPP2, d=0.70). **Within only those who received MDMA, there was a large treatment effect between baseline and the endpoint** (MAPP1: d=2.1; MAPP2: d=1.95). **Interestingly, there was also a large effect found in the placebo groups between baseline and trial end** (MAPP1: d=1.2; MAPP2: d= 1.25).

This finding was mirrored when evaluating if the treatment resulted in a clinically meaningful response. In MAPP2, 87% of the individuals who received MDMA saw a ≥10-point reduction in CAPS-V total severity score, as did 69% of those in the placebo group. At the end of each study, though, **more participants in the MDMA groups no longer met diagnostic criteria for PTSD** (MAPP1: 67%; MAPP2: 71%) than did those in the placebo groups (MAPP1: 32%; MAPP2: 48%). Finally, each study investigated the effects of MDMA-assisted therapy on remission from the disorder. Again, these studies found that **more participants in the MDMA groups met the criteria for remission** (MAPP1: 33%; MAPP2: 46%) than did those in the placebo groups (MAPP1: 5%; MAPP2: 21%).

There were a number of limitations with these phase 3 trials. Between the two studies, **a total of 40% of the participants had any lifetime experience with MDMA**; this is a significant departure from the estimated 0.8% of the US population (12 and older) who have experience with the drug[7]. Next, the intensive psychotherapeutic process utilized in these studies was developed by MAPS, and is not considered a standard therapeutic approach for any disorder, including PTSD. Notably, **participants who received placebo along with this intervention also saw substantial improvements in PTSD symptomology**, which may suggest that there are effects of the psychotherapy itself, without the addition of MDMA. Each of these trials employed strict inclusion criteria, excluding individuals with certain medical conditions, including uncontrolled cardiovascular conditions. A limitation common to all studies of psychedelic drugs is the issue of functional unblinding. Between these two trials, 94% of participants in the MDMA condition correctly guessed which condition they had been assigned to, and 75% of those in the placebo correctly guessed. However, **the results of these two studies suggest that MDMA-assisted psychotherapy is both safe and efficacious in the treatment of PTSD**.

Phase II Trials

Four phase 2 RCTs[1-4] were evaluated. Because the studies were also associated with Lykos Therapeutics, the methods were again largely consistent between trials, and thus pooled analyses could be conducted; two such

analyses were found in the literature[8,9]. Both evaluated data from the same six phase 2 RCTs; four of these trials were those that were reviewed herein[1-4], while the other two were never published. The first pooled analysis investigated the primary outcomes of efficacy and safety from baseline to trial endpoint (Pooled Analysis I[8]), while the second analysis focused on the long-term follow-up data (Pooled Analysis II[9]).

Pooled Analysis I

In the first analysis[8], data from 105 participants were included. Data from participants who received 75mg, 100mg, or 125mg were combined into the experimental active dose group, and those who received 0mg, 25mg, 30mg, or 40mg were considered the control group. Like the phase 3 trials, all studies included three pre-treatment psychotherapy sessions. These phase 2 trials included either two or three 8-hour treatment sessions, with each session followed by three to four post-drug psychotherapy sessions. In all of these studies, the primary outcome was the effect of treatment on PTSD symptomology, measured by the Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV).

There was a statistically significant difference in the change in CAPS-IV total scores from baseline to after the second experimental session between control and active groups, with the active dose group having a greater mean drop in score (this corresponds to a greater improvement). Comparing between active MDMA groups and control groups, the effect size was 0.80, indicating a moderate effect. In the active dose group alone, the difference between baseline and endpoint scores had a large effect size of 1.40. Based on this pooled analysis, **more participants in the active dose group (54.2%) no longer met PTSD diagnostic criteria than those in the control group (22.6%) after two sessions**. When including data from those who received three doses of the drug, CAPS-IV scores continued to decline. This drop between second and third sessions was statistically significant, **indicating the continuation of improvement in PTSD symptomology** between these timepoints. When looking between baseline and a third session in those who received an experimental dose, the effect size of treatment was 1.90, indicating a very large effect of treatment.

Pooled Analysis II

The second pooled analysis[9], evaluating long-term follow-up data from the same six phase 2 trials, reported that 107 participants were included in the analysis. This study also compared changes in CAPS-IV scores, this time between baseline, the primary endpoint of the study, and long-term follow-up (12 months after the final dose of the drug). From the primary endpoint to the long-term follow-up, CAPS-IV scores continued to decrease, with **scores at the long-term follow-up statistically lower than those at treatment exit**. There was a low effect size of 0.23. Additionally, the number of participants who no longer met PTSD criteria increased from treatment exit (56%) to long-term follow-up (67%). When compared with baseline, 82% of participants achieved a clinically significant drop of 15 points or greater in CAPS-IV total scores at treatment exit in response to MDMA-assisted psychotherapy, and 26% had a 15-point or greater decrease from treatment exit to long-term follow-up.

At the long-term follow-up, nearly all of participants across these studies reported experiencing benefits, with over half indicating large benefits that lasted or continued to grow. On the other hand, approximately 10% of participants across reported experiencing harms, and a minority reported those harms were present at the long-term follow-up. A few participants reported a relapse of PTSD symptoms in response to one or more significantly stressful life events since completing the active treatment phase. No participants reported any harms as severe,

and all participants who reported any harm also reported at least one benefit. Something to note is that at the long-term follow-up, almost 10% of participants reported having used ecstasy or MDMA on their own at least once between treatment exit and long-term follow-up. Overall, though, **the results from these analyses indicate that the treatment was considered to be safe and efficacious for individuals with moderate to severe, treatment-resistant PTSD, potentially up to one year after the last session**.

Comparison of Efficacy, PTSD Treatments

Current standard treatments for PTSD include various psychotherapies, including cognitive behavioral therapy, prolonged exposure therapy, cognitive processing therapy, and eye movement desensitization and reprocessing therapy, as well as certain selective serotonin reuptake inhibitors (SSRIs), including sertraline, paroxetine, and fluoxetine, as well as the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine[10,11]. Paroxetine and sertraline are the only FDA-approved treatment options for PTSD, while the American Psychological Association and the Department of Veterans Affairs/Department of Defense PTSD guidelines both also recommend fluoxetine and venlafaxine[12-14]. However, the Department of Veterans Affairs/Department of Defense specifies that trauma-focused psychotherapy is preferable to pharmacotherapy[12]. To compare the efficacy of treatments, five meta-analyses were evaluated[15-19].

Meta-analyses, PTSD

One meta-analysis examined the efficacy of all standard treatments for PTSD, investigating a total of 137 treatment comparisons. Overall, the effect size (using Hedge's g) for all comparisons combined was 0.81, indicating a moderate effect[16]. The study divided treatment types broadly between psychotherapies and pharmacotherapies. Psychotherapy included cognitive behavior therapy (CBT), exposure therapy, and eye movement desensitization and reprocessing (EMDR). **Psychotherapy produced a large effect size of 1.14**, when combining data for all forms. In looking at each individually, the study found an effect size of 1.26 for CBT, 1.08 for exposure therapy, and 1.01 for EMDR[16]**. In terms of pharmacological treatments, effect sizes were typically moderate**. Paroxetine resulted in an effect size of 0.74, the effect size of sertraline was 0.41, the effect size of fluoxetine was 0.43, and the effect size of venlafaxine was 0.48[16]. Pooled Analysis I (above) calculated **an effect size of 0.80[8] for MDMA-assisted psychotherapy** as compared with placebo, and **the effect sizes of the phase 3 trials were 0.70 and 0.91**[5,6] when comparing between the two treatments. In those phase 3 trials, just within those who received the drug, there were very large to huge effect sizes of treatment between baseline and the endpoint, with effect sizes of 1.95 and 2.10. The particular type of psychotherapy employed in these studies is not considered standard treatment for PTSD, and was developed by MAPS specifically for use with MDMA. This intensive form of psychotherapy by itself appears to have some treatment effects, demonstrated by the large effect sizes (1.20, 1.25) in response to this treatment in the placebo groups[5,6]. **Overall, as reported, MDMA-assisted psychotherapy for the treatment of PTSD appears to demonstrate at least comparable efficacy with current standard treatments**.

Anxiety & Social Anxiety Disorder

Two studies investigating the use of MDMA-assisted therapy for anxiety (outside of PTSD) were evaluated[20,21]. One trial investigated its use as a treatment for social anxiety disorder in individuals with autism spectrum

disorder[20], and the other evaluated its use as a treatment for anxiety associated with a life-threatening illness[21]. Methods for these trials were similar to those in the PTSD studies.

Social Anxiety in Autism Spectrum Disorder

To investigate MDMA-assisted psychotherapy as a treatment for social anxiety disorder in those with autism spectrum disorder, 12 participants were randomized to one of two groups, MDMA or placebo[20]. Regardless of group, all participants received three initial non-drug preparatory sessions, lasting 60-90 minutes each and two 8-hour treatment sessions, spaced approximately one month apart. Each treatment session was followed by an additional three integrative psychotherapy sessions, each also lasting 60-90 minutes. The first of these sessions occurred the morning immediately after the treatment session. (Unlike in the PTSD trials, participants were not required to spend the night). The primary endpoint was one month after the second experimental treatment session. Six months after the end of the trial the researchers collected follow-up data.

The primary outcome was the change in social anxiety symptomology from baseline to the end of the study. Additionally, researchers investigated the rate of clinical response, defined as a 20-point reduction in anxiety score. **MDMA-assisted therapy resulted in a statistically significant reduction in the mean anxiety score as compared with the placebo group**. In the treatment group, the effect size was 1.40. In those who received MDMA, 75% showed clinically significant changes in social anxiety disorder symptoms, as compared with 50% of those in the placebo group. At the six-month follow-up, the decline in mean anxiety score from baseline was again significantly greater in those who received MDMA-assisted therapy than in those who received the placebo. At this timepoint, the effect size was 1.10. Overall, in this trial, **MDMA-assisted therapy reduced social anxiety symptomology, and remained at this lower level for at least 6 months**, indicating that MDMA-assisted psychotherapy may provide treatment for autistic adults with social anxiety disorder[20].

Anxiety in Life-Threatening Illnesses

MDMA-assisted psychotherapy was also investigated as a treatment for anxiety surrounding a diagnosis of a life-threatening illness[21]. To test the drug, a total of 18 participants were randomized to either the MDMA-assisted therapy condition or the placebo with therapy condition. All participants received three initial preparatory sessions and two treatment session with an overnight stays, spaced approximately 4 weeks apart. Each treatment session was followed by three integrative psychotherapy sessions, the first of which was the day immediately after treatment. The endpoint of the study was one month after the second session.

The primary outcome was the impact on anxiety scores from baseline to the primary endpoint. Results indicated that the MDMA group had a greater mean change in anxiety scores than did those in the placebo group. The difference between the changes in these groups trended toward, but did not reach, significance. One individual in the placebo group saw substantial improvements in symptomology, potentially acting as an outlier. If the researchers removed this individual, the difference between groups became statistically significant. When comparing between the two groups, the effect size was 1.03. However, when looking just at the mean scores of each group (not the change in the scores) at the end of the trial, those who received MDMA had significantly lower scores than those who received placebo. Overall, **these findings provide preliminary evidence to support that MDMA-assisted psychotherapy may provide treatment for anxiety surrounding a life-threatening illness**[21].

Comparison of Efficacy, Anxiety

Current standard treatments for anxiety disorders include various psychotherapies (including cognitive behavioral therapy (CBT), Acceptance and Commitment Therapy (ACT), others), medication (antidepressants, anti-anxiety medications, beta-blockers), or a combination of the two[22]. Exposure CBT and group CBT are additional treatments for social anxiety disorder[23].

Two meta-analyses were analyzed to compare the efficacy of current treatments against that of MDMA-assisted psychotherapy for both anxiety in general and social anxiety disorder[24,25]. One of these studies investigated pharmaceutical, psychological, and a combination of the two on anxiety (including social anxiety), evaluating data from 234 studies encompassing 37,333 individuals. Effect sizes for SSRIs, SNRIs, and benzodiazepines versus placebo conditions were assessed, and all were found to be above 2.00[24]. These are considered huge treatment effect sizes. Effect sizes for psychotherapies, including individual CBT/exposure therapy and group CBT were calculated as well. The effect sizes were 1.30, and 1.22, respectively. The combination of medication and CBT resulted in an effect size of 2.10[24]. A second meta-analysis investigating the use of CBT as a treatment specifically for treatment of social anxiety disorder found an effect size of 0.74. Looking just within individuals who received CBT, at 12 months post-treatment symptoms of social anxiety continued to improve[25].

In the study investigating MDMA-assisted psychotherapy as a treatment for social anxiety in individuals with autism spectrum disorder, the immediate effect size of treatment was 1.40, and six months after the end of treatment was 1.10, both large effect sizes. At both timepoints, the individuals who received MDMA showed significantly greater improvements than those who did not[20]. In the study evaluating MDMA as a treatment for anxiety in response to a life-threatening illness, the effect size was calculated to be 1.03. However, there were no statistical differences between those who received MDMA and those who did not (likely owing to the presence of an outlier in the control group)[21].

Overall Risks of MDMA as a Treatment

Risks in Clinical Trials

In the clinical trials, nearly all participants reported some sort of adverse effect[1-6,20,21]. Most were considered mild to moderate in severity. Physical effects included headache, muscle tightness, jaw clenching or tightness of jaw, decreased appetite, nausea, dizziness, hyperhidrosis (sweating), and feeling cold. Psychiatric effects included anxiety, low mood, insomnia, fatigue, and suicidal ideation. However, given the nature of PTSD, a substantial number of the participants had a lifetime history of suicidal ideation at baseline. Although the number of participants who reported suicidal ideation in the phase 3 trials varied throughout the visits, prevalence never exceeded baseline and was not exacerbated in response to MDMA. In the phase 2 trials, however, suicidal ideation was found to be more common in the active dose group than in the control group[8]. Occasionally more severe adverse effects occurred, including dissociation and flashback. Some of these adverse effects (e.g., low mood, anxiety, fatigue, headache, nausea) lingered for the week following drug administration, but decreased in severity during this time. These same adverse effects were also seen in trials in health individuals[26]. These clinical trials also reported transient cardiovascular symptoms in response to MDMA, including increases in blood pressure, heart rate, and body temperature, as well as palpitations and vascular

symptoms. These were all considered mild, and typically resolved without medical intervention[1-6,20,21]. Adverse cardiovascular effects were dose-dependent in the clinical trials[3] and in trials of MDMA in healthy individuals[27].

Additionally, there have been reports that adverse effects vary by sex. In trials of healthy individuals, negative drug effects, including subjective effects, were significantly more common in women[27]. Notably, hyponatremia (a low concentration of sodium in the blood) occurs more often in females than in males[28,29]. The greater negative effects of the drug may be due, in part, to lower body weight and correspondingly higher drug dose per body weight in women[30]. Finally, infants born to mothers who had used MDMA during pregnancy have shown worse motor quality development and lower milestone attainment at 4 and 12 months of age, in a dose-dependent manner, as compared with infants not exposed to MDMA[31,32].

Drug-Drug Interactions

Like other psychedelic drugs, MDMA modulates serotonin neurotransmission, and so there is the potential for drug-drug interactions with other medications that also modulate this system. This includes various types of antidepressants (SSRIs, SNRIs, tricyclic antidepressants, monoamine oxidase inhibitors), among others[33], and chronic SSRI use has been shown to dampen the effects of MDMA[34]. While MDMA has been found to negatively impact the function of the immune system and suppress innate immunity[35], one SSRI (paroxetine) was found to blunt this MDMA-induced immunosuppression[36].

Other significant interactions include between MDMA and reversible inhibitors of monoamine oxidase, pro-serotonergic drugs, and those that inhibit the enzyme CYP2D6[37]. Notably, in the last category, are certain SSRIs (fluoxetine, paroxetine) and antiretroviral drugs. There have been instances of fatalities in those taking antiretroviral drugs and MDMA at the same time[38-41]. Finally, concomitant use of caffeine with MDMA may exacerbate changes in body temperature regulation, cardiotoxicity, and potentially lower the threshold for seizure[42].

Abuse Potential and Toxicity

Despite being a Schedule I substance, MDMA is generally considered non-addictive[43]. Though MDMA is less reinforcing than other drugs, there is a low potential for dependence, which may be more psychological than physical[44]. Tolerance and self-reported withdrawal can occur, but any sort of dependence on MDMA seems to be different from other drugs (e.g., alcohol, opioids, etc.). Only a minority of users become concerned enough about their use to seek treatment[43,44].

Studies and case reports have reported various toxic effects of MDMA, including hepatotoxicity[45-47], effects on the kidneys (notably hyponatremia)[28], Parkinsonism[48], as well as instances of minor memory impairment[49,50] and impacts on anxiety and mood[51-53]. Most of these negative effects are rare and occur following use outside of a clinical setting with MDMA of unknown origin and/or dose, or those without experience with the drug; yet another example of how important set and setting are in the use of these substances as treatments[54]. Fatalities following MDMA intoxication are rare as well; in instances of fatalities the blood concentration of MDMA has been found to be around 4000 nanograms (ng) per 1 milliliter (mL) of blood[55]. For reference, peak blood concentration in response to one of the highest clinical doses of MDMA (125mg) is around 236ng/1mL[56].

Institute for Clinical and Economic Review Report

Recently, a draft of an evidence report discussing the data from the phase 3 trials submitted by Lykos Therapeutics to the FDA was released[57]. This report was published by an independent institution, the Institute for Clinical and Economic Review (ICER), a non-profit research organization that evaluates medical evidence. This group reported concerns about the validity of the findings reported in these phase 3 trials, including concerns about functional unblinding, strong, positive baseline beliefs about the benefits of MDMA in those involved (including participants, therapists, and researchers), discouragement of reporting negative effects of the treatment, financial accessibility, and instances of severe boundary violations by therapists[57]. This report has not been peer-reviewed, and was compiled through access to the published papers, speaking with participants, and second-hand information.

Whether or not the claims are substantiated, one particular risk of MDMA-assisted psychotherapy, and indeed all psychedelic-assisted therapies, is the risk of boundary violations by therapists and the vulnerability of the patient. There is a noted power imbalance between therapist and patient in traditional psychotherapies, which can be exacerbated when psychedelic drugs are introduced[58]. Psychedelics can impair cognition[59], enhance suggestibility[60], and may also result in a loss of the sense of self and the blurring of perceived boundaries with others[61]. In particular, MDMA is known to increase plasma oxytocin as well as to increase pro-social, empathetic, and sexual arousal-like effects[62]. This may put the patient in a situation where abuse of power by a therapist could occur more readily[58].

Adverse Effects of Standard Treatments

Since many of the standard treatments for PTSD and anxiety (e.g., CBT, antidepressants, anti-anxiety medications) are used to treat the conditions identified in the psilocybin review, please see the Psilocybin and LSD Overviews for adverse effects of these treatments. Two specific treatments for PTSD that have not been previously addressed are prolonged exposure (PE) therapy and eye movement reprocessing and desensitization (EMDR). Prolonged exposure (PE) therapy is an emotionally demanding form of therapy, and often aggravates the patient's symptoms before they improve[63]. Additionally, PE therapy puts the individual into a heightened state of arousal, with little time to process the experience before leaving the therapy session[17]. On the other hand, low drop-out rates for EMDR suggest that this treatment is fairly well-tolerated, even if the therapy brings up negative thoughts and emotions[64].

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