# Midomafetamine-Assisted Psychotherapy for Post-Traumatic Stress Disorder

**Evidence Report**

**May 14, 2024**

**Prepared for**

| ICER Staff and Consultants | University of Colorado Anschutz Medical Campus Modeling Group |
|---|---|
| **Reem A. Mustafa, MD, MPH, PhD**<br>Associate Professor of Medicine, Division of Nephrology and Hypertension<br>McMaster University<br>Director, Outcomes, and Implementation Research<br>University of Kansas Medical Center<br><br>**Dmitriy Nikitin, MSPH**<br>Senior Research Lead<br>Institute for Clinical and Economic Review<br><br>**Emily Nhan, BA**<br>Senior Research Assistant<br>Institute for Clinical and Economic Review<br><br>**Yasmine Kayali, BA**<br>Health Economics Research Assistant<br>Institute for Clinical and Economic Review<br><br>**Marina Richardson, PhD, MSc**<br>Senior Health Economist<br>Institute for Clinical and Economic Review<br><br>**David M. Rind, MD, MSc**<br>Chief Medical Officer<br>Institute Clinical and Economic Review | **Brett McQueen, PhD**<br>Associate Professor, Department of Clinical Pharmacy<br>University of Colorado Anschutz Medical Campus<br><br>**Antal Zemplenyi, PhD**<br>Visiting Research Associate<br>University of Colorado Anschutz Medical Campus<br><br>**Michael J. DiStefano, PhD**<br>Assistant Professor, Department of Clinical Pharmacy<br>University of Colorado Anschutz Medical Campus<br><br>*The role of the University of Colorado Anschutz Medical Campus is limited to the development of the cost- effectiveness model, and the resulting ICER report does not necessarily represent the view of the University of Colorado Anschutz Medical Campus.* |



**DATE OF PUBLICATION:** May 14, 2024

**How to cite this document:** Mustafa RA, McQueen B, Nikitin D, Nhan E, Zemplenyi A, DiStefano MJ, Kayali Y, Richardson M, Rind DM. MDMA-Assisted Psychotherapy for Post-Traumatic Stress Disorder: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review, May 14, 2024. https://icer.org/assessment/ptsd-2024/#overview

Reem Mustafa served as the lead author for the report. Dmitriy Nikitin led the systematic review and authorship of the comparative clinical effectiveness section in collaboration with Emily Nhan. Brett McQueen developed the cost-effectiveness model and authored the corresponding sections of the report in collaboration with Antal Zemplenyi and Michael DiStefano. Marina Richardson conducted analyses for the budget impact model in collaboration with Yasmine Kayali. David M. Rind provided methodologic guidance on the clinical and economic evaluations. We would also like to thank Yamaya Jean, Grace Ham, Anna Geiger, and Liis Shea for their contributions to this report.

## About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at https://icer.org/.

The funding for this report comes from non-profit foundations, with the largest single funder being Arnold Ventures. No funding for this work comes from health insurers, pharmacy benefit managers (PBMs), or life science companies. ICER receives approximately 22% of its overall revenue from these health industry organizations to run a separate Policy Summit program, with funding approximately equally split between insurers/PBMs and life science companies. The Draft Report erroneously listed Lykos Therapeutics as participating in this program. For a complete list of funders and for more information on ICER's support, please visit https://icer.org/who-we-are/independent-funding/.

For drug topics, in addition to receiving recommendations from the public, ICER scans publicly available information and also benefits from a collaboration with IPD Analytics, an independent organization that performs analyses of the emerging drug pipeline for a diverse group of industry stakeholders, including payers, pharmaceutical manufacturers, providers, and wholesalers. IPD provides a tailored report on the drug pipeline on a courtesy basis to ICER but does not prioritize topics for specific ICER assessments.

## About New England CEPAC

The New England Comparative Effectiveness Public Advisory Council (NE CEPAC) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. NE CEPAC seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The NE CEPAC Panel is an independent committee of medical evidence experts from across New England, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about New England CEPAC is available at New England Comparative Effectiveness Public Advisory Council (NE-CEPAC) - ICER.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

The economic models used in ICER reports are intended to compare the clinical outcomes, expected costs, and cost-effectiveness of different care pathways for broad groups of patients. Model results therefore represent average findings across patients and should not be presumed to represent the clinical or cost outcomes for any specific patient. In addition, data inputs to ICER models often come from clinical trials; patients in these trials may differ in real-world practice settings.

*In the development of this report, ICER's researchers consulted with clinical experts, patients, manufacturers, and other stakeholders. The following individuals served as external reviewers of the draft evidence report:*

## Expert Reviewers

**Diana Chao, BA**
**Executive Director**
**Letters to Strangers**
*No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers. Letter to Strangers has received a $5000 donation from an Executive Board Member at Pfizer, as a private individual donation, and she serves as an advisor on the Mental Health American Youth Council, who may have received funding from health care companies.*

**Arash Javanbakht, MD**
**Director of Stress, Trauma, and Anxiety Research Clinic (STARC)**
**Wayne State University School of Medicine**
*Dr. Javanbakht has received an honorarium in excess of $5,000 from Otsuka Pharmaceutical for providing education on PTSD as a disease, but not on any specific treatments. He is also an inventor of an augmented reality technology used for treatment of PTSD, in which the patent and license for this technology is owned by Wayne State University.*

**Dominic Trépel, PhD**
**Assistant Professor of Health Economics**
**Trinity College Dublin**
*No relevant conflicts of interest to disclose, defined as more than $10,000 in health care company stock or more than $5,000 in honoraria or consultancies during the previous year from health care manufacturers or insurers.*

*None of the external reviewers or other experts we spoke to are responsible for the final contents of this report, nor should it be assumed that they support any part of it. Furthermore, it is possible that external reviewers may not have had the opportunity to review all portions of this report. The report should be viewed as attributable solely to the ICER team and its affiliated researchers.*

*To protect patient confidentiality, ICER does not routinely name individual patients or care partners who provided us with input and feedback.*

*For a list of stakeholders from whom we requested input, or who have submitted public comments so far, please visit:* https://icer.org/wp-content/uploads/2024/05/PTSD_Stakeholder-List_051424.pdf

# Table of Contents

## List of Acronyms and Abbreviations Used in this Report

| | |
|---|---|
| 5Q-5D-5L | EuroQol-5 Dimensions-5 Levels |
| ACE | Adverse childhood experiences |
| AE | Adverse event |
| AHRQ | Agency for Healthcare Research and Quality |
| Asymp | Asymptomatic |
| AUD | Alcohol use disorder |
| AUDIT | Alcohol Use Disorders Identification Test |
| BDI | Beck Depression Inventory |
| BDI-II | Beck Depression Inventory II |
| BP | Blood pressure |
| CAPS | Clinician-Administered PTSD Scale |
| CAPS-4 | Clinician-Administered PTSD Scale for DSM-4 |
| CAPS-5 | Clinician-Administered PTSD Scale for DSM-5 |
| CBT | Cognitive-behavioral therapy |
| CE | Cost-effectiveness |
| CI | Confidence interval |
| CPT | Cognitive processing therapy |
| CRP | C-reactive protein |
| CSSRS | Columbia Suicide Severity Rating Scale |
| DEA | US Drug Enforcement Agency |
| DUDIT | Drug Use Disorders Identification Test |
| EMDR | Eye Movement Desensitization and Reprocessing |
| evLY | Equal value life year |
| FDA | U.S. Food and Drug Administration |
| HIDI | Health Improvement Distribution Index |
| I | Insufficient |
| ID | Identification |
| ITT | Intention to treat |
| LTFUQ | Long-term follow-up questionnaire |
| LSNAP | Lykos-specific non-assisted psychotherapy |
| M | Markov |
| MD | Mean difference |
| MDD | Major depressive disorder |
| MDMA | 3,4-methylenedioxymethamphetamine |
| MDMA-AP | MDMA-assisted psychotherapy |
| Mg | Milligram |
| Mod | Moderate |
| n | Number |
| N | Total Number |
| NA or N/A | Not applicable |
| NCT | National Clinical Trial |
| NH | Non-Hispanic |
| NR | Not reported |
| OUD | Opioid use disorder |
| PC | Placebo-controlled |
| PTGI | Posttraumatic Growth Inventory |
| PTSD | Post-traumatic stress disorder |
| QALY | Quality adjusted life year |
| QoL | Quality of life |
| RR | Relative risk |

| | |
|---|---|
| RCT | Randomized control trial |
| ROB | Risk of bias |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SDS | Sheehan Disability Scale |
| SMD | Standardized mean difference |
| SNRI | Serotonin and norepinephrine reuptake inhibitors |
| SR | Systematic review |
| SSRI | Selective serotonin reuptake inhibitors |
| SUD | Substance use disorder |
| TB | Triple-blind |
| TEAE | Treatment-emergent adverse event |
| TEAESI | Treatment-emergent adverse event of special interest |
| TFP | Trauma-focused psychotherapy |
| Tx | Treatment |
| US | United States |
| VA | United States Department of Veteran's Affairs |
| Vs | Versus |
| WAC | Wholesale acquisition cost |

# Executive Summary

Post-traumatic stress disorder (PTSD) is a complex psychiatric disorder associated with substantial disability and poor quality of life that occurs in people who have experienced or witnessed one or more traumatic events.[1] Traumatic events can include natural disasters, serious accidents, war and combat, rape and sexual assault, intimate partner violence and bullying. PTSD is a heterogeneous syndrome and, in some people, can be difficult to distinguish from anxiety and/or depression. PTSD can involve nightmares, flashbacks to traumatic events, intrusive thoughts, and avoidance of stimuli (including activities or situations) that trigger memories of trauma. Patients describe living with PTSD as a continuous challenge and many report ongoing symptoms over several years. It is common that individuals living with PTSD feel that not one aspect of their life has gone untouched by this condition.

In the United States, approximately 13 million people (5% of the adult population) suffer from PTSD every year with an overall lifetime prevalence of 6.1%.[2,3] PTSD disproportionally affects certain demographics including women, people from different racial and ethnic backgrounds and military veterans.[4] The total economic burden for PTSD in the US surpassed $232.2 billion in 2018, encompassing costs beyond normal health care expenses.[5]

Management of PTSD typically includes treatment with medications that are not specific to PTSD and with trauma-focused psychotherapies. Many patients find the current treatment options to be inadequate.

MDMA-assisted psychotherapy (MDMA-AP) is a novel treatment for PTSD that integrates psychotherapy with the administration of midomafetamine capsules [3,4-Methylenedioxy-methamphetamine](MDMA). MDMA as a street drug is known as “ecstasy” or “molly.” MDMA targets multiple neurotransmitters in the brain, including serotonin, noradrenaline, and dopamine, potentially mitigating fear responses and facilitating trauma-focused therapy sessions.[6] MDMA is administered orally in a clinic setting. In 2017, The Food and Drug Administration (FDA) granted MDMA-AP a breakthrough therapy designation. It is currently undergoing priority review with an expected FDA advisory committee meeting on June 4, 2024 and regulatory decision by August 11, 2024.[7]

The evidence base for MDMA-AP primarily comes from two Phase III clinical trials, MAPP1 and MAPP2 that evaluated the short-term efficacy and safety of MDMA-AP for treating moderate-to-severe PTSD. The two trials enrolled a total of 194 adults who met the DSM-5 criteria for either moderate (14%) or severe (86%) PTSD for at least six months; participants had a diagnosis of PTSD for approximately 15 years at study baseline; patients were 40 years old on average, two thirds (69%) were female. MDMA-AP involves a psychotherapy protocol unique to Lykos; the clinical trials

compared MDMA-AP to that same psychotherapy in combination with placebo. This report refers to the control arm as "LSNAP" (Lykos-specific non-assisted psychotherapy). MDMA-AP included three sessions with AP where treatment facilitated by MDMA was received from two co-therapists, one male and one female, with sessions typically lasting eight hours.

The primary endpoint of the MAPP1 and 2 trials was the reduction in PTSD symptoms as measured by the change from baseline in the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total severity score at approximately 18 weeks over three experimental sessions. In a meta-analysis of the two trials, compared with LSNAP, participants receiving MDMA-AP had a greater reduction in CAPS-5 (Mean difference -10.2). Patients treated with MDMA-AP were more likely than LSNAP to be treatment responders (relative risk [RR] 1.32), achieve a loss of diagnosis of PTSD (RR 1.7) and meet criteria for remission of PTSD (RR 2.86). Treatment-emergent adverse events were more common with MDMA-AP than LSNAP. AEs more commonly observed in patients receiving MDMA-AP included muscle tightness, decreased appetite, bruxism, hyperhidrosis (excessive sweating), and fatigue. Additionally, MDMA-AP led to increased occurrence of psychiatric safety events, including restlessness and insomnia. Our meta-analysis found very low certainty evidence that there was no increase in suicidal ideation with MDMA-AP compared with LSNAP (RR 0.89); patients receiving MDMA-AP were less likely to discontinue treatment (RR 0.32).

If these results are reflective of the expected outcomes if MDMA-AP is administered broadly to people with PTSD, it would be an important addition to treatment options for PTSD, an often severe and disabling condition. However, we have substantial concerns about the validity of the results. Because of the effects of MDMA, the trials were, essentially, unblinded with nearly all patients who received MDMA correctly identifying that they were in the MDMA arm of the trials. This would always raise concerns about bias, but these concerns are particularly heightened as we heard from multiple experts about the very strong prior beliefs of those involved in the trials (as investigators, therapists, and patients) about the benefits of MDMA-AP. Concerns have been raised by some that therapists encouraged favorable reports by patients and discouraged negative reports by patients including discouraging reports of substantial harms, potentially biasing the recording of benefits and harms. ICER discusses its (limited) investigation of these concerns in Section 2.1 and discusses overall uncertainties in "Uncertainties and Controversies."

Although we attempted to explore the concerns raised about MDMA-AP and the MAPP trials, ICER is not able to assess the frequency of misreporting of benefits and/or harms and thus the overall balance of net benefit with MDMA-AP. As such, we conclude that the current publicly-available evidence for MDMA-AP is insufficient ("I"). Given this, the evidence is also insufficient ("I") to compare MDMA-AP with trauma-focused psychotherapies.

Given these "I" ratings, the economic analyses of MDMA-AP in this Evidence Report are only exploratory analyses that provide insights into costs and benefits if it is assumed that the results of

the MAPP trials are accurate. For this reason, ICER is not providing Health Benefit Price Benchmarks for MDMA-AP.

# 1. Background

Post-traumatic stress disorder (PTSD) is a complex psychiatric disorder associated with substantial disability and poor quality of life that occurs in people who have experienced or witnessed one or more traumatic events.[1] Traumatic events can include natural disasters, serious accidents, war and combat, rape and sexual assault, intimate partner violence and bullying. Diagnostic criteria for PTSD require symptoms to have persisted for more than one month after the traumatic event and that the symptoms have caused distress or impairment in social, occupational, or other important areas of functioning.[8] PTSD is a heterogeneous syndrome and, in some people, can be difficult to distinguish from anxiety and/or depression. PTSD can involve nightmares, flashbacks to traumatic events, intrusive thoughts, and avoidance of stimuli (including activities or situations) that trigger memories of trauma. In the United States, approximately 13 million people (5% of the adult population) suffer from PTSD every year with an overall lifetime prevalence of 6.1%.[2,3] PTSD is more prevalent among women, certain ethnic and racial groups, and US veterans.[4] In 2018, the total economic burden beyond normal health care costs for PTSD in the US was estimated at $232.2 billion, or $19,630 per individual with PTSD.[5] The majority of these excess costs came from the civilian population, driven by direct health care and unemployment, while for the military population the main drivers were disability payments and direct health care.[5]

Management of PTSD typically includes treatment with medications and specific forms of psychotherapy. Selected antidepressants, including selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), are commonly used to treat the core symptoms of PTSD and prazosin is frequently used for sleep disturbance.[8] Commonly used psychotherapies include trauma-focused cognitive-behavioral therapy (CBT), prolonged exposure (PE) therapy, and eye movement desensitization and reprocessing (EMDR) therapy. For many patients, however, the current treatment options have been inadequate.

MDMA-assisted psychotherapy (MDMA-AP) is a novel treatment for PTSD that combines psychotherapy with the administration of midomafetamine capsules [3,4-Methylenedioxy-methamphetamine](MDMA). MDMA as a street drug is known as “ecstasy” or “molly.” MDMA affects multiple neurotransmitters in the brain, including serotonin, noradrenaline, and dopamine.[6] It is believed that MDMA may reduce the fear response and thus could facilitate therapy sessions that deal with trauma. MDMA is an oral treatment that can be administered in a clinic setting. Its peak effect occurs within two hours after ingestion and typically lasts three to six hours.[9] The MDMA-AP treatment regimen consists of three preparation sessions, three MDMA sessions, and nine integration sessions. The MDMA sessions typically lasted eight hours. Trial participants received treatment from two co-therapists, one male and one female. In the series of three experimental sessions, the first administration of MDMA consisted of 80 mg, followed by a

supplemental dose of 40 mg. In sessions two and three, the initial dosage was 80 or 120 mg, accompanied by a supplementary dose of 60 mg.

MDMA-AP was granted a breakthrough therapy designation by the Food and Drug Administration (FDA) in 2017. An FDA advisory committee meeting on MDMA-AP is scheduled for June 4, 2024, with the agency expected to make a regulatory decision on approval by August 11, 2024.[7]

# 2. Patient and Caregiver Perspectives

ICER developed this report with input from diverse stakeholders, including individuals living with PTSD and patient groups, researchers, and clinicians. To date, ICER has engaged with clinical and research experts, representatives from organizations which support people with PTSD, and multiple individuals with PTSD who represent different age groups, gender, background, and PTSD triggers. ICER appreciates the engagement with stakeholders throughout this review that provided valuable insights and understanding of the clinical effectiveness and value of treatments for PTSD.

Patients with PTSD have expressed concerns over the lack of new FDA-approved pharmaceutical treatments in the past two decades. Similarly, patients seeking trauma-focused psychotherapies encounter challenges related to accessibility and high dropout rates. As a result, some individuals feel compelled to self-medicate through substance use or to experiment with compounds that are either illegal or lack substantial research evidence.

Despite exhausting various treatment options and coping strategies over the years, many patients continue to report persistent PTSD symptoms. This can be attributed to the pervasive nature of PTSD, making routine activities of daily life, like travel, employment, and relationships with family and friends extremely difficult. Understandably, this can also place a significant burden on caregivers of individuals with PTSD, which in itself can also be a traumatic experience and necessitate the adjustment of responsibilities.

Common comorbidities such as anxiety, depression, and suicidal thoughts further exacerbate the challenges. The stigma surrounding PTSD underscores the importance of receiving a diagnosis to validate one's experiences. Successful PTSD therapy, as recognized by some patients, is one that can reduce symptom severity, enhance coping skills, alleviate suicidal ideation, and foster autonomy without reliance on medications.

In this context, the Department of Veterans Affairs' decision to fund research investigating MDMA alongside psychotherapy for PTSD has generated hope, especially among military veterans.[10] Some view this and other developments in the psychedelic-assisted psychotherapy space (e.g., psilocybin) as signaling a potential paradigm shift in how PTSD is managed.

## 2.1 Concerns About Trials of MDMA-AP

In ICER's engagement with stakeholders, we heard numerous concerns about the conduct of the MDMA-AP trials by Lykos Therapeutics (formerly MAPS Public Benefit Corporation). These included concerns about whether there were design choices that affected the interpretation of the results, but also whether there was misconduct that could have influenced the validity of the trial outcomes or that raised questions about the safety of MDMA-AP if it were implemented broadly outside of

clinical trials. We felt these concerns could potentially affect the interpretation of the evidence for MDMA-AP. As such, ICER conducted a number of interviews with those with firsthand or secondhand knowledge of the trials and related events. In this section, we will review issues raised by those discussions. To date, ICER has received relatively little input from Lykos Therapeutics, the sponsor of the trials. After publication of the Draft Report, Lykos submitted public comments on these concerns but still has not engaged in dialogue with ICER about the issues. The results of the MAPP trials are discussed in Section 3 of this Report.

Two major issues permeate most of the concerns affecting trial validity. The first of these is that the participants in the trials, including therapists and some number of the patients, came from a community with strong prior beliefs about the value of psychedelics for management of serious mental health conditions. The second is that because of the effects of MDMA, the trials were, essentially, unblinded with nearly all patients who received MDMA correctly identifying that they were in the MDMA arm of the trials. Of note, those with concerns about the MAPP trials also have strong beliefs, and this needed to be considered when evaluating information received by ICER.

We initially learned from experts that concerns about the MAPP trials were discussed in a podcast and then learned that complaints were made to Health Canada, the US FDA, and the US Department of Health and Human Services about issues with the trials.[11,12] As a result of this information, we spoke with a small number of people that included people involved with the podcast, subjects in the trials, and a therapist who had been involved in one of the trials. While opinions were not uniform, and we are striving to preserve anonymity, we are reporting in this section on what we heard, what conclusions we drew, and where uncertainty remains.

### *2.1.1. Trial Conduct Separate from Ethical Concerns*

We heard from multiple people that the CAPS-5 measures of improvement failed to capture participants overall response to MDMA-AP. We will discuss other reasons for this in the next section, but we repeatedly heard about participants experiencing improvement or resolution in the single trauma identified for the CAPS-5 measurements while new issues became overwhelming following MDMA-AP. We heard this from multiple people in ways that leave us with no doubt that this occurred – that is, that there were participants who improved on the CAPS-5 outcome while worsening overall – but, as with many issues we encountered, we are unable to assess the frequency of these events.

We heard that therapy was not well standardized in the MAPP trials and, as a result, it is hard to be certain how to generalize from the results. However, we also heard that this problem exists in many trials of psychotherapies for various disorders where it can be hard to separate the effects of the specific therapist from those of the general therapeutic approach.

### *2.1.2. Trial Conduct Entwined with Ethical Concerns*

The pool of therapists and, in some cases, trial participants appears to have pulled heavily from the existing community of those interested and involved in the use of psychedelics for possible psychological benefits ("the community"). This created multiple issues:

- We heard from various people that feelings around psychedelics lead the community to engage with them more like a religious movement than like pharmaceutical products, that these feelings were common in those participating in the MAPP trials, and that these feelings were sometimes inculcated in patients participating in the trials.

- Functional unblinding is a particular concern in this trial. As noted, patients were able to identify when they had received MDMA. Unblinding of therapists was particularly likely given their experience with psychedelic medications.[13] As discussed in Section 3, 40% of patients had prior experience with MDMA.

- We heard repeatedly about pressures to have the results of the MAPP trials be favorable. There apparently was a sense that such therapies are beneficial and needed and that negative results could hinder progress. This led to some participants feeling pressured to report good outcomes and suppress bad outcomes when they were in the MDMA arms of the trials. Additionally, for those who were part of the community, some participants felt they could be shunned if they reported bad outcomes or that it could lead to future patients being denied the benefits of MDMA-AP. We heard that positive reports generated positive feedback and negative reports generated negative feedback. We heard that this is a particular problem in people receiving MDMA as it makes them particularly suggestible and susceptible to context.

- Patients in the trials included therapists who had worked in this space, including some with very close relations with those running the clinical trials. This is unusual and heightens concerns about pressures to tailor reported results.

- We heard firsthand and secondhand reports of extremely severe negative outcomes for participants in the trials that do not seem to have been attributed to the treatment by the trial researchers. Some patients were told by their therapists that their negative outcomes were evidence that they were responding appropriately and would eventually improve. Some patients were prevented from entering the long-term follow-up study and felt this was done to keep these negative outcomes out of the data set.

- We heard of an event where, after the trial was completed and a participant was struggling, that they were told to take their own supply of MDMA at home. We heard secondhand reports of similar events. Even if this was only a singular event, it shows the clear

breakdown of blinding, the inclusion of participants who were anticipated to have access to their own supply of MDMA, and a disregard of good clinical trial practices.

### *2.1.3. Ethical Concerns Not Affecting Trial Results*

We heard a number of concerns from participants about events in the trials that upset them but that do not directly affect the results of the trial. These include concerns about inadequate post-trial support, treatment for trial-related harms not reimbursed by those running the trials, inadequate training of study therapists in management of treatment-associated adverse events, and difficulties receiving promised trial materials such as session video recordings. We include these here so that we are not ignoring what may be legitimate concerns of trial participants even if they do not affect our assessment of MDMA-AP.

### *2.1.4. Safety Concerns*

Based on public reports, there is no question that, despite the trial requiring dual treatment by one male and one female therapist, boundaries, including sexual boundaries, were severely crossed with at least one patient in a Phase II trial. We heard from multiple experts about the concerns this raises for treatment outside of clinical trials. Nearly everyone we spoke with discussed how MDMA breaks down barriers, heightens suggestibility, and creates a substantial risk with any therapists who might choose to take advantage of patients. Additionally, some experts highlighted concerns about lack of long-term data regarding cardiovascular harm.

Because of these concerns, multiple experts felt that the harms with real-world implementation of MDMA-AP will be much greater than would be expected from the clinical trials. As a result, a number of experts felt that more study was required before moving forward with MDMA-AP. However, at least some experts felt that the benefits of MDMA-AP are sufficient that, even given the likely harm to some individuals, overall MDMA-AP is valuable enough to approve.

### *2.1.5. Frequency of Benefits and Harms*

It seems clear that some people with severe PTSD experienced substantial benefit in the MAPP trials. We spoke with some patients who reported experiencing benefits even in the face of important harms and, in speaking with experts, including experts quite skeptical of the safety of MDMA-AP, they reported hearing stories from patients who believe they were greatly helped by MDMA-AP.

It is also clear that at least some people who participated in the MAPP trials experienced very severe harms. There seems to be some disconnect between the reporting of these harms in the clinical trials and what we heard from patients; however, it is possible that this is due to the timing of evaluation measures rather than deliberate attempts to suppress these reports.

Ultimately, based on our limited sample of participants, we are left very uncertain about the frequency of harms and benefits, the reliability of reports of benefits, and the generalizability of MDMA-AP to those outside the community. The difficulty in assessing the balance of benefits and harms is heightened by the very strong feelings of some proponents and skeptics of MDMA-AP that are unusual in most assessments of medical interventions. These myriad uncertainties are reflected in our overall ratings of certainty in Section 3 of this Report.

# 3. Comparative Clinical Effectiveness

## 3.1. Methods Overview

Procedures for the systematic literature review assessing the evidence on MDMA-AP for the treatment of PTSD are described in Supplement Section D1. A research protocol is published on Open Science Framework and registered with PROSPERO (CRD42023492605).

### Scope of Review

We reviewed the clinical effectiveness of MDMA as an add-on to Lykos-specific psychotherapy (MDMA-AP) versus an inactive placebo added on to Lykos-specific non-assisted psychotherapy ("LSNAP" thereafter) for the treatment of PTSD. The psychotherapy protocol used in tandem with the ingested MDMA is unique to Lykos Therapeutics and is available online. Briefly, it is a standardized treatment framework that prioritizes therapeutic alliance between patient and therapist, and employs a nondirective, empathic approach to facilitate healing from trauma.[14] Like other established psychotherapies for PTSD, it utilizes trauma-focused elements like exposure therapy, cognitive restructuring, and management of somatic and dissociative experiences to process traumatic memories. LSNAP is not intended as a standalone treatment for PTSD and its comparative effectiveness against other established psychotherapies has not been evaluated.

Additionally, we evaluated available evidence on the comparative effectiveness of MDMA-AP versus other short-term trauma-focused psychotherapies (TFP) commonly used for the treatment of PTSD. Clinical practice guidelines from the American Psychological Association and US Department of Veterans Affairs/US Department of Defense recommend the following TFPs as first-line treatment: trauma-focused cognitive behavioral therapy (CBT), cognitive processing therapy (CPT), cognitive therapy, prolonged exposure therapy (PE), and eye movement desensitization and reprocessing psychotherapy (EMDR). See Supplement Section C for an overview of PTSD clinical practice guidelines.

We sought evidence on patient-important outcomes, including improvements in PTSD symptoms, changes in patients' comorbidities such as functional impairment and depression, health-related quality of life, and adverse events. The full scope of the review is described in Supplement Section D1.

## Evidence Base

### *Research Question 1: MDMA-AP versus Lykos-Specific Non-Assisted Psychotherapy*

Our search identified 15 trials within the MDMA-AP clinical trial development program for the treatment of PTSD, including thirteen Phase II and two Phase III trials.[15] Prior systematic reviews of Phase II trial evidence (see Supplement Section D5) contributed to the Breakthrough Therapy designation by the FDA and revised study design of Phase III trials for MDMA-AP.[16]

This review primarily focuses on MAPP1 and MAPP2, the pivotal and confirmatory Phase III clinical trials that evaluated the short-term efficacy and safety of MDMA-AP for treating moderate-to-severe PTSD. The two trials enrolled a total of 194 adults who met the DSM-5 criteria for either moderate (14%) or severe (86%) PTSD for at least six months (see Table 3.1). Trial participants had a diagnosis of PTSD for approximately 15 years at study baseline; patients were 40 years old on average, two thirds (69%) were female, and the majority were White (71%). A majority of participants (85%) had multiple sources of trauma in connection with their PTSD. Previous treatment with a trauma-focused psychotherapy was common, with a smaller subset of participants reporting prior use of pharmacotherapy (sertraline or paroxetine). A notable subsection of the trial population (22%) had the dissociative PTSD subtype, hypothesized by some to be associated with more severe PTSD symptoms and more difficult to treat.[17,18] However, these hypotheses have not yet been conclusively validated.[19-21] A large subset of the trial population (~40%) had previous lifetime experience with MDMA; it is not clear whether this use constitutes therapeutic or recreational use of the drug. Nonetheless, the baseline use of MDMA in the trial population starkly contrasts with the estimated 0.8% of US population aged 12 and older who have used MDMA in 2021.[6] See Supplement Table D8 for additional study details and baseline information.

The trials applied various medical and psychiatric exclusion criteria. Participants were excluded if they had a primary psychotic disorder, bipolar I disorder, dissociative identity disorder, or an eating disorder involving purging. Also, exclusionary were major depression with psychosis, personality disorders, or severe substance use disorders not in remission. Recent substance use or frequent ecstasy use also prevented participation. For safety, those at serious suicide risk or with certain medical risks from stimulants due to possible elevated blood pressure and heart rate were excluded. See Supplement Table D7 for a full list of exclusion criteria.

The MDMA-AP treatment regimen consisted of three preparation sessions, three experimental sessions, nine integration sessions, and four endpoint assessments over the course of 18 weeks, concluding with a final study termination visit. Patients who were on psychiatric medications underwent a taper and washout period prior to baseline CAPS-5 assessment. Trial participants received treatment from two co-therapists with an estimated 84 therapist hours. In the series of three experimental sessions, the first administration of MDMA consisted of 80 mg, followed by a

supplemental dose of 40 mg. In sessions two and three, the initial dosage was 80 or 120 mg, accompanied by a supplementary dose of 60 mg.

We conducted a meta-analysis using evidence from the Phase III MAPP1 and 2 trials. Differences in trial design, measured outcomes, and data availability with previous phase II trials on MDMA-AP led to the exclusion of these trials from the meta-analysis (see Supplement Table D5). Evidence from Phase II trials are described qualitatively to provide a holistic picture of the treatment durability and safety profile of MDMA-AP, when appropriate. Results are presented as rate ratios (RR) for treatment response, suicidal ideation, and treatment discontinuation, and as mean (MD) and standardized mean differences (SMD) for change in PTSD and functional impairment symptoms, using fixed effect meta-analyses. See Supplement Section D2 for additional information on the methodology of the meta-analysis.

### *Research Question 2: MDMA-AP versus Trauma Focused Psychotherapies*

Our literature search did not find any head-to-head comparisons of MDMA-AP versus TFPs for PTSD. Therefore, we conducted qualitative indirect comparisons across several domains of interest, including treatment effect sizes, rates of remission and treatment discontinuation, and total hours of therapy. Evidence for this comparison was derived from the above clinical trials and supplemented with several publications that provided a narrative overview of MDMA-AP versus TFPs.[22-26]

**Table. 3.1. Overview of Key Studies[27-29]**

| Trial | | MAPP1 | | MAPP2 | |
|---|---|---|---|---|---|
| **Arms** | | **MDMA-AP** | **LSNAP** | **MDMA-AP** | **LSNAP** |
| **N** | | **46** | **44** | **53** | **51** |
| **Age, mean years (SD)** | | 43.5 (12.9) | 38.2 (10.4) | 38.2 (11) | 40 (9.6) |
| **Female, n (%)** | | 27 (58.7) | 32 (72.7) | 32 (60.4) | 42 (82.4) |
| **Hispanic or Latino ethnicity, n (%)** | | 5 (10.9) | 3 (6.8) | 17 (32.1) | 11 (21.6) |
| **Race, n (%)** | **Asian** | 2 (4.3) | 5 (11.4) | 5 (9.4) | 6 (11.8) |
| | **Black or African American** | 0 (0) | 2 (4.5) | 5 (9.4) | 3 (5.9) |
| | **White** | 39 (84.8) | 30 (68.2) | 37 (69.8) | 32 (62.7) |
| | **Multiple** | 2 (4.3) | 6 (13.6) | 6 (11.3) | 7 (13.7) |
| **Education level, n (%)** | **≤High school graduate** | 5 (10.9) | 1 (2.3)* | NR | NR |
| | **Some college** | 9 (19.6) | 11 (25.6)* | NR | NR |
| | **≥College graduate** | 32 (69.6) | 31 (72.1)* | NR | NR |
| **PTSD Duration, mean years (SD)** | | 14.8 (11.6) | 13.2 (11.4) | 16.3 (14.3) | 16.1 (12.4) |
| **PTSD severity, n (%)** | **Moderate†** | N/A | N/A | 13 (24.5) | 15 (29.4) |
| | **Severe‡** | 46 (100) | 44 (100) | 40 (75.5) | 36 (70.6) |
| **CAPS-5 total score, mean (SD)** | | 44 (6) | 44.2 (6.2) | 39.4 (6.6) | 38.7 (6.7) |

| Trial | | MAPP1 | | MAPP2 | |
|---|---|---|---|---|---|
| Arms | | MDMA-AP | LSNAP | MDMA-AP | LSNAP |
| N | | 46 | 44 | 53 | 51 |
| PTSD Dissociative subtype, n (%) | | 6 (13) | 13 (29.5) | 13 (24.5) | 11 (21.6) |
| Comorbid major depression, n (%) | | 42 (91.3) | 40 (90.9) | 49 (92.5) | 51 (100) |
| Pre-study PTSD medications, n (%) | Sertraline | 8 (17.4) | 9 (20.5) | 15 (28.3) | 10 (19.6) |
| | Paroxetine | 3 (6.5) | 3 (6.8) | 1 (1.9) | 1 (2) |
| Pre-study therapy, n (%) | CBT | 12 (26.1) | 22 (50) | 15 (28.3) | 14 (27.5) |
| | EMDR | 17 (37) | 13 (29.5) | 17 (32.1) | 18 (35.3) |
| | Group therapy | 19 (41.3) | 14 (31.8) | 9 (17) | 15 (29.4) |
| | Prolonged exposure therapy | 1 (2.2) | 0 (0) | 2 (3.8) | 0 (0) |
| | Psychodynamic | 11 (23.9) | 10 (22.7) | 15 (28.3) | 11 (21.6) |
| | Other | 41 (89.1) | 38 (86.4) | 41 (77.4) | 42 (82.4) |
| SDS modified score, mean (SD) | | 6.8 (2.1) | 7.4 (1.6) | 6 (NR)§ | 6.1 (NR)§ |
| Lifetime C-SSRS, n (%) | Positive lifetime suicidal ideation | 42 (91.3) | 41 (93.2) | 44 (83) | 47 (92.2) |
| | Serious lifetime suicidal ideation | 20 (43.5) | 17 (38.6) | 15 (28.3) | 18 (35.3) |
| Prior report of MDMA use in lifetime, n (%) | | 18 (39.1) | 11 (25) | 22 (41.5) | 26 (51) |

CAPS-5: Clinician-Administered PTSD Scale for DSM-5, CBT: cognitive behavioral therapy, C-SSRS: Columbia Suicide Severity Rating Scale, EMDR: eye movement desensitization and reprocessing, LSNAP: Lykos-specific non-assisted psychotherapy, MDMA: 3,4-Methylenedioxymethamphetamine, MDMA-AP: MDMA-assisted psychotherapy, n: number, N: total number, N/A: not applicable, NR: not reported, PTSD: Post-traumatic stress disorder, SD: standard deviation, SDS: Sheehan Disability Scale
*N=43.
†Moderate PTSD was defined as a CAPS-5 score between 28-34.
‡Severe PTSD was defined as a CAPS-5 score ≥35.
§Data were averaged across available SDS subscale data.

# 3.2. Results

## Research Question 1: MDMA-AP versus Lykos-Specific Non-Assisted Psychotherapy

### *Maintenance of Blinding*

The psychoactive and physiological effects of MDMA may make it difficult to maintain blinding of participants and therapists. The MAPP2 trial assessed the accuracy of participants' conclusions about whether they had received MDMA or placebo. As shown in Table 3.2, 94% of trial participants in the MDMA-AP arm correctly guessed their assigned treatment, while in the LSNAP arm, 75% did so. An informal evaluation of blinding in MAPP1 trial participants indicated comparable levels of awareness regarding their treatment assignment. Maintenance of blinding among trial therapists was not assessed in either trial.

**Table 3.2. Maintenance of Blinding Among Trial Participants**

| Trial | MAPP2 | |
|---|---|---|
| **Arms** | **MDMA-AP** | **LSNAP** |
| **N** | **52** | **44** |
| **MDMA - I am positive** | 41 (78.8) | 2 (4.5) |
| **MDMA - I think** | 8 (15.4) | 7 (15.9) |
| **LSNAP - I am positive** | 1 (1.9) | 19 (43.2) |
| **LSNAP - I think** | 0 (0) | 14 (31.8) |
| **Cannot tell** | 2 (3.8) | 2 (4.5) |

MDMA: 3,4-Methylenedioxymethamphetamine, MDMA-AP: MDMA-assisted psychotherapy, LSNAP: Lykos-specific non-assisted psychotherapy, N: total number

### *Clinical Benefits*

*Reduction in PTSD Symptoms*

The primary endpoint of the MAPP1 and 2 trials was the reduction in PTSD symptoms as measured by the change from baseline in the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total severity score at approximately 18 weeks over three experimental sessions. The CAPS-5 was developed and validated using a predominantly male military population.[30] The scale requires the identification of a single index trauma for symptom inquiry. See Supplement Section A1 for additional information on CAPS-5 and other study outcome definitions.

There is no agreed upon definition of a clinically meaningful treatment response on the CAPS-5 measurement tool.[31] Manufacturer collaboration with the FDA via a Special Protocol Assessment established that a 10-point or greater reduction in the CAPS-5 total severity score as clinically meaningful.[27]

After three experimental sessions, trial participants in the MDMA-AP study arm achieved a favorable 10-point difference versus LSNAP [Mean difference (MD) -10.18 (95% CI -13.80, -6.56)](Table 3.3).The standardized measure of effect size, Cohen's *d*, between the two groups was 0.8 (95% CI 0.49 to 1.1) standard deviation units, suggesting a large treatment effect size.

In addition to the numerical change in CAPS-5 total score, the differential impact of MDMA-AP versus LSNAP on PTSD symptoms was also presented via the exploratory outcome of three responder categories: responder (≥10-point reduction from baseline), loss of diagnosis (≥10-point reduction from baseline and no longer meeting PTSD diagnostic criteria), and remission (CAPS-5 Total Severity Score of 11 or less and no longer meeting PTSD diagnostic criteria). Patients treated with MDMA-AP were more likely than LSNAP to be treatment responders ((RR) 1.32 (95% CI: 1.11 to

1.58), achieve a loss of diagnosis (RR 1.7; 95% CI: 1.26 to 2.29) and meet the criteria for remission (RR 2.86; 95% CI: 1.58 to 5.16) (Table 3.3).

*Durability of Treatment Effect*

The reduction in PTSD symptoms seen in Phase III trial participants was measured two months after the third and final experimental session, demonstrating a short-term health benefit. Long-term follow-up (LTFU) data of MAPP1 and 2 are not yet available. MPLONG is an ongoing LTFU observational study of trial participants from Phase II and III trials who have completed at least one experimental session of MDMA-AP (see Supplement Section D4). Non-quantitative preliminary results of MPLONG were released in 2023, suggesting that participants displayed improvements in PTSD symptoms as measured by CAPS-5 total severity score at least six months after the final dosing session.[32,33] These results have not yet been published in a peer-reviewed article.

An earlier pooled analysis of six Phase II trials found that among participants who received active doses of MDMA (75-125 mg) plus psychotherapy in blinded or open-label sessions, there was a small further reduction in PTSD symptom severity scores (as assessed by an older version of the CAPS tool) and an increase in the proportion who no longer met criteria for PTSD.[34] This was observed at a follow-up timepoint of at least 12 months after initially completing the studies. However, the lack of a control group, differences in trial designs, and potential confounding effects of post-study psychotherapy or medication use greatly limit the certainty and conclusiveness of these LTFU findings.

*Change in Functional Impairment*

The Sheehan Disability Scale (SDS) is a measure of functional impairment in the three domains of work/school, social life, and family life/home responsibilities. Like the CAPS-5 outcome, evidence on functional impairment was reported as a change from baseline at 18 weeks over three experimental sessions using a modified SDS score that represented an average of the three domain scores.

A greater mean reduction in modified SDS score was seen with MDMA-AP than LSNAP (-1.5; 95% CI: -1.6 to -1.4). There is no established threshold for what constitutes a clinically meaningful reduction in SDS score among PTSD patients; the Cohen's d between-group effect size indicated a small-to-medium effect (SMD: 0.42; 95% CI: 0.17 to 0.66) (Table 3.3).[35] Changes within the three domains of the SDS were reported only in MAPP2; the drop in SDS score among the three domains appeared to be similar in magnitude.

*Impact on PTSD Comorbidities*

The effects of MDMA-AP on common comorbidities associated with PTSD, such as depression, alcohol use disorder, cannabis use, and eating disorders, were assessed through several exploratory outcomes. However, published evidence on these outcomes was limited to the MAPP1 study.

In MAPP1, the reduction in depressive symptoms was measured using the Beck Depression Inventory (BDI-II) at 18 weeks compared to baseline. MDMA-AP showed a greater reduction in the BDI-II score (-19.7 points) compared to LSNAP (-10.8 points) (P = 0.0026). Both MDMA-AP and LSNAP resulted in notable reductions in depressive symptoms, with a decrease of 65% and 31% in BDI-II score, respectively. These findings meet the criteria for a minimal clinically important difference, as defined by either the National Institute for Health and Care Excellence (NICE) guidelines (which suggest a difference of $\geq$ 3 BDI-II points) or a patient-centered approach that considers a 17.5% reduction in scores from baseline as clinically significant based on the patient's self-reported improvement.[36]

Trial participants with an active alcohol, substance abuse, or eating disorder were not eligible for inclusion in the MAPP1 trial. Baseline mean scores of AUDIT (Alcohol Use Disorders Identification Test), DUDIT (Drug Use Disorders Identification Test), and EAT-26 (Eating Attitudes Test 26) did not meet their respective thresholds for clinical diagnosis.[29,37] The small sample sizes and narrow distribution of baseline scores greatly limit the generalizability of these exploratory analyses.

*Other Patient-Important Outcomes*

We identified additional patient-important outcomes that were in the scope of our review (Supplement Section D1 for PICOTS) for which data were collected in the MAPP1/2 trials but not reported (See Supplement Table D6 for overview of MAPP1 and 2 outcome availability).[9,38] These include health related quality of life (measured via EQ-5D-5L) and health and work-related productivity (Health and Productivity Questionnaire Short Form).

**Table 3.3. Meta-Analysis of Key Clinical Efficacy Results[27,28]**

| Outcome | MAPP1 | | MAPP2 | | Overall Effect Estimates |
|---|---|---|---|---|---|
| | MDMA-AP | LSNAP | MDMA-AP | LSNAP | |
| **N*** | **46** | **44** | **53** | **51** | |
| **CAPS-5 Between Group Difference, Treatment Effect (SE)** | -11.9 (2.83) | | -8.9 (2.44) | | MD (95% CI): -10.18 (-13.80, -6.56) |
| **CAPS-5 Effect Size, Cohen's *d*,† Treatment Effect (SE)** | 0.91 (0.23) | | 0.7 (0.21) | | SMD (95% CI): 0.80 (0.49, 1.10) |
| **Treatment Responder§, n/N** | *37/42‡* | *23/37‡* | *45/52‡* | *29/42‡* | RR (95% CI): 1.32 (1.11,1.58) |
| **Loss of Diagnosis#, n/N** | 28/42 | 12/37 | *37/52‡* | *20/42‡* | RR (95% CI): 1.70 (1.26, 2.29) |
| **Remission¤, n/N** | 14/42 | 2/37 | *24/52‡* | *9/42‡* | RR (95% CI): 2.86 (1.58, 5.16) |
| **SDS Score (After Session 3), Mean (SD)** | *3.7 (0.5)‡* | *5.3 (0.4)‡* | *2.7 (0.4)‡* | *4.1 (0.4)‡* | MD (95% CI): -1.48 (-1.60, -1.36) |
| **SDS Effect Size, Cohen's *d*,† Treatment Effect (SE)** | 0.43 (0.17) | | 0.4 (0.18) | | SMD (95% CI): 0.42 (0.17, 0.66) |

CAPS-5: Clinician-Administered PTSD Scale for DSM-5, CI: confidence interval, LSNAP: Lykos-specific non-assisted psychotherapy, MD: mean difference, MDMA-AP: MDMA-assisted psychotherapy, n: number, N: total number, RR: relative risk, SD: standard deviation, SDS: Sheehan Disability Scale, SE: standard error, SMD: standardized mean difference, vs.: versus

*The number of participants differ by each outcome. See Supplement Table D9 for more details.

†Cohen's *d* effect size is defined as a value measuring the size of the difference between the treatment and control groups.

‡Data were digitized.

§Responder was defined as ≥10-point decrease in CAPS-5.

#Loss of diagnosis was defined as ≥10-point reduction in CAPS-5 and not meeting PTSD diagnostic criteria.

¤Remission was defined as loss of diagnosis and a total CAPS-5 score of ≤11.

### *Harms*

During the 18-week follow-up period in the MAPP1 and 2 trials, treatment-emergent adverse events (TEAEs) were common, occurring in 96-100% of participants.[27,28] The MDMA-AP arm had a higher incidence of these events compared to LSNAP (Table 3.4). These events were generally of short duration and characterized as mild to moderate in terms of severity. AEs more commonly observed in patients receiving MDMA-AP versus LSNAP included muscle tightness, decreased appetite, bruxism, hyperhidrosis (excessive sweating), and fatigue. Additionally, MDMA-AP led to increased occurrence of psychiatric safety events, including restlessness and insomnia. Additional safety data from MAPP1 and 2 can be found in Supplement Table D10. Increases in blood pressure, body temperature, and heart rate were observed, but were transient and expected based on Phase II safety data. Adverse events from a pooled analysis of six Phase II trials demonstrated a similar safety profile. Among the 72 trial participants receiving 75 to 125 mg of MDMA-AP in two or three experimental sessions, the most frequent AEs included anxiety (72%), jaw clenching/tight jaw (64%), and headache (53%).[16]

Higher rates of discontinuation occurred in the LSNAP arms of the MAPP1 and 2 trials (16% in both MAPP1 and 2) compared to the MDMA-AP arms (1.9 and 8.7%), with meta-analysis results indicating that MDMA-AP lowered the risk of treatment withdrawals (RR: 0.32; 95% CI: 0.12-0.85) (Table 3.5). Although a small number of discontinuations were linked to safety concerns, there was at least one instance where a participant who suspected they were receiving LSNAP treatment withdrew from the study.[28]

For harms of special interest, there were reports of cardiac AEs, such as palpitations and tachycardia, but they were infrequent and mild in severity. There were no reported data on long-term cardiovascular events. MDMA-AP did not lead to increased risk of MDMA abuse during or after the therapy.

The MAPP1 and 2 trials used the Columbia Suicide Severity Rating Scale (C-SSRS) to monitor suicidal risk at baseline and each site visit. Patients at serious imminent suicide risk at baseline were

excluded. At baseline, 90% reported a lifetime history of suicidal ideation, 36% reported serious suicidal ideation, and 32% (reported in MAPP1 only) reported a history of suicidal behavior. These percentages reflect the established high prevalence of suicide risk in PTSD patients.[39] Due to inconsistent reporting of suicidal events between MAPP1 and MAPP2 publications, suicidal ideation events were extracted from ClinicalTrials.gov results for both Phase III trials. Our meta-analysis found very low certainty that there is no increased risk of suicidal ideation with MDMA-AP (RR: 0.89; 95% CI: 0.64-1.24) (Table 3.5).

Lastly, a case of high safety concern related to inappropriate therapist behavior emerged in a previous Phase II clinical trial. One study participant reported an incident of sexual misconduct during a study session, in which the psychiatrist and her unlicensed therapist husband deviated from the study protocol to perform intimate physical contact with the participant during a distress episode, while she was in a mind-altered state under MDMA treatment. The participant also reported nonconsensual sexual relations occurring with the unlicensed therapist after the completion of the experimental sessions, but during enrollment of the trial.[40,41] Due to concerns of participant safety and therapist compliance, the Phase II study was temporarily suspended to prioritize federal review of all trials involving MDMA.[42]

Our findings are consistent with other groups' independent assessment showing that MDMA-AP may be associated with increased risk of harm with very low certainty about the exact magnitude of the effect due to concerns about study conduction, as well as a discrepancy between published articles and clinicaltrials.gov pages for four serious adverse events, including one case of suicidal behavior.[43] These findings also highlight the need for additional studies to better characterize the safety profile of MDMA-AP.

**Table 3.4. Key Trial Harms[27,28,44,45]**

| Trial | | MAPP1 | | MAPP2 | |
|---|---|---|---|---|---|
| Arms | | MDMA-AP | LSNAP | MDMA-AP | LSNAP |
| N | | 46 | 44 | 53 | 51 |
| Timepoint | | 18 Weeks | | 18 Weeks | |
| AEs, n (%) | Muscle tightness | 29 (63)* | 5 (11.4)* | 31 (58.5) | 13 (25.5) |
| | Decreased appetite | 24 (52.2) | 5 (11.4) | 19 (35.8) | 5 (9.8) |
| | Hyperhidrosis (excessive sweating) | 9 (19.6)* | 1 (2.3) | 18 (34.0) | 3 (5.9) |
| | Headache | 33 (71.7) | 24 (54.6) | 38 (71.7) | 31 (60.8) |
| | Mydriasis (dilated pupils) | 7 (15.2) | 0 (0) | 6 (11.3) | 0 (0) |
| | Bruxism (teeth grinding) | 6 (13) | 1 (2.3) | 7 (13.2) | 1 (2) |
| | Nystagmus (uncontrolled repetitive eye movement) | 6 (13) | 0 (0) | 7 (13.2) | 1 (2) |
| | Blood Pressure Increased | 5 (10.9) | 0 (0) | NR | NR |

| Trial | | | MAPP1 | | MAPP2 | |
|---|---|---|---|---|---|---|
| Arms | | | MDMA-AP | LSNAP | MDMA-AP | LSNAP |
| N | | | 46 | 44 | 53 | 51 |
| Timepoint | | | 18 Weeks | | 18 Weeks | |
| | Feeling Jittery | | 5 (10.9)* | 0 (0) | 8 (15.1) | 0 (0) |
| | Palpitations | | 4 (8.7)† | 6 (13.6)† | 5 (9.4) | 1 (2.0) |
| | Fatigue | | 14 (30.4)† | 14 (31.8)† | 14 (26.4) | 9 (17.7) |
| | Restlessness | | 7 (15.2) | 0 (0) | 8 (15.1) | 2 (3.9) |
| | Anger | | 3 (6.5)† | 6 (13.6)† | NR | NR |
| | Anxiety | | 15 (32.6) | 17 (38.6) | 15 (28.3)† | 12 (23.5)† |
| | Depressed mood | | 5 (10.9)† | 4 (9.1)† | 5 (9.4)† | 6 (11.8)† |
| | Insomnia | | 20 (43.4)† | 13 (29.6)† | 19 (35.9)† | 15 (29.4)† |
| | Suicidal Ideation | | 21 (45.6)† | 21 (47.73)† | 18 (34)† | 21 (41.2)† |
| | Intentional self-injury | | 1 (2.2)† | 4 (9.1)† | NR | NR |
| Treatment-Emergent AESIs, n (%) | Suicidality | Non-suicidal self-injurious behavior | NR | NR | 1 (1.9) | 1 (2) |
| | | Trichotillomania (urge to pull out hair) | NR | NR | 0 (0) | 1 (2) |
| | Abuse potential for MDMA | | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

AE: adverse event, AESI: adverse event of special interest, LSNAP: Lykos-specific non-assisted psychotherapy, MDMA: 3,4-Methylenedioxymethamphetamine, MDMA-AP: MDMA-assisted psychotherapy, n: number, N: total number, NR: not reported

*There is a discrepancy between publication and ClinicalTrials.gov data value. This value is from the publication.

†Data found only on ClinicalTrials.gov.

**Table 3.5. Meta-Analysis Key Safety Results[27,28,44,45]**

| Outcome | MAPP1 | | MAPP2 | | Overall Effect Estimates |
|---|---|---|---|---|---|
| | MDMA-AP | LSNAP | MDMA-AP | LSNAP | |
| N | 46 | 44 | 53 | 51 | |
| Treatment Discontinuation, n/N | 4/46 | 7/44 | 1/53 | 8/51 | RR (95% CI): 0.32 (0.12, 0.85) |
| Suicide Ideation, n/N | 21/46* | 21/44* | 18/53* | 21/51* | RR (95% CI): 0.89 (0.64, 1.24) |

CI: confidence interval, LSNAP: Lykos-specific non-assisted psychotherapy, MDMA-AP: MDMA-assisted psychotherapy, n: number, N: total number, RR: relative risk

*Data are from ClinicalTrials.gov.

## Subgroup Analyses and Heterogeneity

We reviewed exploratory analyses to evaluate whether demographics and clinical characteristics impacted treatment response to MDMA-AP in our phase III trials (See Supplement Table D13-14). Specifically, we examined the effects of PTSD subtype (dissociative PTSD), sex assigned at birth, age,

race/ethnicity, prior SSRI use, military service, and prior psychotherapy on MDMA-AP versus LSNAP for PTSD symptom severity outcomes (CAPS-5). Irrespective of treatment, dissociative PTSD in one trial (MAPP1) and sex assigned at birth in the other trial (MAPP2) were shown to impact PTSD symptoms. Similarly, dissociative subtype in MAPP1 and SSRI use in MAPP2 were significantly associated with differential treatment responses; however, these subgroup effects were not consistent across both studies. Age did not impact response. Racial and ethnic differences, military service, and prior psychotherapy's role were not investigated as part of these analyses. These analyses, which were likely underpowered and did not correct for multiple covariate comparisons, do not provide any definitive conclusions regarding the differential treatment response to MDMA-AP.

## Research Question 2: MDMA-AP versus Trauma-Focused Therapies

Differences in study design, baseline medication use, sample sizes, patient criteria, and the therapies themselves make it challenging to directly compare the effectiveness of MDMA-AP to other trauma-focused psychotherapies based on available research.[22] More head-to-head studies controlling for these factors would be needed to better understand the relative effectiveness. Below, we provide a qualitative overview of some notable comparisons between MDMA-AP and TFPs.

### *Clinical Benefits*

*Treatment Effect Size*

MDMA-AP has demonstrated a moderate to large treatment effect for reducing PTSD symptoms as compared to LSNAP with a Cohen's *d* of 0.8 (95% CI 0.49 to 1.1) per meta-analysis of Phase III trial data. Meta-analysis results of TFPs versus comparators of a waitlist and standard of care have demonstrated treatment effect sizes of similar magnitude.[25] A network meta-analysis showed that EMDR (SMD=2.07, 95% CI 1.44-2.70) and TF-CBT (SMD=1.46, 95% CI 1.05-1.87) had large effects on reducing PTSD symptoms compared to waitlist.[46] Another meta-analysis found that CBT (SMD= 0.90; 95% CI 0.68-1.11), exposure therapy (SMD=1.05; 95% CI 0.58-1.52), and EMDR (SMD=1.26; 95% CI: 0.51 to 2.01) were more effective than usual care for complex PTSD.[47] However, the treatment effect sizes of TFPs may be overinflated considering their use of an inactive comparator, whereas MDMA-AP was compared to LSNAP, that, on its own, demonstrated a clinically meaningful reduction in PTSD symptoms (approximately 14-point drop in CAPS-5 score in both MAPP1/2 trials).

*Rates of Remission*

Across the MAPP1 and 2 trials, approximately 40% of participants treated with MDMA-AP over 18 weeks no longer met the criteria for a PTSD diagnosis and achieved a score of 11 or lower on the CAPS-5, indicating remission from PTSD. A meta-analysis of 20 CBT for PTSD trials found a mean rate

of remission of 53.3% (95 CI: 45.3%–61.1%) in its intention-to-treat population, with an increase to 62.8 % (95 CI: 52.1%- 72.3%) among completers.[48] Comparing the findings between the MAPP1 and 2 trials and the meta-analysis of CBT for PTSD trials is challenging due to variations in the definitions of remission criteria and the duration of the trials.

***Harms***

*Treatment Discontinuation*

One barrier to widespread adoption of trauma-focused psychotherapies is that they may induce emotional distress during exposure-based elements. The intensity of trauma processing can result in high dropout rates from therapy ranging from 13-30% across different TFPs.[49-51] Although TFPs can be delivered through different treatment formats, an intensive approach involving more frequent sessions with fewer days between each session has been associated with lower dropout rates. Notably, intensive TFPs have demonstrated a pooled attrition rate of 5%.[52]

MDMA-AP is hypothesized to work by reducing fear and avoidance of trauma-related memories and thoughts, allowing them to be accessed and processed with less distress.[53] This comparison appears to be promising; within the MAPP1/2 trials, the MDMA-AP treatment arm had a low (5%) rate of treatment discontinuation, with a reduced risk of dropout compared to LSNAP (RR 0.32; 95% CI: 0.12, 0.85).[49,50] However, the difference in dropout may be partially explained by the functional unblinding seen in both MAPP trials and the corresponding heightened expectancy effect outlined in Section 2.1 of the report.

*Duration of Treatment/Resource Utilization*

The MDMA-AP protocol requires three 90-minute preparation sessions, three 8-hour MDMA-AP assisted sessions, and nine 90-minute integration sessions, totaling approximately 42 hours of therapy. It involves two therapists per patient, with at least one holding a master's degree or higher, and additional training.[27] This requirement contrasts with typical TFPs which may involve only 8 to 20 hours of exposure with one therapist.[25]

## Uncertainty and Controversies

- As discussed above, the rates of accurate conclusion by participants as to whether they had received MDMA or placebo means that the MAPP trials were functionally unblinded. This makes it very difficult to assess outcomes in comparison with a control arm.

- Differences in co-interventions in the intervention and control arms of the MAPP trials are concerning. In MAPP1, more patients in the MDMA-AP arm than the LSNAP arm received additional integrative sessions.

- As discussed in Section 2.1, we have concerns that investigator/therapist biases may have influenced reporting of benefits and harms within the MAPP trials. The safety data collection relied on site therapists, unlike the primary and secondary study outcomes which were assessed by blinded and independent raters.[27]

- CAPS-5 focuses on a single index trauma and changes in symptoms related to that event. We heard multiple concerns that, with MDMA-AP, multiple other traumas could come to the forefront such that changes in CAPS-5 might not reflect changes in global PTSD symptomatology and may lead to misleading results. Related to this, CAPS-5 was developed and validated using a predominantly male military population. It is unclear how well it captures changes in PTSD in a population of women and those who may have experienced repeated physical and/or sexual traumas.

- Important prespecified endpoints have not been consistently reported across the two MAPP trials. This raises concerns about reporting bias.

- A large percentage of patients (40%) in the MAPP trials had prior experience with MDMA. This raises generalizability concerns to a population naïve to psychedelics.

- The comparison arm in the MAPP trials was an unproven therapy.[54] This makes it difficult to know how MDMA-AP compares with trauma-focused therapies. Hence, it is unclear whether MDMA added to existing trauma-focused therapies might have superior efficacy to MDMA-AP.

- Harms reported in published clinical trials of MDMA-AP, are unlikely to represent all potential adverse effects of the therapy due to small sample sizes and short follow-up periods. We heard from experts that MDMA can have cardiovascular risks and that there are concerns about safety in a population that is not carefully screened for pre-existing cardiovascular disease. We also have concerns about the use of MDMA-AP in patients with concurrent substance abuse. These patients were excluded from the MAPP trials, but substance abuse is common in people with PTSD. Clinical experts have emphasized that certain cardiovascular and long-term neurological impacts may be challenging to detect within the confines of short-term studies and additional data are needed to evaluate them.

- We heard concerns about the abuse potential of MDMA if it becomes a legally prescribed medication. While MDMA-AP did not lead to increased risk of MDMA abuse during or after the therapy in the trails, longer-term data are needed to better understand the abuse potential of MDMA beyond the clinical trial setting.

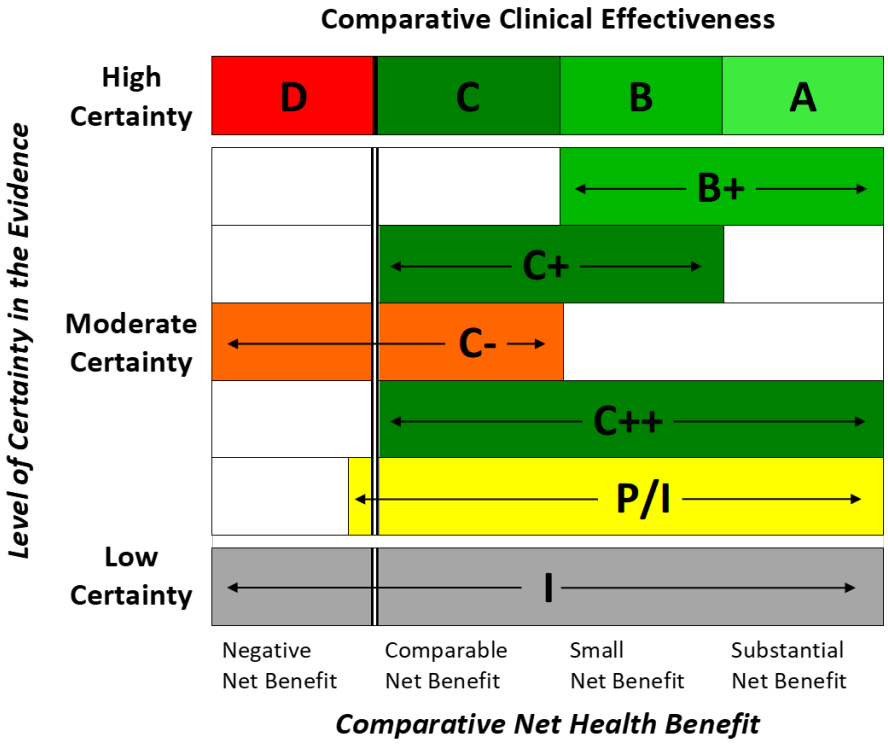
- Even in carefully controlled clinical trials with two therapists of different sexes, therapist misbehavior occurred. We heard concerns about much greater risks if MDMA-AP is administered outside of such controlled settings. Additionally, we heard skepticisms that it would be affordable/workable to have dual therapists in most clinical situations.

- Implementing MDMA-AP would be challenging for health care systems like the VA,[55] which already faces increasing mental health demand and staff shortages. The substantial therapist time and specialized training required could make widescale MDMA-AP adoption difficult.[56]

## 3.3. Summary and Comment

An explanation of the ICER Evidence Rating Matrix (Figure 3.1) is provided here.

**Figure 3.1. ICER Evidence Rating Matrix**




***A = "Superior" -*** *High certainty of a substantial (moderate-large) net health benefit*
***B = "Incremental" -*** *High certainty of a small net health benefit*
***C = "Comparable"-*** *High certainty of a comparable net health benefit*
***D= "Negative"-*** *High certainty of an inferior net health benefit*
***B+= "Incremental or Better" –*** *Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
***C+ = "Comparable or Incremental" -*** *Moderate certainty of a comparable or small net health benefit, with high certainty of at least a comparable net health benefit*
***C- = "Comparable or Inferior" –*** *Moderate certainty that the net health benefit is either comparable or inferior with high certainty of at best a comparable net health benefit*
***C++ = "Comparable or Better" -*** *Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
***P/I = "Promising but Inconclusive"*** *- Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit*
***I = "Insufficient" –*** *Any situation in which the level of certainty in the evidence is low*

The MAPP trials reported important improvements in many patients treated with MDMA-AP and relatively few short-term harms. If these results are reflective of the expected outcomes if MDMA-AP is administered broadly to people with PTSD, it would be an important addition to treatment options for PTSD, an often severe and disabling condition. However, for the reasons discussed in Section 2.1 and in "Uncertainties and Controversies," we have substantial concerns about the validity and generalizability of the results of the MAPP trials. We heard from multiple experts separate from those raising the concerns discussed in Section 2.1 that, while very hopeful about potential benefits from using psychedelics as part of PTSD treatment, they believed additional trials were needed to prove that the potential benefits of MDMA-AP outweigh potential harms.

Although we attempted to explore the concerns raised about MDMA-AP and the MAPP trials, ICER is not able to assess the frequency of misreporting of benefits and/or harms and thus the overall balance of net benefit with MDMA-AP. As such, we conclude that the current publicly-available evidence for MDMA-AP is insufficient ("I"). Given this, the evidence is also insufficient ("I") to compare MDMA-AP with trauma-focused psychotherapies.

**Table 3.6. Evidence Ratings**

| Treatment | Comparator | Evidence Rating |
|---|---|---|
| **Adults with moderate to severe PTSD** | | |
| **MDMA-AP** | Lykos specific non-assisted psychotherapy | I |
| **MDMA-AP** | Trauma Focused Psychotherapies | I |

MDMA-AP: MDMA-assisted psychotherapy, I: insufficient, PTSD: Post-traumatic stress disorder

# 4. Long-Term Cost Effectiveness

## 4.1. Methods Overview

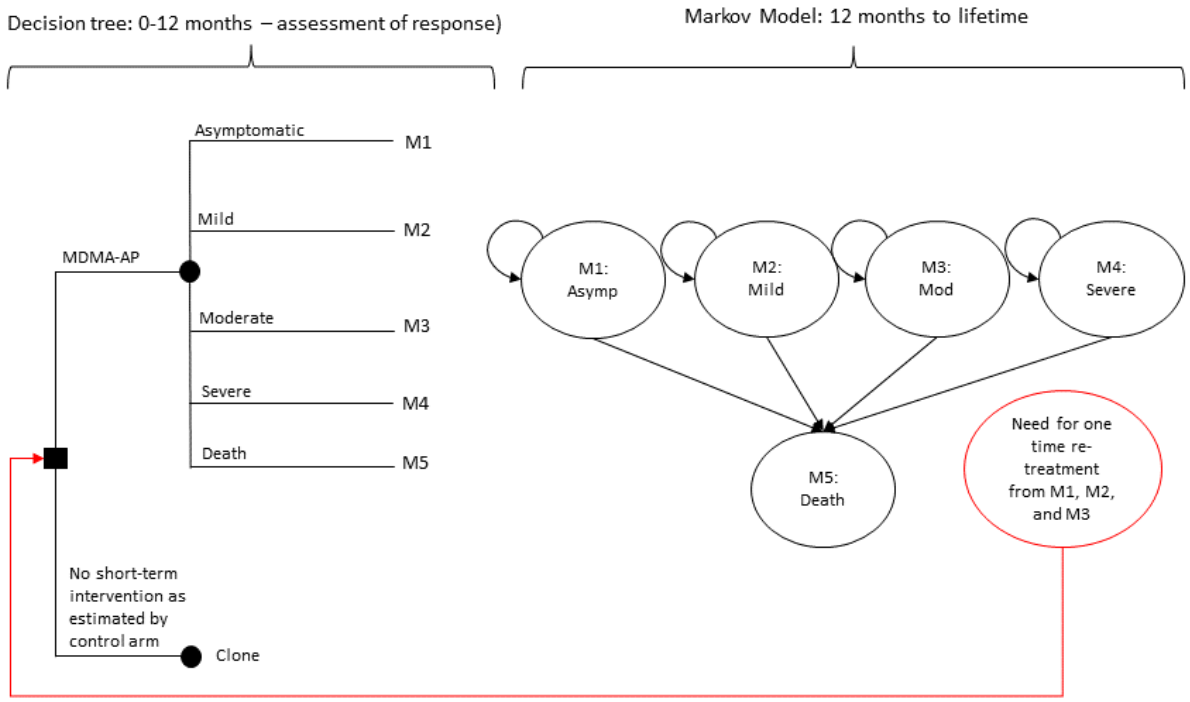
We developed a de novo decision analytic model for this evaluation, informed by key clinical trials and prior relevant economic models.[57,58] this is an exploratory analysis using results from the MAPP1 and MAPP2 trials as the clinical evaluation, discussed above, found this evidence insufficient.[28] This exploratory analysis compared MDMA-AP to no short-term intervention for PTSD as estimated by the effectiveness of the control arm of the randomized trial (LSNAP) assuming that LSNAP would be equivalent to no additional intervention for PTSD and so had no costs above health state costs inclusive of treatment for PTSD. We refer to the comparator as "placebo" for the remainder of this section. The model focused on an intention-to-treat analysis, with a hypothetical cohort of people with moderate-to-severe PTSD. Health states were defined by PTSD severity (e.g., asymptomatic, mild, moderate, and severe PTSD) and death (including PTSD-related mortality and all-cause mortality), and an annual cycle length (Figure 4.1). An up-front decision tree using an annual time horizon was used to capture initial state and post-intervention distributions to determine changes in quality of life, costs, and mortality during the intervention and up to one-year post-intervention. The decision tree was also used to allocate hypothetical patients to a post-intervention Markov cohort model to extrapolate outcomes over the lifetime horizon of the model. Evidence suggests a proportion of patients who responded to treatment will have a need for re-treatment within the first five years of a short-term intervention for PTSD.[59] A one-time MDMA-AP re-treatment was applied during the cycle length of the tunnel state and allowed for hypothetical patients to improve back to less severe PTSD health states using the same effectiveness evidence applied from the trial evidence to the upfront decision tree (red arrows in Figure 4.1 moving from asymptomatic, mild, moderate health states to the front of the decision tree or re-treatment). Re-treatment was applied in the placebo arm as well. We assessed outcomes over a lifetime horizon. In addition, cost-effectiveness was estimated for shorter time horizons.

Key model inputs included clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs differed to reflect varying effectiveness between interventions.

Health outcomes and costs depended on time spent in each health state and direct medical costs. The health outcomes of each intervention were evaluated in terms of the change in distribution across PTSD severity states following treatment completion compared with the baseline, and other possible measures of quality of life improvement or symptom reductions, life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years gained (evLYG). Quality of life weights were applied to each health state. Utilities were derived from EQ-5D-5L surveys completed by participants in the published phase three trials that assessed MDMA-AP. The model included

direct medical costs of the intervention and health state costs associated with PTSD. Productivity changes and other indirect costs were included in a separate modified societal perspective analysis (Supplement Table E10). All costs were inflated to 2024 US dollars. Results were expressed in terms of the incremental cost per QALY gained, cost per evLYG, cost per life year gained, and other possible outcomes (e.g., cost per death averted). Costs and outcomes were discounted at 3% per year.

**Figure 4.1. Model Structure**




Asymp: Asymptomatic, M: Markov, Mod: moderate

In response to public comments, changes to the economic evaluation between the draft Evidence Report and the revised Evidence report include:

- Updates to the model schematic (Figure 4.1) to indicate the movement for hypothetical patients from need for a re-treatment back to the decision tree effectiveness and costs for both treatment arms with clarification in the text.
- Added references in Table 4.2 that were incorrectly omitted in the draft Evidence Report.
- Added text in the controversies and uncertainties section on the need for future research to assess changes in comorbidities from short-term interventions such as MDMA-AP.

- Additional input Table E3 in the Supplement with corresponding text to explain our approach to calculating PTSD health state costs.
- The Figure E2 was incorrect in the draft Evidence Report and has been corrected in the revised Evidence Report.
- A correction on the costs included in the modified societal perspective shown in Table E6 with corresponding text and a correction to the Impact Inventory Table in the Supplement.

## 4.2. Key Model Assumptions and Inputs

The exploratory analysis used a health care system perspective and focused on direct medical care costs only. Outcomes were estimated over a lifetime time horizon to capture the potential impacts of short-term and ongoing morbidity and mortality. Model assumptions are described in Table 4.1 and key inputs are described in Table 4.2.

**Table 4.1. Key Model Assumptions**

| Assumption | Rationale |
|---|---|
| Utilities across PTSD severity distributions from the most recent phase 3 trial were used to estimate treatment effects on quality of life outcomes at follow-up for both arms of the model. | EQ-5D-5L scores were presented as health state utility scores with no reference to comparisons between pre- and post-trial treatment effects. |
| The cost of standard of care reflected real-world treatment scenarios instead of protocol driven assumptions on treatment without MDMA. | The comparator in practice will be reflective of real-world psychotherapy for PTSD, including a market basket of medications prescribed to treat PTSD. |
| In order to estimate changes in post-intervention distributions across all health states, we simulated CAPS-5 scores from recent phase three trial evidence to generate a posterior distribution of CAPS-5 scores to inform post-intervention health state distributions for health states. | Recent trial evidence on moderate-to-severe PTSD did not include post-intervention distributions across mild, moderate, severe, and extreme PTSD. Without the post-intervention distribution, we could not calculate the outcomes of the modeling analysis. We calibrated the simulation based on evidence from the most recent phase three trial. |
| We assumed patients who did not need re-treatment over five years would stay stable and not need re-treatment for the remainder of the model. | Evidence suggests a higher likelihood of progression within five years as compared to a longer time period for those that do not progress after five years. |
| No additional improvement in PTSD symptoms occurred after MDMA-AP sessions concluded. | MDMA-AP is a short-term intervention studied within a six-month time period. There is no evidence to suggest additional improvements occur for patients beyond the intervention time period. |
| Those who needed re-treatment would pursue re-treatment one time for those in asymptomatic, mild, and moderate PTSD health states. | Evidence was limited about whether repeat treatments with MDMA-AP would occur or be beneficial for patients who do not respond. For those who did not respond (e.g., those that stayed in severe PTSD state) we did not include the costs and benefits of re-treatment. |

EQ-5D-5L: EuroQol-5 Dimensions-5 Levels, CAPS-5: Clinician-Administered PTSD Scale for DSM-5, MDMA-AP: MDMA-assisted psychotherapy, PTSD: Post-traumatic stress disorder

### Table 4.2. Key Model Inputs

| Parameter | Input† | | | Source |
|---|---|---|---|---|
| **Initial and post-trial state distributions (PTSD severity)*:** | **Baseline** | **MDMA-AP** | **Placebo** | |
| ***Asymptomatic*** | 0% | 46.2% | 21.4% | Mitchell et al. 2023;[28] authors' calculation |
| ***Mild*** | 0% | 23.9% | 27.3% | |
| ***Moderate*** | 26.92% | 20.0% | 25.7% | |
| ***Severe*** | 73.08% | 9.9% | 25.7% | |
| **Annualized retreatment rate** | 6% | | | Benitez et al. 2012[59] |
| **PTSD all-cause mortality risk** | RR 1.47 (95% CI: 1.06–2.04) | | | Nilaweera et al. 2023[60] |
| **PTSD suicide mortality risk** | RR 2.09 (95% CI: 1.11–3.94) | | | Akbar et al. 2022[39] |
| **PTSD health state utility:** | | | | |
| ***Asymptomatic*** | 0.90 | | | Marseille et al. 2022[57] |
| ***Mild*** | 0.83 | | | |
| ***Moderate*** | 0.74 | | | |
| ***Severe*** | 0.61 | | | |
| **Cost of intervention (MDMA + Lykos-specific manualized therapy)[16]** | $23,117 | | | Marseille et al. 2020; Mitchell et al. 2023; CPT codes[61] |
| **Mean annual direct medical costs by level of PTSD severity*:** | | | | |
| **Parameter** | **Input†** | | | **Source** |
| ***Asymptomatic*** | $4,830 | | | Davis et al. 2022; Walker et al. 2003 ; National Institute of Mental Health: PTSD statistics 2007. [5,62,63]Authors' calculation. |
| ***Mild*** | $9,670 | | | |
| ***Moderate*** | $13,340 | | | |
| ***Severe*** | $19,720 | | | |

MDMA: 3,4-methylenedioxymethamphetamine, MDMA-AP: MDMA-assisted psychotherapy, PTSD: Post-traumatic stress disorder, RR: relative risk

*CAPS-5 score categories

†Inputs varied in sensitivity analyses

### *Transition Probabilities*

The phase three trials of MDMA-AP did not report treatment response in terms of PTSD severity states. Therefore, using the most recent phase three trial we estimated the post-treatment distribution across severity states using the reported post-treatment mean and standard error of CAPS-5 score and the reported post-treatment percent of participants in remission.[28] We assumed that remission is equivalent to asymptomatic PTSD and that this group had a mean CAPS-5 score of five. We then derived the post-treatment mean and standard deviation CAPS-5 score for remaining trial participants separately for each arm. We verified this approach by comparing the estimated means to the phase three trial post-treatment means. Assuming a normal distribution, we estimated the post-treatment distribution of trial participants across the remaining PTSD severity states (mild, moderate, severe) separately for each arm using 10,000 simulations. Evidence suggests PTSD patients achieving remission may need re-treatment within five years.[54] We therefore incorporated movement to a re-treatment tunnel state with similar effectiveness at post-trial completion for both arms of the model.

### *Mortality*

A review of the available evidence showed that individuals with PTSD have a higher risk of mortality compared to the general population. Part of this increased risk can be attributed to death due to suicide. Although the MDMA phase three clinical trials have not measured mortality endpoints, there may be an indirect benefit of reductions in mortality from avoiding severe PTSD health states.

We retrieved data from the Centers for Disease Control and Prevention's Wide-ranging Online Data for Epidemiologic Research (CDC WONDER) database for the USA in 2020 to calculate the baseline all-cause and suicide crude death rates by age. After identifying the increased risks of both all-cause (RR 1.47) and suicide (RR 2.09) mortality linked to PTSD, we calculated the mortality risk irrespective of severity across PTSD states (from mild to severe) by multiplying the increased PTSD mortality ratio with the baseline crude death rate.[39,60,64] Subsequently, we estimated the mortality risk in the asymptomatic state by multiplying the PTSD-related suicide mortality risk with the baseline suicide mortality rate and subtracting this risk from the increased PTSD-related (all-cause) mortality. In the results, we present deaths averted as a function of PTSD-related deaths by suicide which may occur each cycle across mild, moderate, and severe PTSD states. These estimates of PTSD-related deaths by suicide isolate the indirect effect of MDMA-AP on mortality and are comparable to reported CDC estimates.

### *Health State Utilities*

Health state utilities for asymptomatic, mild, moderate, and severe PTSD were reported in an existing cost-effectiveness analysis of MDMA-AP and derived from EQ-5D-5L surveys completed by participants in a phase three trial of MDMA-AP.[57] The EQ-5D-5L scores were presented as health

state utility scores with no reference to comparisons between pre- and post-trial treatment effects. Therefore, the treatment effect on quality of life EQ-5D-5L scores assumed that patients who transitioned to less severe PTSD states receive the quality of life benefits associated with changing health states.

***Drug Costs[65]***

Since there is no publicly available list or net price for MDMA, we relied on an estimate from IPD Analytics suggesting a price for MDMA of approximately $5,000 to $15,000 per course (all three sessions). We chose the midpoint for the exploratory analysis of $10,000 for all three sessions. This placeholder price represents the cost of the drug; non-drug costs associated with MDMA-AP sessions are included as separate costs in the cost-effectiveness model.

***Non-Drug Costs[61]***

To determine the MDMA-AP non-drug costs, we adopted the micro-costing method of Marseille et al. 2023 and used the Current Procedural Terminology (CPT) codes associated with the MDMA-AP activities.[8] Resource utilization for psychotherapy sessions, including the number of sessions and clinicians present, were based on the protocol detailed in the phase three clinical trial described by Mitchell et al. 2023. Additionally, the cost of a pregnancy test preceding an MDMA-AP session was factored in based on the proportion of women in the trial population. More detail is available in the Supplement.

***Health State Costs and Indirect Costs[5]***

In considering the medical care costs and indirect costs for patients with PTSD in different health states, we derived estimates from a recent literature review conducted by Davis et al. 2022.[9] This study utilized data from commercial, Medicare, and Medicaid sources, encompassing both civilian and military populations. The data were weighted to reflect the distribution of individual characteristics in the US population. The study presented excess costs attributable to PTSD, aligning with its prevalence in the overall US population. To align the cost estimates with the different levels of PTSD severity observed in the recent phase three trial, we referred to existing literature to determine the prevalence of PTSD across severity states. Additionally, we explored the relationship between the severity of PTSD and the corresponding mean costs to make appropriate adjustments. Additional detail is available in the Supplement.

## 4.3. Results

### Exploratory Analysis Results

The exploratory comparison was MDMA-AP versus placebo in patients with moderate-to-severe PTSD. The total discounted costs, life years (LYs), quality-adjusted life years (QALYs), equal value of

life years (evLYs) gained, and the proportion who achieved response over the lifetime time horizon are detailed in Table 4.3. MDMA-AP had a total discounted cost of $221,000 with discounted QALYs, LYs, and evLYs of 17.5, 21.50, and 17.5, respectively. Undiscounted PTSD-related deaths by suicide per 100,000 people was 478 in the MDMA-AP arm of the model. Placebo had a total discounted cost of $269,000 with discounted QALYs, LYs, and evLYs of 16.2, 21.48, and 16.2, respectively. Undiscounted PTSD-related deaths by suicide per 100,000 people was 697 in the MDMA-AP arm of the model.

**Table 4.3. Results for the Exploratory Analysis for MDMA-AP Compared to Control**

| Treatment | Intervention Costs | Non-intervention Costs | Total Cost | PTSD-Related Deaths by Suicide per 100,000 people | QALYs | Life Years | evLYs |
|---|---|---|---|---|---|---|---|
| **MDMA-AP** | $28,000 | $207,000 | $235,000 | 478 | 17.5 | 21.50 | 17.5 |
| **Placebo** | $0 | $271,000 | $271,000 | 697 | 16.2 | 21.48 | 16.2 |

evLYs: equal value of life years, MDMA-AP: MDMA-assisted psychotherapy, PTSD: Post-traumatic stress disorder, QALY: quality-adjusted life year

**Table 4.4. Incremental Cost-Effectiveness Ratios for the Exploratory Analysis**

| Treatment | Comparator | Cost per QALY Gained | Cost per Life Year Gained | Cost per evLY Gained | Cost per death by suicide averted |
|---|---|---|---|---|---|
| **MDMA-AP** | **Placebo** | Less costly, more effective | Less costly, more effective | Less costly, more effective | Less costly, more effective |

evLY: equal value of life year, MDMA-AP: MDMA-assisted psychotherapy, QALY: quality-adjusted life year

Table 4.4 presents the discounted lifetime incremental results from the exploratory analysis, which include incremental cost-effectiveness ratios for incremental cost per QALY gained, cost per LY gained, and cost per evLY gained. Total discounted costs for MDMA-AP were approximately $36,000 less than control; gains in QALYs, LYs, and evLYs were 1.26, 0.02, and 1.26 in relation to placebo. There were 219 fewer PTSD-related deaths by suicide when comparing MDMA-AP to placebo. This resulted in incremental cost-effectiveness ratios that were dominant or less costly and more effective across all health outcomes.

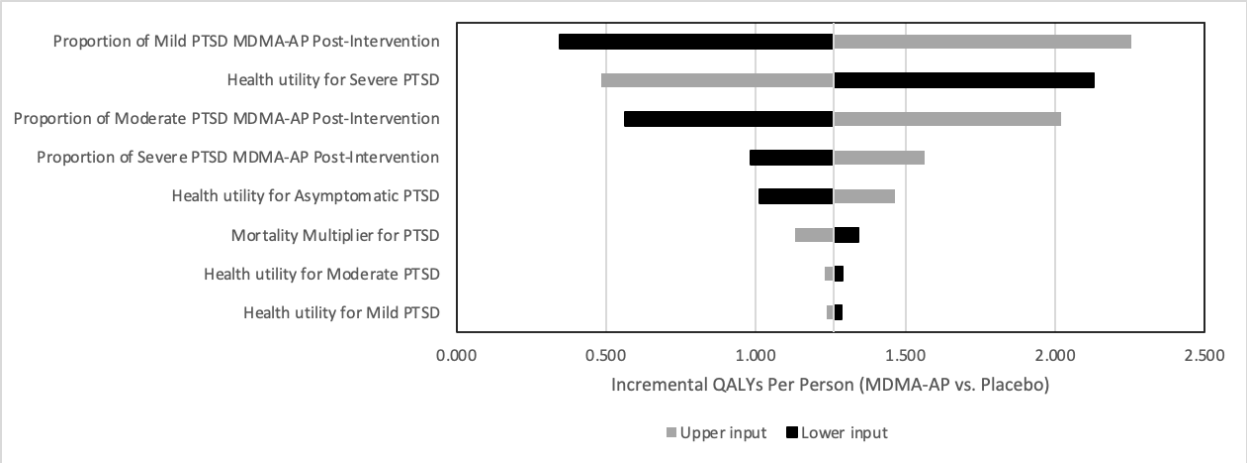
## Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors or plausible parameter ranges). Given the analyses produced dominant scenarios with negative ICERs (less costly, more effective), we present separate tornado diagrams for health outcomes and incremental costs. Figure 4.2 and Figure 4.3 present the tornado diagram resulting from the one-way sensitivity

analysis for MDMA-AP versus placebo. Key drivers of changes in QALYs include post-intervention proportions of patients allocated to PTSD severity levels and health utility scores by severity level. Key drivers of changes in incremental costs include costs of treating PTSD by severity level and proportions of patients allocated to PTSD severity levels. These one-way sensitivity analyses suggest the treatment effect in terms of improvements in PTSD-related symptoms and quality of life are key drivers of value when considering MDMA-AP compared to placebo.

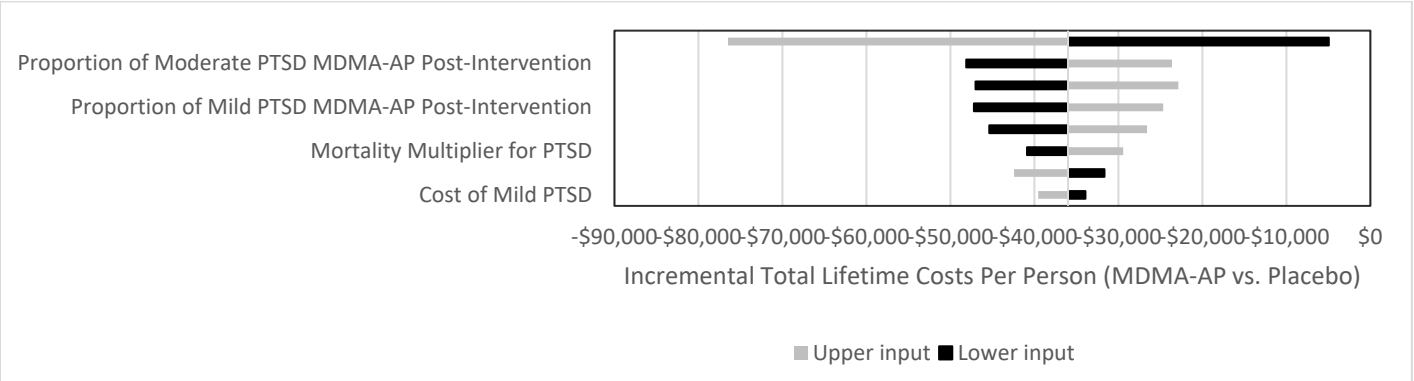
Probabilistic sensitivity analyses were also performed by jointly varying multiple model parameters over 1,000 simulations, then calculating 95% credible range estimates for each model outcome based on the results. Tables 4.5 and 4.6 present the probability of reaching certain cost-effectiveness thresholds for MDMA-AP versus placebo. A total of 100% of iterations for MDMA-AP versus placebo were beneath a threshold of $150,000 per QALY and $150,000 per evLY. Additional information on sensitivity analyses are available in Supplement E4.

**Figure 4.2. Tornado Diagram: MDMA-AP versus Placebo on Incremental QALYs**




MDMA-AP: MDMA-assisted psychotherapy, PTSD: post-traumatic stress disorder

**Figure 4.3. Tornado Diagram: MDMA-AP versus Placebo on Incremental Costs**



MDMA-AP: MDMA-assisted psychotherapy, PTSD: post-traumatic stress disorder

**Table 4.5. Probabilistic Sensitivity Analysis Cost per QALY Gained Results: MDMA-AP versus Placebo**

| | Cost Effective at $50,000 per QALY Gained | Cost Effective at $100,000 per QALY Gained | Cost Effective at $150,000 per QALY Gained | Cost Effective at $200,000 per QALY Gained |
|---|---|---|---|---|
| **MDMA-AP** | 100% | 100% | 100% | 100% |

MDMA-AP: MDMA-assisted psychotherapy, QALY: quality-adjusted life year

**Table 4.6. Probabilistic Sensitivity Analysis Cost Per evLY Gained Results: MDMA-AP versus Placebo**

| | Cost Effective at $50,000 per evLY Gained | Cost Effective at $100,000 per evLY Gained | Cost Effective at $150,000 per evLY Gained | Cost Effective at $200,000 per evLY Gained |
|---|---|---|---|---|
| **MDMA-AP** | 100% | 100% | 100% | 100% |

evLY: equal value of life years, MDMA-AP: MDMA-assisted psychotherapy

## Scenario Analyses

Results of all scenario analyses are presented in Supplement Section E5.

## Threshold Analyses

Given the rating of insufficient, we will not present threshold pricing and instead present the model analysis as a scenario analysis.

## Model Validation

We used several approaches to validate the model. First, we provided the preliminary model structure, methods and assumptions to manufacturers, patient groups, and clinical experts. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using internal reviewers. As part of ICER's efforts in acknowledging modeling transparency, we offered to share the model with the relevant manufacturer for external verification. Finally, we compared results to other cost-effectiveness models in this therapy area. The outputs from the model were against the trial/study data of the interventions and any relevant observational datasets. One specific area of validation was in reference to PTSD-related mortality. The model's predicted number of deaths by suicide aligned with the range (12-20) estimated per 100,000 population in the CDC data. For example, in cycle one

of the model, the control arm estimates 19 deaths by suicide per 100,000 people per year and the MDMA arm estimates 13 deaths by suicide per 100,000. This change from the upper range of deaths by suicide to the lower range of deaths by suicide per 100,000 people per year reflects the effect of shifting PTSD severity in the MDMA-AP arm as compared to the control arm.

## Controversies and Uncertainties

As discussed in the comparative clinical effectiveness section of this report, the phase three trials did not assess MDMA-AP compared to standard of care psychotherapy or pharmacotherapy. As such, we excluded the cost of Lykos-specific psychotherapy from the comparator arm of the cost-effectiveness analysis as non-representative of real-world standard of care costs. Furthermore, we know of no evidence comparing the effectiveness of Lykos-specific psychotherapy to standard of care treatments for PTSD.

Data regarding the impact of MDMA-AP in terms of a change in the distribution of PTSD across stages of severity (i.e., asymptomatic, mild, moderate, severe) was requested from Lykos Therapeutics and not provided. As described in the methods, we estimated the post-treatment distribution across severity states for both trial arms based on the most recent phase three trial. Although this estimate introduces some uncertainty, this approach allowed us to incorporate the PTSD health state utilities derived from trial participants and reported in an existing cost-effectiveness analysis as well as health state costs by severity.

There were no observed treatment effect estimates on health-related quality of life utility scores available from the MAPPS trials. We relied on EQ-5D scores published in prior cost-effectiveness analyses. The model therefore estimates changes in health state distribution and associated changes in health-related quality of life as opposed to changes in EQ-5D scores pre-intervention against post-intervention. We requested both pre- and post-intervention EQ-5D scores from Lykos Therapeutics but did not receive these estimates.

Appropriate areas for future research include generating evidence on healthcare resource utilization, mortality, and quality of life for PTSD patients overall and by severity level. The evidence on PTSD distribution by severity in the United States is limited, yet largely determines the changes in health state costs, health-related quality of life, and mortality from any short-term intervention for PTSD. Beyond PTSD, research on comorbidities is needed to incorporate potential reductions in other associated costs and improvements in health-related quality of life from MDMA-AP. Given exclusions for moderate to severe alcohol and cannabis use in MAPP1 and MAPP2, short-term and long-term research on substance abuse and changes in substance abuse from MDMA-AP is needed to advance modeling of other comorbidities associated with PTSD.

## 4.4. Summary and Comment

Given the rating of "I" (insufficient), we present an exploratory analysis based on the results of the MAPP trials. This is exploratory because it assumes that the results of the trials represent the expected outcomes of patients treated with MDMA-AP, but we do not have sufficient certainty in these results. Under this assumption, MDMA-AP provides clinical benefit in terms of gains in QALYs, evLYs, and deaths by suicide as compared to no short-term intervention. Key drivers were short-term improvements in PTSD-related symptoms and quality of life by severity of PTSD-related symptoms. Given this was an exploratory analysis, we are not presenting threshold prices.

# 5. Benefits Beyond Health and Special Ethical Priorities

Our reviews seek to provide information on benefits beyond health and special ethical priorities offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that was not available in the evidence base nor could be adequately estimated within the cost-effectiveness model. These elements are listed in the table below, with related information gathered from patients and other stakeholders. Following the public deliberation on this report the appraisal committee will vote on the degree to which each of these factors should affect overall judgments of long-term value for money of the interventions in this review.

**Table 5.1. Benefits Beyond Health and Special Ethical Priorities**

| Benefits Beyond Health and Special Ethical Priorities | Relevant Information |
|---|---|
| **There is substantial unmet need despite currently available treatments.** | While current treatment options for PTSD such as trauma-focused psychotherapies (e.g. CBT) and medications (e.g., sertraline, paroxetine) have shown effectiveness in clinical studies, some research indicates these treatments may have issues with tolerability and adherence that compromise their real-world impact.[66]<br><br>To inform unmet need as a benefit beyond health, the results for the evLY and QALY absolute and proportional shortfalls have been reported below:<br>evLY shortfalls:<br>• Absolute shortfall: 7.4<br>• Proportional shortfall: 21%<br>QALY shortfalls:<br>• Absolute shortfall: 6.2<br>• Proportional shortfall: 19%<br>The absolute and proportional shortfalls represent the total and proportional health units of remaining quality-adjusted life expectancy, respectively, that would be lost due to untreated illness. Please refer to the ICER Reference Case – Section 2. Quantifying Unmet Need (QALY and evLY Shortfalls) for the shortfalls of other conditions assessed in prior ICER reviews. |

| Benefits Beyond Health and Special Ethical Priorities | Relevant Information |
|---|---|
| **This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the health care system.** | Some racial/ethnic minority groups in the US not only have a higher burden of PTSD based on lifetime prevalence estimates, but they also face greater barriers to accessing and receiving adequate treatment for their PTSD symptoms once developed, compared to White individuals. Addressing these health inequalities is important for ensuring equitable PTSD care across diverse populations.[67]<br><br>ICER calculated the Health Improvement Distribution Index (HIDI), looking at the relative proportion of any health gains from treatment of PTSD for the following groups with a higher prevalence of PTSD than the general US population (see Supplement A1):<br>• Black, non-Hispanic = 1.18 |
| **The treatment is likely to produce substantial improvement in caregivers' quality of life and/or ability to pursue their own education, work, and family life.** | There is a relationship between PTSD symptom severity and caregiver burden.[68] The extent to which MDMA-AP may impact caregivers' quality of life and functioning is unclear, due to uncertainty around the therapy's effectiveness in reducing patients' PTSD symptoms. |
| **The treatment offers a substantial opportunity to improve access to effective treatment by means of its mechanism of action or method of delivery.** | Multiple experimental, preparatory, and integration sessions with at least two therapists leaves questions about feasibility of MDMA-AP administration. Additionally, some participants in the trials have discontinued MDMA-AP treatment due to adverse events. |

CBT: Cognitive behavioral therapy, HIDI: Health Improvement Distribution Index, MDMA-AP: MDMA-assisted psychotherapy, PTSD: post-traumatic stress disorder, QALY: quality-adjusted life year, QoL: Quality of life

# 6. Health Benefit Price Benchmarks

Given the evidence rating of "I" above, the economic analysis was only exploratory. As such, no Health Benefit Price Benchmarks (HBPBs) for MDMA-AP are presented in this Report.

# 7. Potential Budget Impact

Given the "I" rating for the clinical evidence, the potential budget impact of MDMA-AP in this Draft Report should be considered an exploratory analysis. These analyses were carried out to provide insight into the potential budgetary impact of MDMA-AP assuming that the results of the MAPP trials are accurate.

## 7.1. Overview of Key Assumptions

Results from the cost-effectiveness model were used to estimate the total potential budgetary impact of MDMA-AP for adults with PTSD. Potential budget impact is defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over a five-year time horizon. In line with the exploratory cost-effectiveness analysis, a placeholder price of $10,000 per treatment course for MDMA-AP was used in our estimate of budget impact. This placeholder price represents the cost of the drug; non-drug costs associated with MDMA-AP sessions are included as separate costs in the cost-effectiveness model.

This potential budget impact analysis included the estimated number of individuals in the US who would be eligible for treatment. To estimate the size of the potential candidate populations for treatment, we used inputs for the size of the adult US population 271,616,592 (average over 2024-2028), the prevalence of PTSD in adults (5%),[2] and the percentage of patients with PTSD who are considered to have moderate-to-severe PTSD (69.7%).[62] Applying these sources results in estimates of 9,465,838 eligible patients in the US. For the purposes of this analysis, we assumed that 20% of these patients would initiate treatment in each of the five years, or 1,893,168 patients per year. This may represent an overestimate of the potentially eligible population if the FDA-approved indication for MDAM-AP is restricted based on trial exclusion criteria. Avancena 2022,[69] for example, estimated that between 13% and 42% of adults with chronic and severe PTSD would have a disqualifying condition and would not be eligible for MDMA-AP. Given the uncertainty in the anticipated FDA indication and the intent of ICER's budget impact analysis, we used the broadest anticipated prevalence estimates in our Draft Evidence Report.

## 7.2. Results

Results showed that at the placeholder price of $10,000 per treatment course, 2.11% of eligible patients could be treated over the span of five years without crossing the ICER potential budget impact threshold of $735 million per year. Given that the data used to inform our estimate of eligible patients may be an overestimation, we explored the impact of a further reduction in the

potentially eligible patient population informed by estimates reported by Avancena 2022 (i.e., up to 42% of adults with chronic and severe PTSD would have a disqualifying condition). Under this assumption, the percentage of the eligible patient population that could be treated without reaching the potential budget impact threshold remained less than 5%.

Figure 7.1 illustrates the cumulative per patient potential budget impact for MDMA-AP. At the placeholder price for MDMA-AP, the average annual budget impact per patient was $21,635 in Year one with cumulative net annual costs increasing to $45,032 per patient in Year five.

**Figure 7.1. Annual Budgetary Impact of MDMA-AP in Patients with PTSD at a Placeholder Price**

# References


1. Alonso J, Angermeyer MC, Bernert S, et al. Disability and quality of life impact of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl*. 2004;(420):38-46. doi:10.1111/j.1600-0047.2004.00329.x
2. U.S. Department of Veterans Affairs. How Common Is PTSD in Adults? U.S. Department of Veterans Affairs,. Accessed January 25, 2024. https://www.ptsd.va.gov/understand/common/common_adults.asp
3. Isaacson B. Mental Disorders: Posttraumatic Stress Disorder. *FP Essent*. Aug 2020;495:23-30.
4. Goldstein RB, Smith SM, Chou SP, et al. The epidemiology of DSM-5 posttraumatic stress disorder in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *Soc Psychiatry Psychiatr Epidemiol*. Aug 2016;51(8):1137-48. doi:10.1007/s00127-016-1208-5
5. Davis LL, Schein J, Cloutier M, et al. The Economic Burden of Posttraumatic Stress Disorder in the United States From a Societal Perspective. *J Clin Psychiatry*. Apr 25 2022;83(3)doi:10.4088/JCP.21m14116
6. National Institute on Drug Abuse (NIDA). *MDMA (Ecstasy) Abuse Research Report*. 2022. December 19, 2022. Accessed January 27, 2024. https://nida.nih.gov/publications/research-reports/mdma-ecstasy-abuse/
7. Lykos Therapeutics Announces FDA Acceptance and Priority Review of New Drug Application for MDMA-Assisted Therapy for PTSD. PR Newswire; February 9, 2024, 2024. Accessed February 10, 2024. https://www.prnewswire.com/news-releases/lykos-therapeutics-announces-fda-acceptance-and-priority-review-of-new-drug-application-for-mdma-assisted-therapy-for-ptsd-302058901.html
8. Merians AN, Gross G, Spoont MR, Bellamy CD, Harpaz-Rotem I, Pietrzak RH. Racial and ethnic mental health disparities in U.S. Military Veterans: Results from the National Health and Resilience in Veterans Study. *J Psychiatr Res*. May 2023;161:71-76. doi:10.1016/j.jpsychires.2023.03.005
9. MAPS Public Benefit Corporation. MAPP1 Protocol Amendment 4 Version 1. 2020
10. To improve care for Veterans, VA to fund studies on new therapies for treating mental health conditions. January 5, 2024, 2024. Accessed February 14, 2024. https://news.va.gov/press-room/to-improve-care-for-veterans-va-to-fund-studies-on-new-therapies-for-treating-mental-health-conditions/
11. Tumilty E. Health Canada Investigation of MDMA Clinical Trials Findings — A Response. July 25, 2022, 2022. https://medium.com/@emmatumilty/health-canada-investigation-of-mdma-clinical-trials-findings-a-response-c8b535895aa8
12. Psymposia NYMa. Cover Story. Accessed January 1, 2024. https://www.psymposia.com/powertrip-2/
13. Flameling LJ, Aday JS, van Elk M. Expectancy Effects Cannot Be Neglected in MDMA-Assisted Therapy Research. *ACS Chem Neurosci*. Dec 6 2023;14(23):4062-4063. doi:10.1021/acschemneuro.3c00692
14. Multidisciplinary Association for Psychedelic Studies. A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder: Version 8.1. 2017
15. Multidisciplinary Association for Psychedelic Studies. *MDMA Investigator's Brochure: U.S. 14th Ed: 18 March 2022*. 2022. March 18, 2022. https://maps.org/wp-content/uploads/2022/03/MDMA-IB-14th-Edition-FINAL-18MAR2022.pdf
16. Mithoefer MC, Feduccia AA, Jerome L, et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized

controlled trials. *Psychopharmacology (Berl)*. Sep 2019;236(9):2735-2745. doi:10.1007/s00213-019-05249-5
17. Cloitre M, Petkova E, Wang J, Lu F. AN EXAMINATION OF THE INFLUENCE OF A SEQUENTIAL TREATMENT ON THE COURSE AND IMPACT OF DISSOCIATION AMONG WOMEN WITH PTSD RELATED TO CHILDHOOD ABUSE. *Depression and Anxiety*. 2012;29(8):709-717. doi:https://doi.org/10.1002/da.21920
18. Deen A, Biedermann SV, Lotzin A, et al. The dissociative subtype of PTSD in trauma-exposed individuals: a latent class analysis and examination of clinical covariates. *Eur J Psychotraumatol*. 2022;13(1):2031591. doi:10.1080/20008198.2022.2031591
19. Hoeboer CM, De Kleine RA, Molendijk ML, et al. Impact of dissociation on the effectiveness of psychotherapy for post-traumatic stress disorder: meta-analysis. *BJPsych Open*. 2020;6(3):e53. e53. doi:10.1192/bjo.2020.30
20. Burton MS, Feeny NC, Connell AM, Zoellner LA. Exploring evidence of a dissociative subtype in PTSD: Baseline symptom structure, etiology, and treatment efficacy for those who dissociate. *J Consult Clin Psychol*. May 2018;86(5):439-451. doi:10.1037/ccp0000297
21. Zoet HA, Wagenmans A, van Minnen A, de Jongh A. Presence of the dissociative subtype of PTSD does not moderate the outcome of intensive trauma-focused treatment for PTSD. *Eur J Psychotraumatol*. 2018;9(1):1468707. doi:10.1080/20008198.2018.1468707
22. Amoroso T, Workman M. Treating posttraumatic stress disorder with MDMA-assisted psychotherapy: A preliminary meta-analysis and comparison to prolonged exposure therapy. *Journal of Psychopharmacology*. 2016;30(7):595-600. doi:10.1177/0269881116642542
23. Benjamin R. Lewis, M.D. , and, Kevin Byrne, M.D. A Review of MDMA-Assisted Therapy for Posttraumatic Stress Disorder. *FOCUS*. 2023;21(3):247-256. doi:10.1176/appi.focus.20220088
24. Feduccia AA, Jerome L, Yazar-Klosinski B, Emerson A, Mithoefer MC, Doblin R. Breakthrough for Trauma Treatment: Safety and Efficacy of MDMA-Assisted Psychotherapy Compared to Paroxetine and Sertraline. Review. *Frontiers in Psychiatry*. 2019-September-12 2019;10doi:10.3389/fpsyt.2019.00650
25. Halvorsen JØ, Naudet F, Cristea IA. Challenges with benchmarking of MDMA-assisted psychotherapy. *Nature Medicine*. 2021/10/01 2021;27(10):1689-1690. doi:10.1038/s41591-021-01525-0
26. Illingworth BJ, Lewis DJ, Lambarth AT, et al. A comparison of MDMA-assisted psychotherapy to non-assisted psychotherapy in treatment-resistant PTSD: A systematic review and meta-analysis. *Journal of Psychopharmacology*. 2021;35(5):501-511. doi:10.1177/0269881120965915
27. Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nature Medicine*. 2021/06/01 2021;27(6):1025-1033. doi:10.1038/s41591-021-01336-3
28. Mitchell JM, Ot'alora G M, van der Kolk B, et al. MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nature Medicine*. 2023/09/14 2023;doi:10.1038/s41591-023-02565-4
29. Brewerton TD, Wang JB, Lafrance A, et al. MDMA-assisted therapy significantly reduces eating disorder symptoms in a randomized placebo-controlled trial of adults with severe PTSD. *Journal of Psychiatric Research*. 2022/05/01/ 2022;149:128-135. doi:https://doi.org/10.1016/j.jpsychires.2022.03.008
30. Weathers FW, Bovin MJ, Lee DJ, et al. The Clinician-Administered PTSD Scale for DSM-5 (CAPS-5): Development and initial psychometric evaluation in military veterans. *Psychol Assess*. Mar 2018;30(3):383-395. doi:10.1037/pas0000486
31. Halvorsen JØ. Defining clinically significant change. *British Journal of Psychiatry*. 2016;209(1):85-85. doi:10.1192/bjp.209.1.85
32. Mitchell JM. 41.4 Primary Findings From a Long-Term Observational Follow-Up Study on MDMA-Assisted Therapy for Treatment of PTSD: MPLONG. presented at: ACNP 62nd Annual Meeting: Panels,

Mini-Panels and Study Groups; 2023/12/01 2023; https://doi.org/10.1038/s41386-023-01754-6 Neuropsychopharmacology
33. STATEMENT: MAPS-Funded Phase 3 Research Reports Results from Long-Term Observational Follow-Up Study on MDMA-Assisted Therapy for PTSD. April 5, 2023, 2023. Accessed December 20, 2023. https://maps.org/2023/04/05/statement-maps-funded-phase-3-research-reports-results-from-long-term-observational-follow-up-study-on-mdma-assisted-therapy-for-ptsd/
34. Jerome L, Feduccia AA, Wang JB, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology*. 2020/08/01 2020;237(8):2485-2497. doi:10.1007/s00213-020-05548-2
35. Sheehan KH, Sheehan DV. Assessing treatment effects in clinical trials with the Discan metric of the Sheehan Disability Scale. *International Clinical Psychopharmacology*. 2008;23(2)doi:10.1097/YIC.0b013e3282f2b4d6
36. Button KS, Kounali D, Thomas L, et al. Minimal clinically important difference on the Beck Depression Inventory--II according to the patient's perspective. *Psychol Med*. Nov 2015;45(15):3269-79. doi:10.1017/s0033291715001270
37. Nicholas CR, Wang JB, Coker A, et al. The effects of MDMA-assisted therapy on alcohol and substance use in a phase 3 trial for treatment of severe PTSD. *Drug and Alcohol Dependence*. 2022/04/01/ 2022;233:109356. doi:https://doi.org/10.1016/j.drugalcdep.2022.109356
38. MAPS Public Benefit Corporation. MAPP2 Protocol Amendment 4 Version 1. 2021
39. Akbar R, Arya V, Conroy E, Wilcox HC, Page A. Posttraumatic stress disorder and risk of suicidal behavior: A systematic review and meta-analysis. *Suicide and Life-Threatening Behavior*. 2023;53(1):163-184. doi:https://doi.org/10.1111/sltb.12931
40. Lindsay B. Footage of therapists spooning and pinning down patient in B.C. trial for MDMA therapy prompts review. Canadian Broadcasting Corporation (CBC). Updated March 29, 2022. Accessed October 20, 2023.
41. Lindsay B. B.C. psychiatrist resigns licence after patient complains of abuse during psychedelic therapy study. Canadian Broadcasting Corporation (CBC),. Updated October 16, 2023. Accessed October 20, 2023.
42. Lindsay B. Patient safety issues halt trial for MDMA-assisted psychotherapy during Health Canada review. Canadian Broadcasting Corporation (CBC),. Updated July 18, 2022. Accessed October 20, 2023.
43. Colcott J, Guerin AA, Carter O, Meikle S, Bedi G. Side-effects of mdma-assisted psychotherapy: a systematic review and meta-analysis. *Neuropsychopharmacology*. Apr 23 2024;doi:10.1038/s41386-024-01865-8
44. Clinicaltrials.gov. A Multi-Site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD (MAPP1). Updated January 4, 2024. Accessed December 20, 2023. https://www.clinicaltrials.gov/study/NCT03537014
45. Clinicaltrials.gov. A Multi-Site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD (MAPP2). Updated January 4, 2024. Accessed January 20, 2023. https://clinicaltrials.gov/study/NCT04077437
46. Mavranezouli I, Megnin-Viggars O, Daly C, et al. Psychological treatments for post-traumatic stress disorder in adults: a network meta-analysis. *Psychol Med*. Mar 2020;50(4):542-555. doi:10.1017/s0033291720000070
47. Karatzias T, Murphy P, Cloitre M, et al. Psychological interventions for ICD-11 complex PTSD symptoms: systematic review and meta-analysis. *Psychol Med*. Aug 2019;49(11):1761-1775. doi:10.1017/s0033291719000436

48. Springer KS, Levy HC, Tolin DF. Remission in CBT for adult anxiety disorders: A meta-analysis. *Clinical Psychology Review*. 2018/04/01/ 2018;61:1-8. doi:https://doi.org/10.1016/j.cpr.2018.03.002
49. Imel ZE, Laska K, Jakupcak M, Simpson TL. Meta-analysis of dropout in treatments for posttraumatic stress disorder. *J Consult Clin Psychol*. Jun 2013;81(3):394-404. doi:10.1037/a0031474
50. Lewis C, Roberts NP, Gibson S, Bisson JI. Dropout from psychological therapies for post-traumatic stress disorder (PTSD) in adults: systematic review and meta-analysis. *Eur J Psychotraumatol*. 2020;11(1):1709709. doi:10.1080/20008198.2019.1709709
51. Varker T, Jones KA, Arjmand H-A, et al. Dropout from guideline-recommended psychological treatments for posttraumatic stress disorder: A systematic review and meta-analysis. *Journal of Affective Disorders Reports*. 2021/04/01/ 2021;4:100093. doi:https://doi.org/10.1016/j.jadr.2021.100093
52. Sciarrino NA, Warnecke AJ, Teng EJ. A Systematic Review of Intensive Empirically Supported Treatments for Posttraumatic Stress Disorder. *Journal of Traumatic Stress*. 2020;33(4):443-454. doi:https://doi.org/10.1002/jts.22556
53. Feduccia AA, Mithoefer MC. MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms? *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2018/06/08/ 2018;84:221-228. doi:https://doi.org/10.1016/j.pnpbp.2018.03.003
54. Cristea IA, Halvorsen JØ, Cosgrove L, Naudet F. New treatments for mental disorders should be routinely compared to psychotherapy in trials conducted for regulatory purposes. *The Lancet Psychiatry*. 2022;9(12):934-936. doi:10.1016/S2215-0366(22)00340-6
55. U.S. Government Accountability Office. *Veterans Health Care: Staffing Challenges Persist for Fully Integrating Mental Health and Primary Care Services*. 2022. December 15, 2022. https://www.gao.gov/products/gao-23-105372
56. Schnurr PP, Hamblen JL, Wolf J, et al. The Management of Posttraumatic Stress Disorder and Acute Stress Disorder: Synopsis of the 2023 U.S. Department of Veterans Affairs and U.S. Department of Defense Clinical Practice Guideline. *Ann Intern Med*. Feb 27 2024;doi:10.7326/m23-2757
57. Marseille E, Mitchell JM, Kahn JG. Updated cost-effectiveness of MDMA-assisted therapy for the treatment of posttraumatic stress disorder in the United States: Findings from a phase 3 trial. *PLoS One*. 2022;17(2):e0263252. doi:10.1371/journal.pone.0263252
58. Elliot Marseille JK, Berra Yazar-Klosinski, Rick Doblin. The cost-effectiveness of MDMA-assisted psychotherapy for the treatment of chronic, treatment-resistant PTSD. *Plos One*. 2020;
59. Pérez Benítez CI, Zlotnick C, Stout RI, et al. A 5-year longitudinal study of posttraumatic stress disorder in primary care patients. *Psychopathology*. 2012;45(5):286-93. doi:10.1159/000331595
60. Nilaweera D, Phyo AZZ, Teshale AB, et al. Lifetime posttraumatic stress disorder as a predictor of mortality: a systematic review and meta-analysis. *BMC Psychiatry*. Apr 10 2023;23(1):229. doi:10.1186/s12888-023-04716-w
61. Marseille E, Stauffer CS, Agrawal M, et al. Group psychedelic therapy: empirical estimates of cost-savings and improved access. *Front Psychiatry*. 2023;14:1293243. doi:10.3389/fpsyt.2023.1293243
62. National Institute of Mental Health. Post-Traumatic Stress Disorder (PTSD). Accessed 1/29/2024, https://www.nimh.nih.gov/health/statistics/post-traumatic-stress-disorder-ptsd
63. Walker EA, Katon W, Russo J, Ciechanowski P, Newman E, Wagner AW. Health care costs associated with posttraumatic stress disorder symptoms in women. *Arch Gen Psychiatry*. Apr 2003;60(4):369-74. doi:10.1001/archpsyc.60.4.369
64. CDC. CDC WONDER. Centers for Disease Control and Prevention. https://wonder.cdc.gov/controller/datarequest/D158
65. Review IfCaE. Payer & Provider Insights. Accessed March 7, 2024. https://www.ipdanalytics.com

66. Levi O, Ben Yehuda A, Pine DS, Bar-Haim Y. A Sobering Look at Treatment Effectiveness of Military-Related Posttraumatic Stress Disorder. *Clinical Psychological Science*. 2022;10(4):690-699. doi:10.1177/21677026211051314
67. Roberts AL, Gilman SE, Breslau J, Breslau N, Koenen KC. Race/ethnic differences in exposure to traumatic events, development of post-traumatic stress disorder, and treatment-seeking for post-traumatic stress disorder in the United States. *Psychological Medicine*. 2011;41(1):71-83. doi:10.1017/S0033291710000401
68. Calhoun PS, Beckham JC, Bosworth HB. Caregiver burden and psychological distress in partners of veterans with chronic posttraumatic stress disorder. *J Trauma Stress*. Jun 2002;15(3):205-12. doi:10.1023/a:1015251210928
69. Avanceña ALV, Kahn JG, Marseille E. The Costs and Health Benefits of Expanded Access to MDMA-assisted Therapy for Chronic and Severe PTSD in the USA: A Modeling Study. *Clin Drug Investig*. Mar 2022;42(3):243-252. doi:10.1007/s40261-022-01122-0
70. Beck AT, Steer RA. Internal consistencies of the original and revised Beck Depression Inventory. *J Clin Psychol*. Nov 1984;40(6):1365-7. doi:10.1002/1097-4679(198411)40:6<1365::aid-jclp2270400615>3.0.co;2-d
71. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess*. Dec 1996;67(3):588-97. doi:10.1207/s15327752jpa6703_13
72. Beck AT, Ward CH. Dreams of depressed patients. Characteristic themes in manifest content. *Arch Gen Psychiatry*. Nov 1961;5:462-7. doi:10.1001/archpsyc.1961.01710170040004
73. National Center for PTSD. Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). U.S. Department of Veterans Affairs. Accessed February 10, 2024. https://www.ptsd.va.gov/professional/assessment/adult-int/caps.asp
74. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. Dec 2011;168(12):1266-77. doi:10.1176/appi.ajp.2011.10111704
75. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. Jul 2007;164(7):1035-43. doi:10.1176/ajp.2007.164.7.1035
76. Columbia University. Columbia–Suicide Severity Rating Scale Scoring and Data Analysis Guide Version 2.0. 2013
77. European Medicines Agency. *ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials*. 2020. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e9-r1-addendum-estimands-and-sensitivity-analysis-clinical-trials-guideline-statistical-principles-clinical-trials-step-5_en.pdf
78. Gogtay NJ, Ranganathan P, Aggarwal R. Understanding estimands. *Perspect Clin Res*. Apr-Jun 2021;12(2):106-112. doi:10.4103/picr.picr_384_20
79. American Psychiatric Association. What is Posttraumatic Stress Disorder (PTSD)? Accessed February 10, 2024. https://www.psychiatry.org/patients-families/ptsd/what-is-ptsd
80. American Psychiatric Association. About DSM-5-TR. Accessed February 10, 2024. https://www.psychiatry.org/psychiatrists/practice/dsm/about-dsm
81. Sheehan DV. *The Anxiety Disease*. Scribner; 1983.
82. Coles T, Coon C, DeMuro C, McLeod L, Gnanasakthy A. Psychometric evaluation of the Sheehan Disability Scale in adult patients with attention-deficit/hyperactivity disorder. *Neuropsychiatr Dis Treat*. 2014;10:887-95. doi:10.2147/ndt.S55220

83. American Psychological Association. *Clinical Practice Guideline for the Treatment of Posttraumatic Stress Disorder (PTSD) in Adults (2017)*. 2017. https://www.apa.org/ptsd-guideline/ptsd.pdf
84. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med*. Mar 1 1997;126(5):376-80.
85. Higgins J, Thomas, J, Chandler, J, Cumpston, M, Li, T, Page, MJ, Welch, VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). https://training.cochrane.org/handbook/current
86. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. Mar 29 2021;372:n71. doi:10.1136/bmj.n71
87. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898
88. Ollendorf D, Pearson, SD. ICER Evidence Rating Matrix: A User's Guide. Updated January 31, 2020. https://icer.org/evidence-rating-matrix/
89. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care*. Jun 2010;48(6 Suppl):S145-52. doi:10.1097/MLR.0b013e3181d9913b
90. Bahji A, Forsyth A, Groll D, Hawken ER. Efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for posttraumatic stress disorder: A systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2020/01/10/ 2020;96:109735. doi:https://doi.org/10.1016/j.pnpbp.2019.109735
91. Tedesco S, Gajaram G, Chida S, et al. The Efficacy of MDMA (3,4-Methylenedioxymethamphetamine) for Post-traumatic Stress Disorder in Humans: A Systematic Review and Meta-Analysis. *Cureus*. May 17 2021;13(5):e15070. doi:10.7759/cureus.15070
92. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. *Jama*. Sep 13 2016;316(10):1093-103. doi:10.1001/jama.2016.12195
93. Pickard AS, Law EH, Jiang R, et al. United States Valuation of EQ-5D-5L Health States Using an International Protocol. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Aug 2019;22(8):931-941. doi:10.1016/j.jval.2019.02.009
94. Institute for Clinical and Economic Review. 2020-2023 Value Assessment Framework. https://icer.org/our-approach/methods-process/value-assessment-framework/
95. Pearson SD. The ICER Value Framework: Integrating Cost Effectiveness and Affordability in the Assessment of Health Care Value. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Mar 2018;21(3):258-265. doi:10.1016/j.jval.2017.12.017

# Supplemental Materials

# A. Background: Supplemental Information

## A1. Definitions

**3,4-Methylenedioxymethamphetamine (MDMA):**[6] MDMA is a synthetic drug with stimulant and hallucinogenic properties. Demonstrated benefits include altered sensations, reduced defenses and fear of emotional injury, enhanced communication and introspection, and increased openness and empathy.

**Beck Depression Inventory II (BDI-II):**[70-72] The revised BDI-II is a 21-item, self-report questionnaire that measures the severity of depressive symptoms. The inventory ranges from 0 to 63, with higher scores indicating more depressive symptoms. Severity cut-off scores include: 0 to 13 for minimal depression, 14 to 19 for mild depression, 20 to 28 for moderate depression, and 29 to 63 for severe depression.

**Clinician-Administered PTSD Scale for DSM-5 (CAPS-5):**[30,73] CAPS-5 is a 30-item questionnaire that assesses DSM-5-defined PTSD diagnostic status and symptom severity. Total severity scores are calculated by summing individual item severity scores and range from 0 to 80. Severe PTSD has been defined as a CAPS-5 score of 35 or more, and moderate to severe PTSD has been defined as a CAPS-5 score of 23 or more. Additionally, clinical response has been defined by the following CAPS-5 score changes:[9]

- Responder or clinically significant improvement: 10-point or more decrease on CAPS-5
- Loss of diagnosis: 10-point or more decrease on CAPS-5 and no longer meeting PTSD diagnostic criteria
- Remission: Total CAPS-5 score of 11 points or less and loss of diagnosis
- Non-responder: Less than 10-point decrease on CAPS-5

**Columbia Suicide Severity Rating Scale (C-SSRS):**[74-76] The C-SSRS is a clinician-administered suicide risk assessment tool that detects the severity and immediacy of suicide risk. It includes both a Lifetime version and a Since Last Visit version, is made up of 10 categories, and assesses three composite endpoints of suicidal ideation, ideation intensity, and behavior. Scores for suicide ideation range from 0, indicating no presence of ideation, to 5. A C-SSRS ideation score of 4 or 5 indicates serious suicidal ideation.

**Estimand:**[77,78] An estimand is the quantity of a treatment effect in a statistical analysis to address a clinical trial's research question and objective, with the purpose of adding precision to the research question under different treatment conditions. It consists of five attributes: population, treatment, variable or endpoint, intercurrent events, and summary measure.

- De jure estimand: measures the effects of a drug if taken as directed (randomized treatment estimand)
- De facto: measures the effects of a drug if taken as assigned, regardless of adherence (treatment policy estimand)

**Post-Traumatic Stress Disorder (PTSD):**[79,80] PTSD is a psychiatric disorder in which a person has experienced or witnessed a traumatic event or set of circumstances. It negatively affects a person's ability to function, maintain relationships, and effectively work and has been linked to comorbid conditions such as substance abuse, depression, and suicide risk. This disorder is typically diagnosed through the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), which is utilized by clinicians, researchers, and other health care professionals to diagnose and classify mental disorders.

**Sheehan Disability Scale (SDS):**[81,82] SDS is a self-reported assessment measuring degree of functional impairment within the domains of work/school, social life, and family/home life. Subscale scores can be combined to produce a global impairment rating, ranging from 0 to 30, with higher scores indicating higher levels of functional impairment. Lykos clinical trials produced a "modified SDS score" by calculating the mean of the three domain scores.

**Health Improvement Distribution Index (HIDI)**: The HIDI identifies a subpopulation that has a higher prevalence of the disease of interest and therefore, creates an opportunity for proportionately more health gains within the subpopulation. This opportunity may be realized by achieving equal access both within and outside the identified subpopulation to an intervention that is known to improve health. The HIDI is defined as the disease prevalence in the subpopulation divided by the disease prevalence in the overall population. For example, if a disease has a prevalence of 10% among Black Americans whereas the disease prevalence among all Americans is 4%, then the Health Improvement Distribution Index is 10%/4% = 2.5. In this example, a HIDI of 2.5 means that Black Americans as a subpopulation would benefit more on a relative basis (2.5 times more) from a new effective intervention compared with the overall population. HIDIs above 1 suggest that more health may be gained on the relative scale in the subpopulation of interest when compared to the population as a whole. This statistic may be helpful in characterizing a treatment's contextual considerations and potential other benefits (Section 5).

An analysis of the 2004-2005 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) (N = 34,653) found the lifetime prevalence of PTSD to be 7.3%.[67] Comparison of racial/ethnic differences showed that lifetime prevalence of PTSD was highest among Black respondents at 8.7%, intermediate among Hispanic and White respondents at 7.0% and 7.4% respectively, and lowest among Asian respondents at 4.0%.

**Table A1: ICER Health Improvement Distribution Index**

| Subgroup | HIDI |
|---|---|
| Asian/Hawaiian/Pacific Islander, NH | 0.55 |
| Black, NH | 1.18 |
| Hispanic | 0.96 |
| White, NH | 1.01 |

HIDI: Health Improvement Distribution Index, NH: non-Hispanic

# A2. Potential Cost-Saving Measures in PTSD

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create headroom in health care budgets for higher-value innovative services (for more information, see https://icer.org/our-approach/methods-process/value-assessment-framework/). These services are ones that would not be directly affected by therapies for PTSD (e.g., need for ongoing therapy), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of PTSD beyond the potential offsets that arise from a new intervention. During stakeholder engagement and public comment periods, ICER encouraged all stakeholders to suggest services (including treatments and mechanisms of care) currently used for patients with PTSD that could be reduced, eliminated, or made more efficient. No suggestions were received.

# B. Patient Perspectives: Supplemental Information

## B1. Methods

We gathered feedback on the experiences of people living with PTSD by speaking to PTSD patient organizations, interviewing people living with PTSD, and reviewing available material in the public domains from patients' testimony. We spoke with representatives from two organizations that support patients with PTSD and their families: Letters to Strangers, a youth-run nonprofit working to destigmatize mental illness and increase access to affordable, quality treatment, and a second organization that focuses on helping U.S. veterans overcome PTSD and other military trauma, which did not wish to be cited by name. We held a focus group that included three individuals living with PTSD who come from diverse backgrounds. Finally, we conducted five interviews that included participants living with PTSD and researchers with knowledge on the MAPP trials. A summary of what we heard is included in Section 2 of the main report.

# C. Clinical Guidelines

## American Psychological Association (2017) Clinical Practice Guideline for the Treatment of Post-Traumatic Stress Disorder (PTSD) in Adults[83]

These clinical practice guidelines on the psychological and pharmacological treatment of PTSD were developed by the American Psychological Association (APA) in 2017. Recommendations were made based on the strength of evidence, treatment net benefits (including PTSD symptom reduction and serious harms), patient preferences, and applicability to various PTSD populations. Recommendations with strong certainty include the use of psychotherapies for adults with PTSD, including cognitive behavioral therapy (CBT), cognitive processing therapy (CPT), and prolonged exposure therapy (PE). Additionally, the panel suggests using brief eclectic psychotherapy (BEP), eye movement desensitization and reprocessing therapy (EMDR), and narrative exposure therapy (NET). The conclusions surrounding EMDR and NET may potentially change to a stronger recommendation given the updates in evidence between 2012 and 2016. The panel determined that the evidence for Seeking Safety (SS) or relaxation (RLX) is insufficient. In terms of medications, the guideline suggests offering fluoxetine, paroxetine, sertraline, and venlafaxine, while noting the insufficient evidence regarding risperidone and topiramate.

## Department of Veterans Affairs/Department of Defense (2023) Clinical Practice Guideline for Management of Post-Traumatic Stress Disorder and Acute Stress Disorder[8]

These clinical practice guidelines on the management of PTSD were developed by the Department of Veterans Affairs (VA) and the Department of Defense (DoD). The guideline determined their recommendations based on the relationship between care options and health outcomes and quality of evidence, with the goal of improving patient outcomes and local management of PTSD patients. Major recommendations cover the diagnosis and assessment of PTSD, prevention of PTSD, treatment of PTSD, and treatment of PTSD with co-occurring conditions. Regarding diagnosis, guidelines suggest using the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) to screen for PTSD, the Clinician-Administered PTSD Scale or PTSD Symptom Scale – Interview Version for confirmation of PTSD diagnosis, and the PTSD Checklist for DSM-5 (PCL-5) or a structured clinician-administered interview such as the Clinical-Administered PTSD Scale (CAPS-5) to detect changes in symptom severity. For the prevention of PTSD, the panel concluded that there is insufficient evidence to recommend any preventative treatment immediately after individuals have been exposure to trauma. The guidelines related to treatment of PTSD strongly recommend prioritizing individual trauma-focused psychotherapies, including Cognitive Processing Therapy, Eye Movement Desensitization and Reprocessing, or Prolonged Exposure and weakly recommend Ehlers' Cognitive Therapy for PTSD, Present-Centered Therapy, or Written Exposure Therapy, over medications.

Regarding pharmacotherapies, guidelines strongly recommend paroxetine, sertraline, or venlafaxine for the treatment of PTSD. Additionally, they strongly recommend against using benzodiazepines, cannabis, and suggest against using divalproex, guanfacine, ketamine, prazosin, risperidone, tiagabine, or vortioxetine for PTSD treatment. There is insufficient evidence to form practical recommendations about the combination of psychotherapies and medications, including MDMA-AP. The panel also weakly suggests against using aripiprazole, asenapine, brexpiprazole, cariprazine, iloperidone, lumateperone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, or ziprasidone for the augmentation of PTSD medications. Regarding non-pharmacologic biological treatments, the panel suggests against using electroconvulsive therapy or vagus nerve stimulation for PTSD treatment. For alternative approaches, the panel weakly recommends using Mindfulness-Based Stress Reduction. Guidelines strongly recommend using secure teleconferencing to deliver treatments if that therapy has been validated for teleconferencing use or when other options are unavailable. For patients who have both PTSD and other co-occurring conditions, guidelines suggest that the presence of co-occurring disorder should not preclude recommended treatments for PTSD.

# D. Comparative Clinical Effectiveness: Supplemental Information

## D1. Detailed Methods

### PICOTS

#### *Population*

The population of focus for the review is adults with a diagnosis of moderate-to-severe PTSD.

Data permitting, we will evaluate the evidence for subpopulations defined by:

- PTSD subtype (e.g., dissociative PTSD)
- History of prior use of psychotherapy or pharmacotherapy for management of PTSD symptoms
- Sex
- Gender
- Age
- Race/ethnicity
- Military service

#### *Interventions*

Our intervention of interest for this review is MDMA-assisted Psychotherapy (MDMA-AP; Lykos Therapeutics).

#### *Comparators*

We intend to compare MDMA as an add-on to Lykos-specific psychotherapy (MDMA-AP) to an inactive placebo added on to Lykos-specific non-assisted psychotherapy (LSNAP).

Data permitting, we also intend to compare MDMA-AP to other short-term trauma-focused psychotherapies (TFP) commonly used for the treatment of PTSD (e.g., CBT for trauma [such as cognitive processing]; EMDR; exposure therapy [such as prolonged exposure]).

### *Outcomes*

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Change in PTSD Symptoms
        - Treatment response (change from baseline in clinical measure scores)
        - Loss of diagnosis
        - Remission
    - Outcomes on comorbidities of PTSD (e.g., functional impairment, depression, anxiety)
    - Health related quality of life
    - Impact on employment and education
    - Impact on alcohol and substance use
    - Adverse events including
        - Suicide ideation, behavior, and self-harm
        - Changes in vital signs (e.g., blood pressure, heart rate, etc.)
        - Serious adverse events
        - Treatment-related discontinuation

### *Timing*

Evidence on intervention efficacy, safety, and effectiveness will be collected from studies of any duration.

### *Settings*

Evidence from all relevant settings will be considered, including inpatient, outpatient/clinic, office, and home settings.

### *Study Design*

Randomized controlled trials, non-randomized controlled trials, and observational studies with any sample size will be considered.

**Table D1. PRISMA 2020 Checklist**

| Section and Topic | Item # | Checklist Item |
|---|---|---|
| **TITLE** | | |
| **Title** | 1 | Identify the report as a systematic review. |
| **ABSTRACT** | | |
| **Abstract** | 2 | See the PRISMA 2020 for Abstracts checklist. |
| **INTRODUCTION** | | |
| **Rationale** | 3 | Describe the rationale for the review in the context of existing knowledge. |
| **Objectives** | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. |
| **METHODS** | | |
| **Eligibility Criteria** | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. |
| **Information Sources** | 6 | Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. |
| **Search Strategy** | 7 | Present the full search strategies for all databases, registers, and websites, including any filters and limits used. |
| **Selection Process** | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. |
| **Data Collection Process** | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. |
| **Data Items** | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g., for all measures, time points, analyses), and if not, the methods used to decide which results to collect. |
| | 10b | List and define all other variables for which data were sought (e.g., participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. |
| **Study Risk of Bias Assessment** | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. |
| **Effect Measures** | 12 | Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results. |

| Section and Topic | Item # | Checklist Item |
|---|---|---|
| **Synthesis Methods** | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g., tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)). |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g., subgroup analysis, meta-regression). |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. |
| **Reporting Bias Assessment** | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). |
| **Certainty Assessment** | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. |
| **RESULTS** | | |
| **Study Selection** | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. |
| **Study Characteristics** | 17 | Cite each included study and present its characteristics. |
| **Risk of Bias in Studies** | 18 | Present assessments of risk of bias for each included study. |
| **Results of Individual Studies** | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g., confidence/credible interval), ideally using structured tables or plots. |
| **Results of Syntheses** | 20a | For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies. |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g., confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. |
| **Reporting Biases** | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. |
| **Certainty of Evidence** | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. |

| Section and Topic | Item # | Checklist Item |
|---|---|---|
| **DISCUSSION** | | |
| **Discussion** | 23a | Provide a general interpretation of the results in the context of other evidence. |
| | 23b | Discuss any limitations of the evidence included in the review. |
| | 23c | Discuss any limitations of the review processes used. |
| | 23d | Discuss implications of the results for practice, policy, and future research. |
| **OTHER INFORMATION** | | |
| **Registration and Protocol** | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. |
| **Support** | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. |
| **Competing Interests** | 26 | Declare any competing interests of review authors. |
| **Availability of Data, Code, and Other Materials** | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. |

*From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *PLoS Med.* 2021;18(3):e1003583.

## Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on MDMA-AP for PTSD followed established best research methods.[84,85] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[86] The PRISMA guidelines include a checklist of 27 items (see Table D1).

We searched MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials for relevant studies. Each search was limited to English-language studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, or news items. We included abstracts from conference proceedings identified from the systematic literature search. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described above. The proposed search strategies included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms.

To supplement the database searches, we performed manual checks of the reference lists of included trials and systematic reviews and invited key stakeholders to share references germane to the scope of this project. We also supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see the Policy on Inclusion of Grey Literature in Evidence Reviews.

**Table D2. Search Strategy of EMBASE Search**

| | |
|---|---|
| #1 | 'posttraumatic stress disorder'/exp OR 'posttraumatic stress disorder' |
| #2 | (PTSD OR 'post-traumatic stress disorder' OR 'acute stress disorder' OR 'posttraumatic neurosis' OR 'posttraumatic stress' OR 'posttraumatic syndrome' OR 'trauma syndrome' OR 'traumatic stress'):ti,ab |
| #3 | #1 OR #2 |
| #4 | midomafetamine/exp OR midomafetamine |
| #5 | (methylenedioxymethamphetamine OR MDMA OR 'MDMA-assisted therapy' OR '3,4-methylenedioxymethamphetamine'):ti,ab |
| #6 | #4 OR #5 |
| #7 | #3 AND #6 |
| #8 | ('case report'/de OR 'human tissue'/de OR 'nonhuman'/de OR 'practice guideline'/de OR 'questionnaire'/de OR 'chapter'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it) |
| #9 | #7 NOT #8 |
| #10 | ('animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp) NOT 'human'/exp |
| #11 | #9 NOT #10 |
| #12 | #11 AND [English]/lim |

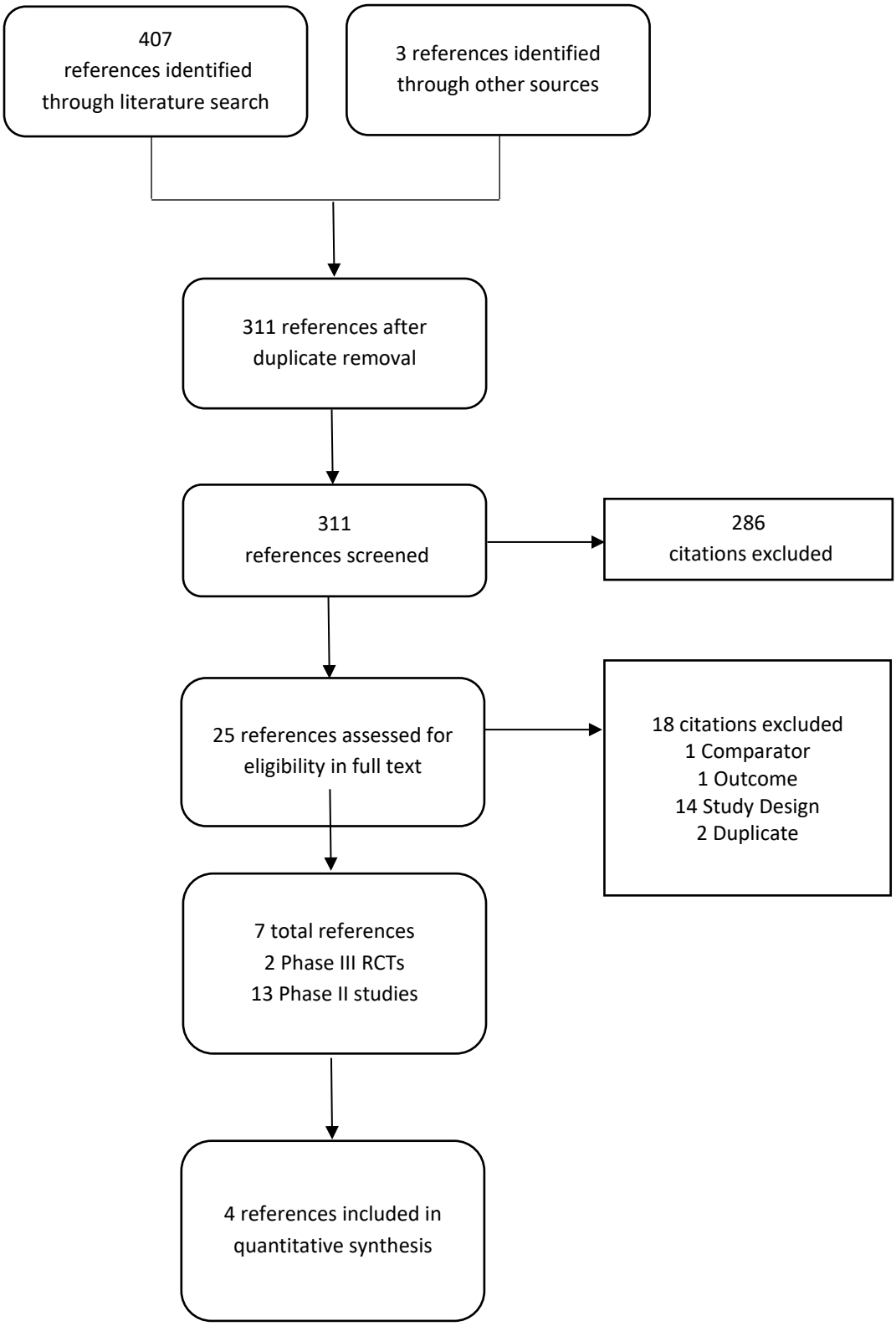
*Search last updated on April 5, 2024.

**Table D3. Search Strategy of Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other NonIndexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present, Cochrane Central Register of Controlled Trials, and APA PsychInfo 1967 to Present**

| | |
|---|---|
| 1 | Exp Stress Disorders, Post-Traumatic/ |
| 2 | ("Stress Disorders, Traumatic" or "Stress Disorders, Traumatic, Acute" or "Trauma and Stressor Related Disorders" or "posttraumatic neuroses" or "psychological trauma" or "posttraumatic syndrome" or PTSD).ti,ab |
| 3 | 1 OR 2 |
| 4 | Exp N-Methyl-3,4-methylenedioxyamphetamine/ |
| 5 | (Methylenedioxymethamphetamine or "MDMA-Assisted Therapy" or MDMA).ti,ab |
| 6 | 4 OR 5 |
| 7 | 3 AND 6 |
| 8 | ("address" or "autobiography" or "bibliography" or "biography" or "case reports" or "comment" or "congress" or "consensus development conference" or "duplicate publication" or "editorial" or "guideline" or "interview" or "lecture" or "legal case" or "legislation" or "letter" or "news" or "newspaper article" or "patient education handout" or "periodical index" or "personal narrative" or "portrait" or "practice guideline" or "review" or "video-audio media").pt. |
| 9 | 7 NOT 8 |
| 10 | (animals not (humans and animals)).sh. |
| 11 | 9 NOT 10 |
| 12 | Limit 11 to English language |
| 13 | Remove duplicates from 12 |

*Search last updated on April 5, 2024.

**Figure D1. PRISMA flow Chart Showing Results of Literature Search for MDMA-AP for PTSD**



## Study Selection

We performed screening at both the abstract and full-text level. Two investigators independently screened all titles and abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier using Nested Knowledge (Nested Knowledge, Inc, St. Paul, MN); a third reviewer worked with the initial two reviewers to resolve any issues of disagreement through consensus. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

## Data Extraction

Data were extracted into Microsoft Excel. The basic design and elements of the extraction forms followed those used for other ICER reports. Elements included a description of patient populations, sample size, duration of follow-up, funding source, study design features, interventions (agent, dosage, frequency, schedules), concomitant therapy allowed and used (agent, dosage, frequency, schedules), outcome assessments, results, and risk of bias for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.
2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

## Risk of Bias Assessment

We examined the risk of bias for each randomized control trial in this review using criteria published in the Cochrane Risk of Bias Assessment Tool Version 2.[85,87] Risk of bias was assessed by study outcome for each of the following aspects of the trials: randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and overall risk of bias. Two reviewers independently assessed these domains. Any disagreements were resolved through discussion or by consulting a third reviewer. We did not assess the risk of bias in trials where we only had access to conference abstracts/presentations.

To assess the risk of bias in trials, we rated the categories as: “low risk of bias,” “some concerns,” or “high risk of bias.” Guidance for risk of bias ratings using these criteria is presented below:

***Low risk of bias****: The study is judged to be at low risk of bias for all domains for this result.*

***Some concerns****: The study is judged to raise some concerns in at least one domain for this result, but not to be at high risk of bias for any domain.*

***High risk of bias****: The study is judged to be at high risk of bias in at least one domain for this result or the study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.*

We examined the risk of bias for the primary study outcome of Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). See Table D4.

**Table D4. Risk of Bias Assessment**

| | MAPP1 |
|---|---|
| **Randomization Process** | **Low Risk**<br><br>The study utilized a centralized, computer-generated randomization scheme managed by an independent vendor to allocate participants into double-blind MDMA-assisted psychotherapy and placebo control conditions. Randomization was concealed from study staff, participants, and the sponsor until after the database was locked. Baseline comparisons between arms showed no statistically significant differences, though there were some minor imbalances in distributions of the dissociative subtype diagnosis, pre-study CBT experience, and lifetime reported MDMA use—however, these differences did not necessarily suggest problems with the randomization process. |
| **Deviation from the Intended Interventions** | **High Risk**<br><br>Most study participants were aware of their assigned intervention during the trial, as blinding participants to receiving MDMA vs placebo was challenging given the psychoactive and physiological effects of MDMA. For these same reasons, it is likely that therapists were aware of the treatment arm that their participants were in. Blinding quality and outcome expectancies were not assessed over time.[13]<br><br>When participants were contacted after the trial to inform them of their assigned group, only 4.3% of participants in the treatment group and 15.9% in the placebo group incorrectly guessed their treatment arm, fewer than the expected 50% threshold in a perfectly blinded study.<br><br>The study protocol permitted participants to request additional integrative visits, and there was an uneven distribution in the number of participants who opted for these visits. Specifically, the MDMA arm had a higher proportion, with 10 out of 14 participants choosing to have additional integrative visits. |
| **Missing Outcome Data** | **Some Concerns**<br><br>Intention to Treat (ITT) analysis of the 91 randomized participants was not possible due to 1 person in the placebo arm withdrawing consent before first dosing. Modified ITT analysis included 90 participants.<br><br>For the main outcome of CAPS-5 measured at primary endpoint (T4), data was not available for 4 of 46 participants in the MDMA-AP arm and 4 of 44 in the placebo + therapy arm, a total of 8.9% missing values. |

| MAPP1 | |
|---|---|
| **Measurement of the Outcome** | **Some Concerns**<br><br>The CAPS-5 is considered the gold standard for measuring PTSD and was appropriately used as the primary outcome measure in this study, though it may not be ideally suited for assessing non-military populations and individuals whose PTSD did not originate from a singular traumatic trigger event.<br><br>Outcome measurement and ascertainment did not differ between the intervention groups, as independent raters conducted blinded CAPS-5 assessments at comparable time points following each experimental session and following the final session. Interrater reliability was high.<br><br>Outcome assessors were blinded to intervention status, as the CAPS-5 was administered by a centralized pool of independent raters via telemedicine who were trained to interview in a neutral, non-leading manner to minimize potential for bias.<br><br>We heard concerns that therapists encouraged favorable reports by patients and discouraged negative reports by patients including discouraging reports of substantial harms. Additionally, participants felt pressured to not disappoint the "community" giving the excitement about MDMA-AP as a new treatment option. The extent to which these issues happened and affected the overall results is unclear. However, these concerns could have potentially biased the recording of benefits and harms. |
| **Selection of the Reported Result** | **Some Concern**<br><br>The statistical analysis plan of the MAPP1 study identified the primary objective as evaluating the de jure efficacy of MDMA-AP using the CAPS-5 measure.<br><br>The mean change in CAPS-5 scores from baseline to 18 weeks after baseline was reported using the per protocol set (participants who completed three experimental sessions and assessments). Reporting of modified ITT analyses were limited to reporting of between-group difference and effect size. |
| **Overall Risk of Bias** | **High Risk of Bias**<br><br>MAPP1 employed rigorous methods to minimize bias, such as centralized randomization, allocation concealment, and blinded outcome assessment. However, there were concerns regarding unblinding due to the psychoactive effects of MDMA, and the inability to conduct a true intention-to-treat analysis due to missing data. While the primary outcome measure (CAPS-5) is considered the gold standard for PTSD, its suitability for non-military populations is uncertain. The statistical analysis plan focused on a per-protocol analysis rather than a full intention-to-treat approach, which may have introduced bias. Additionally, concerns about participants feeling pressured and wanting to avoid disappointing others may have played a role in biasing the results about benefits and harms. |

| MAPP2 | |
|---|---|
| **Randomization Process** | **Low Risk**<br><br>The study utilized a centralized, computer-generated randomization scheme managed by an independent vendor to allocate participants into double-blind MDMA-assisted psychotherapy and placebo control conditions. Randomization was concealed from study staff, participants, and the sponsor until after the database was locked. Baseline comparisons between arms showed no statistically significant differences, though there were some minor imbalances in distributions of female participants and reported MDMA use in the past 10 years, however, these differences did not necessarily suggest problems with the randomization process. |
| **Deviation from the Intended Interventions** | **High Risk**<br><br>Participants were aware of their assigned intervention during the trial, as blinding participants to receiving MDMA vs placebo was challenging given the psychoactive and physiological effects of MDMA. For these same reasons, it is likely that therapists were aware of the treatment arm that their participants were in.<br><br>Blinding was formally assessed in MAPP2; when participants were contacted after the trial to inform them of their assigned group, 94.2% of participants in the treatment group and 75% in the placebo group guessed their treatment condition correctly, much greater than the expected 50% threshold in a perfectly blinded study.<br><br>Outcome expectancies were not assessed over time. |
| **Missing Outcome Data** | **Some Risk**<br><br>Intention to Treat (ITT) analysis of the 104 randomized participants was not possible due to 1 person in the placebo arm discontinuing treatment with no outcome data. Modified ITT analysis included 103 participants.<br><br>For the main outcome of CAPS-5 measured at primary endpoint (T4), data was not available for 1 of 53 participants in the MDMA-AP arm and 8 of 51 in the placebo + therapy arm, indicating some potential attrition risk. An additional participant in the placebo + arm completed the T4 visit but did not have complete item-level data, for a total of 9.6% missing values. |

| MAPP2 | |
|---|---|
| **Measurement of the Outcome** | **Some Concern**<br><br>The CAPS-5 is considered the gold standard for measuring PTSD and was appropriately used as the primary outcome measure in this study, though it may not be ideally suited for assessing non-military populations and individuals whose PTSD did not originate from a singular traumatic trigger event.<br><br>Outcome measurement and ascertainment did not differ between the intervention groups, as independent raters conducted blinded CAPS-5 assessments at comparable time points following each experimental session and following the final session. Interrater reliability was not reported for the MAPP2 trial but was assumed to be of similar magnitude of MAPP1 due to identical study design.<br><br>Outcome assessors were blinded to intervention status, as the CAPS-5 was administered by a centralized pool of independent raters via telemedicine who were trained to interview in a neutral, non-leading manner to minimize potential for bias.<br><br>Like MAPP1, the testimonies about pressure on participants to report favorable outcomes and avoid reporting certain harms are concerning. |
| **Selection of the Reported Result** | **Some Concern**<br><br>The statistical analysis plan of the MAPP2 study identified the primary objective as evaluating the de jure efficacy of MDMA-AP using the CAPS-5 measure.<br><br>The mean change in CAPS-5 scores from baseline to 18 weeks after baseline was reported using the de jure estimand (effects of a drug if taken as directed) as well as the de facto estimand (drug taken as assigned, regardless of adherence), which was conducted as a supportive sensitivity analysis. The between-group difference and treatment effect size were also calculated the de jure estimand. |
| **Overall Risk of Bias** | **High Risk of Bias**<br><br>MAPP2 employed rigorous randomization and allocation concealment methods to minimize selection bias. However, the psychoactive effects of MDMA made participant and therapist blinding extremely challenging, with a substantial proportion correctly guessing their treatment assignment. This raises concerns about potential performance and detection bias, despite blinded outcome assessors. There was some attrition and missing data, though the risk is likely modest. The use of the gold-standard CAPS-5 outcome measure is a strength, although its suitability for non-military PTSD populations is uncertain. Notably, the statistical analysis adhered to the pre-specified plan, analyzing both the de jure and de facto estimands, which enhances the study's internal validity. |

CAPS-5: Clinician-Administered PTSD Scale for DSM-5, CBT: cognitive behavioral therapy, MDMA: 3,4-Methylenedioxymethamphetamine, MDMA-AP: MDMA-assisted psychotherapy, PTSD: Post-traumatic stress disorder

## Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit among each of the interventions of focus (see Appendix D).[88,89]

## Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for MDMA-AP using ClinicalTrials.gov. Search terms included "midomafetamine," "3,4-methylenedioxymethamphetamine-assisted therapy," "MDMA," and "MDMA-assisted psychotherapy." Three phase II trials, MP-3 (NCT00402298), MP-4 (NCT01958593) and MP-9 (NCT01689740), did not present results via peer-reviewed publications and were limited to ClinicalTrials.gov. Table D6 identifies several MAPP1 and 2 trial outcomes that were measured but whose results remain unpublished.

## D2. Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Section D3) and synthesized quantitatively and qualitatively in the body of the review. We evaluated the feasibility of conducting a quantitative synthesis by exploring the differences in study populations, study design, analytic methods, and outcomes. We did not include any Phase II trials from the Lykos clinical development program due to key differences across trials in patient characteristics and trial design (Table D5).

For comparison of MDMA-AP with LSNAP, fixed-effect pairwise meta-analyses were performed for CAPS-5 (between-group difference, treatment effect size, and treatment response categories of response, remission, and loss of diagnosis), SDS (between-group difference and treatment effect size), and safety events (suicidal ideation and treatment discontinuation). Continuous outcomes such as CAPS-5 were represented as mean difference (MD) and associated confidence intervals (95%). Binary outcomes, such as likelihood of remission were represented as rate ratios (RR) and associated confidence intervals (95%). Meta-analyses were performed using R Statistical Software (version 4.2.2) and data packages tidyverse, meta, and dmetar. Results of the meta-analysis are reported in the main report Tables 3.3 and 3.5.

A decision to use the fixed-effect (common-effect) model was made on the basis of several conditions: the small number of included studies, two Phase III trials (MAPP1 and MAPP2), that were identical in study design and intervention (three experimental sessions of identical MDMA dosages), with overlap of sites and study therapists. Furthermore, the trials recruited a similar population made up largely of patients with long-term severe PTSD with comorbidity of major depression and multi-source trauma. Based on these factors, an assumption of an identical effect size between trials was considered reasonable.

**Table D5. Phase 2 Trials and Exclusion from Meta-Analysis Reasons[15]**

| Study | NCT | Location | Population | MDMA dose | Comparator Dose | MDMA Sessions Completed | Long-Term Follow Up | Exclusion from Meta-Analysis Reason |
|---|---|---|---|---|---|---|---|---|
| MP-1 | NCT00090064 | South Carolina, U.S. | Treatment-resistant PTSD (moderate to severe) from military/crime | 125 mg (+62.5 mg supplemental dose) (n=15) | Inactive placebo (equivalent dose) (n=8) | 1 (n=2)<br>2 (n=11)<br>3 (n=9) | CAPS-4 (n=16)<br>LTFUQ (n=19) | Data from session 3 were eliminated from analysis |
| MP-2 | NCT00353938 | Switzerland | Treatment-resistant PTSD (CAPS-4≥50) | 25 mg (n=5)<br>125 mg (n=9) | N/A | 3 (n=12) | CAPS-4 (n=11)<br>LTFUQ (n=0) | No placebo comparator |
| MP-3 | NCT00402298 | Israel | War or terrorism-related PTSD | 125 mg (+62.5 mg supplemental dose) (n=3)<br>25 mg (+12.5 mg supplemental dose (n=2) | N/A | 2 (n=4) | CAPS-4 (n=4) | 2 blinded sessions; no placebo comparator; terminated early |
| MP-4 | NCT01958593 | Vancouver, Canada | Moderate-severe PTSD (CAPS-4≥60) | 125 mg (+62.5 mg supplemental dose) (n=4) | 0 mg (n=2) | 3 (n=6) | CAPS-4 (n=6)<br>LTFUQ (n=6) | 2 blinded sessions; 3rd session after unblinding; terminated early |
| MP-8 | NCT01211405 | South Carolina, U.S. | Veterans, firefighters, police with moderate-severe PTSD | 30 mg (n=7)<br>75 mg (n=7)<br>125 mg (n=12) | N/A | 1 (n=1)<br>3 (n=18)<br>5 (n=5)<br>6 (n=1) | CAPS-4 (n=24)<br>LTFUQ (n=24) | No placebo comparator; various number of MDMA sessions |
| MP-9 | NCT01689740 | Israel | Chronic, moderate-severe PTSD | 25 mg (n=3)<br>125 mg (n=7) | N/A | 2 (n=9) | CAPS-4 (n=9)<br>LTFUQ (n=9) | No placebo comparator; only 2 MDMA sessions |
| MP-12 | NCT01793610 | Colorado, U.S. | Chronic, moderate-severe PTSD | 40 mg (n=6)<br>100 mg (n=9)<br>125 mg (n=13) | N/A | 3 (n=26) | CAPS-4 (n=25)<br>LTFUQ (n=25) | No placebo comparator |

| Study | NCT | Location | Population | MDMA dose | Comparator Dose | MDMA Sessions Completed | Long-Term Follow Up | Exclusion from Meta-Analysis Reason |
|---|---|---|---|---|---|---|---|---|
| MP-16 | NCT03282123 | U.S. sites | Severe or greater PTSD | 80 or 120 mg (+40-60 mg supplemental dose) (n=38) | N/A | 3 (n=33) | CAPS-5 (n=33) | No placebo comparator; different MDMA doses pooled |
| MP-17 | NCT03485287 | Canada | Severe or greater PTSD | 100 or 125 mg (+50-62.5 mg supplemental dose) (n=4) | N/A | 3 (n=4) | CAPS-5 (n=4) | No placebo comparator; different MDMA doses pooled |
| MP1-E2 | NCT01458327 | South Carolina, U.S. | Participants who relapsed after prior participation in an MDMA-AP trial | 125 mg (+62.5 mg supplemental dose) (n=3) | N/A | 1 (n=3) | CAPS-4 (n=3) | 1 experimental session; no placebo comparator |
| MPVA-1 | NCT02876172 | South Carolina, U.S. | Participants with chronic PTSD & their partners | 75 mg (n=12) | N/A | 2 (n=12) | CAPS-5 (n=12) | No placebo comparator; not all participants have PTSD |
| Bouso 2008 | NR | Spain | Women with treatment-resistant PTSD who are victims of assault | 50 mg (n=3)<br>75 mg (n=1) | Inactive placebo (n=2) | 1 (n=6) | No CAPS outcome | CAPS not utilized in this trial; terminated early due to political reasons |

CAPS: Clinician-Administered PTSD Scale, CAPS-4: Clinician-Administered PTSD Scale for DSM-4, CAPS-5: Clinician-Administered PTSD Scale for DSM-5, LTFUQ: Long-term follow-up questionnaire, MDMA: 3,4-methylenedioxymethamphetamine, mg: milligram, N/A: not applicable, NCT: national clinical trial, n: number, NR: Not Reported, PTSD: Post-traumatic stress disorder, U.S., United States

# D3. Evidence Tables

### Table D6. Outcomes Assessed

| Outcome | Availability | |
|---|---|---|
| | MAPP1 | MAPP2 |
| **Primary Outcome** | | |
| CAPS-5 | Yes | Yes |
| **Secondary Outcome** | | |
| Sheehan Disability Scale (SDS) | Yes | Yes |
| **Safety Outcomes** | | |
| Adverse events (AEs) | No | No |
| Treatment-emergent adverse events (TEAEs) | Yes | Yes |
| Adverse events of special interest (AESI) | Yes | Yes |
| Serious adverse events (SAEs) | Yes | Yes |
| Use of concomitant medication | No | No |
| Use of psychiatric concomitant medication | No | No |
| Columbia Suicide Severity Rating Scale (C-SSRS) | Yes | Yes |
| Changes in BP, heart rate, body temperature | Yes | Yes |
| **Exploratory Outcomes** | | |
| Life Events Checklist for PTSD (LEC-5) | No | No |
| CAPS-5 subscales | No | No |
| Adverse Childhood Experiences (ACE) | No | No |
| Dissociative Subtype of PTSD Interview (DSP-I) | No | No |
| Beck Depression Inventory (BDI-II) | Yes | No |
| Chronic Pain Grade Scale (CPGS) | No | No |
| Quality of life (EQ-5D-5L) | No | No |
| Inventory of Altered Self-Capacities (functioning) (IASC) | Yes | No |

| Outcome | Availability | |
|---|---|---|
| | MAPP1 | MAPP2 |
| Inventory of Psychosocial Functioning (IPF) | No | No |
| Self-Compassion Scale (SCS) | Yes | No |
| Toronto Alexithymia Scale (TAS-20) | Yes | No |
| Alcohol Use Disorder (AUDIT) | Yes | No |
| Drug Use Disorder (DUDIT) | Yes | No |
| Self-Reported Nicotine Use (SRNU) | No | No |
| Eating Attitudes Test (EAT-26) | Yes | No |
| Workplace Productivity (HPQSF) | No | No |
| Healthcare Utilization (UFEC) | No | No |

BP: blood pressure, CAPS-5: Clinician-Administered PTSD Scale for DSM-5, EQ-5D-5L: EuroQol-5 Dimensions-5 Levels

**Table D7. Study Design**

| Trial (NCT) | Study Design & Follow-Up | Population, N | Arms & Dosing Regimen | Inclusion / Exclusion Criteria | Key Outcomes [Timepoint] |
|---|---|---|---|---|---|
| **MAPP1**[27,44]<br><br>Mitchell 2021 Nature<br><br>NCT03537014 | Phase III, TB, PC, RCT<br><br>Follow-up: 18 weeks post-enrollment | **Patients with severe PTSD**<br><br>N=90 | MDMA-assisted therapy (3 doses of MDMA [80 or 120 mg, + supplemental dose] + therapy sessions)<br><br>LSNAP | **Inclusion Criteria:**<br>-Adults (18+ years) that meet DSM-5 criteria for current **severe PTSD** for at least 6 months (CAPS-5 score ≥35)<br>-Must remain overnight at the study site after each Experimental Session and be driven home after, and commit to medication dosing, therapy, and study procedures<br><br>**Exclusion Criteria:**<br>-Have uncontrolled hypertension, marked baseline prolongation of QT/QTc interval, a history of additional risk factors for Torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome), or history of hyponatremia or hyperthermia<br>-Have evidence or history of significant medical disorders<br>-Have symptomatic liver disease<br>-Weight <48 kg<br>-Are pregnant or nursing<br>-Are abusing illegal drugs | **Primary Outcome:** Change from baseline in CAPS-5 [Baseline to 18 weeks post enrollment confirmation] |

| Trial (NCT) | Study Design & Follow-Up | Population, N | Arms & Dosing Regimen | Inclusion / Exclusion Criteria | Key Outcomes [Timepoint] |
|---|---|---|---|---|---|
| **MAPP2**[28,45]<br><br>Mitchell 2023 Nature<br><br>NCT04077437 | Phase III, TB, PC, RCT<br><br>Follow-up: 18 weeks post-enrollment | **Patients with moderate-to-severe PTSD**<br><br>N=104 | MDMA-assisted therapy (3 doses of MDMA [80 or 120 mg, + supplemental dose] + therapy sessions)<br><br>LSNAP | **Inclusion Criteria:**<br>-Adults (18+ years) that meet DSM-5 criteria for **moderate or greater severity PTSD** for at least 6 months (CAPS-5 score ≥28)<br>-Must remain overnight at the study site after each Experimental Session and be driven home after, and commit to medication dosing, therapy, and study procedures<br><br>**Exclusion Criteria:**<br>-Have uncontrolled hypertension, marked baseline prolongation of QT/QTc interval, a history of additional risk factors for Torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome), or history of hyponatremia or hyperthermia<br>-Have evidence or history of significant medical disorders<br>-Have symptomatic liver disease<br>-Weight<48 kg<br>-Are pregnant or nursing<br>-Are abusing illegal drugs | **Primary Outcome:**<br>Change from baseline in CAPS-5 [Baseline to 18 weeks post enrollment confirmation] |

CAPS-5: Clinician-Administered PTSD Scale for DSM-5, kg: Kilogram, LSNAP: Lykos-specific non-assisted psychotherapy, MDMA: 3,4-methylenedioxymethamphetamine, N: total number, PC: placebo-controlled, PTSD: Post-traumatic stress disorder, RCT: randomized controlled trial, TB: triple-blind

**Table D8. Baseline Characteristics[27-29,37]**

| Trial | | MAPP1 | | MAPP2 | |
|---|---|---|---|---|---|
| **Arms** | | **MDMA-AP** | **LSNAP** | **MDMA-AP** | **LSNAP** |
| **N** | | **46** | **44** | **53** | **51** |
| **Age, mean years (SD)** | | 43.5 (12.9) | 38.2 (10.4) | 38.2 (11) | 40 (9.6) |
| **Sex, n (%)** | **Male** | 19 (41.3) | 12 (27.3) | 21 (39.6) | 9 (17.6) |
| | **Female** | 27 (58.7) | 32 (72.7) | 32 (60.4) | 42 (82.4) |
| **Ethnicity, n (%)** | **Hispanic or Latino** | 5 (10.9) | 3 (6.8) | 17 (32.1) | 11 (21.6) |
| | **Not Hispanic or Latino** | 41 (89.1) | 40 (90.9) | 36 (67.9) | 39 (76.5) |
| **Race, n (%)** | **American Indian or native Alaskan** | 3 (6.5) | 0 (0) | 0 (0) | 2 (3.9) |
| | **Asian** | 2 (4.3) | 5 (11.4) | 5 (9.4) | 6 (11.8) |
| | **Black or African American** | 0 (0) | 2 (4.5) | 5 (9.4) | 3 (5.9) |
| | **Native Hawaiian or other Pacific Islander** | 0 (0) | 0 (0) | 0 (0) | 1 (2) |
| | **White** | 39 (84.8) | 30 (68.2) | 37 (69.8) | 32 (62.7) |
| | **Multiple** | 2 (4.3) | 6 (13.6) | 6 (11.3) | 7 (13.7) |
| **Education level, n (%)** | **<High school** | 3 (6.5) | 0 (0)* | NR | NR |
| | **High school graduate** | 2 (4.4) | 1 (2.3)* | NR | NR |
| | **Some college** | 9 (19.6) | 11 (25.6)* | NR | NR |
| | **College graduate** | 13 (28.3) | 17 (39.5)* | NR | NR |
| | **>College** | 19 (41.3) | 14 (32.6)* | NR | NR |
| **BMI, mean kg/m2 (SD)** | | 26 (4.8) | 24.8 (4.2) | 26.3 (5.6) | 24.7 (4.9) |
| **PTSD Duration, mean years (SD)** | | 14.8 (11.6) | 13.2 (11.4) | 16.3 (14.3) | 16.1 (12.4) |
| **PTSD Dissociative subtype, n (%)** | | 6 (13) | 13 (29.5) | 13 (24.5) | 11 (21.6) |
| **Psychiatric disorder, n (%)** | **Comorbid major depression** | 42 (91.3) | 40 (90.9) | 49 (92.5) | 51 (100) |
| | **Suicide ideation** | 17/46 (37) | 14/44 (32) | 13 (24.5) | 12 (23.5) |

| Trial | | MAPP1 | | MAPP2 | |
|---|---|---|---|---|---|
| Arms | | MDMA-AP | LSNAP | MDMA-AP | LSNAP |
| N | | 46 | 44 | 53 | 51 |
| Trauma history, n (%) | Developmental | 40 (87) | 36 (81.8) | 49 (92.5) | 43 (84.3) |
| | Combat exposure | 6 (13) | 5 (11.4) | 9 (17) | 6 (11.8) |
| | Veteran Status | 10 (21.7) | 6 (13.6) | 9 (17) | 7 (13.7) |
| | Multiple trauma | 41 (89.1) | 38 (86.4) | 40 (75.5) | 45 (88.2) |
| Pre-study PTSD medications, n (%) | Sertraline | 8 (17.4) | 9 (20.5) | 15 (28.3) | 10 (19.6) |
| | Paroxetine | 3 (6.5) | 3 (6.8) | 1 (1.9) | 1 (2) |
| Pre-study therapy, n (%) | CBT | 12 (26.1) | 22 (50) | 15 (28.3) | 14 (27.5) |
| | Cognitive processing therapy | NR | NR | 1 (1.9) | 1 (2) |
| | DBT | NR | NR | 4 (7.5) | 2 (3.9) |
| | EMDR | 17 (37) | 13 (29.5) | 17 (32.1) | 18 (35.3) |
| | Group therapy | 19 (41.3) | 14 (31.8) | 9 (17) | 15 (29.4) |
| | Holotropic breathwork | NR | NR | 0 (0) | 3 (5.9) |
| | Prolonged exposure therapy | 1 (2.2) | 0 (0) | 2 (3.8) | 0 (0) |
| | Psychodynamic | 11 (23.9) | 10 (22.7) | 15 (28.3) | 11 (21.6) |
| | Other | 41 (89.1) | 38 (86.4) | 41 (77.4) | 42 (82.4) |
| | None | 1 (2.2) | 1 (2.3) | NR | NR |
| CAPS-5 total score, mean (SD) | | 44 (6) | 44.2 (6.2) | 39.4 (6.6) | 38.7 (6.7) |
| SDS modified score, mean (SD) | | 6.8 (2.1) | 7.4 (1.6) | *6 (NR)*† | *6.1 (NR)*† |
| SDS total score by domain, mean (SD) | Family life/home | NR | NR | 5.1 (2.7) | 5.6 (2) |
| | Social/leisure activities | NR | NR | 6.2 (2.3) | 6.5 (2) |
| | Work/school | NR | NR | 6.8 (2.6) | 6.3 (2.5) |
| PTSD severity, n (%) | Moderate‡ | N/A | N/A | 13 (24.5) | 15 (29.4) |
| | Severe§ | 46 (100) | 44 (100) | 40 (75.5) | 36 (70.6) |
| C-SSRS score, mean (SD) | Suicidal ideation | 3 (1.8) | 3 (1.5)* | 0.4 (0.8) | 0.3 (0.6) |
| | Ideation intensity | NR | NR | 3 (5.5) | 2.8 (5.3) |

| Trial | | MAPP1 | | MAPP2 | |
|---|---|---|---|---|---|
| Arms | | MDMA-AP | LSNAP | MDMA-AP | LSNAP |
| N | | 46 | 44 | 53 | 51 |
| Lifetime C-SSRS, n (%) | Positive lifetime suicidal ideation | 42 (91.3) | 41 (93.2) | 44 (83) | 47 (92.2) |
| | Serious lifetime suicidal ideation | 20 (43.5) | 17 (38.6) | 15 (28.3) | 18 (35.3) |
| | Positive lifetime suicidal behavior | 16 (34.8) | 13 (29.5) | NR | NR |
| BDI-II total score, mean (SD) | | 30.5 (13.1) | 34.9 (12.6) | 25.4 (11.9) | 25.5 (11.3) |
| Current alcohol use disorder, n (%) | | 0 (0) | 0 (0) | NR | NR |
| AUDIT, mean (SD) | | 4.1 (4.2) | 2.8 (3.2) | NR | NR |
| Current substance disorder, n (%) | | 0 (0) | 2 (5) | NR | NR |
| DUDIT, mean (SD) | | 2.7 (4.3) | 3.5 (4.5) | NR | NR |
| ACE Questionnaire score, mean (SD) | | 5 (2.7) | 5 (2.9) | 4.8 (2.9) | 4.5 (2.7) |
| Current eating disorder, n (%) | | 15 (15.7)# | | NR | NR |
| EAT-26, mean (SD) | | 9.3 (9.9) | 8.9 (7.1) | NR | NR |
| Prior report of MDMA use, n (%) | Lifetime reported use | 18 (39.1) | 11 (25) | 22 (41.5) | 26 (51) |
| | Reported use in the past 10 years | 9 (19.6) | 10 (22.7) | 13 (24.5) | 18 (35.3) |

ACE: adverse childhood experiences, AUDIT: Alcohol Use Disorders Identification Test, BMI: body mass index: BDI-II: Beck Depression Inventory II, CAPS-5: Clinician-Administered PTSD Scale for DSM-5, CBT: cognitive behavioral therapy, C-SSRS: Columbia Suicide Severity Rating Scale, DBT: dialectical behavior therapy, DUDIT: Drug Use Disorders Identification Test, EAT-26: Eating Attitudes Test-26, EMDR: eye movement desensitization and reprocessing, kg: kilogram, LSNAP: Lykos-specific non-assisted psychotherapy, m: meter, MDMA: 3,4-Methylenedioxymethamphetamine, MDMA-AP: MDMA-assisted psychotherapy, n: number, N: total number, N/A: not applicable, NR: not reported, PTSD: Post-traumatic stress disorder, SD: standard deviation, SDS: Sheehan Disability Scale

*N=43.

†Data were averaged across available SDS subscale data.

‡Moderate PTSD was defined as a CAPS-5 score between 28-34.

§Severe PTSD was defined as a CAPS-5 score ≥35.

#N=89.

**Table D9. Meta-Analysis of Key Clinical Efficacy Results[27,28]**

| Outcome | Arm | Data | MAPP1 | MAPP2 | Summary Estimate - Common Effect Meta-Analysis of MDMA-AP vs. Psychotherapy |
|---|---|---|---|---|---|
| **CAPS-5 Between Group Difference** | **Treatment Effect (SE)** | | -11.9 (2.83) | -8.9 (2.44) | MD (95% CI): -10.18 (-13.80, -6.56) |
| **CAPS-5 Effect Size, Cohen's *d*** | **Treatment Effect (SE)** | | 0.91 (0.23) | 0.7 (0.21) | SMD (95% CI): 0.80 (0.49, 1.10) |
| **Treatment Responder†** | **MDMA-AP** | **n/N** | *37/42** | *45/52** | RR (95% CI): 1.32 (1.11,1.58) |
| | **LSNAP** | **n/N** | *23/37** | *29/42** | |
| **Loss of Diagnosis‡** | **MDMA-AP** | **n/N** | 28/42 | *37/52** | RR (95% CI): 1.70 (1.26, 2.29) |
| | **LSNAP** | **n/N** | 12/37 | *20/42** | |
| **Remission§** | **MDMA-AP** | **n/N** | 14/42 | *24/52** | RR (95% CI): 2.86 (1.58, 5.16) |
| | **LSNAP** | **n/N** | 2/37 | *9/42** | |
| **SDS Mean Score (After Session 3)** | **MDMA-AP** | **N** | 46 | 53 | MD (95% CI): -1.48 (-1.60, -1.36) |
| | | **Mean (SD)** | *3.7 (0.5)** | *2.7 (0.4)** | |
| | **LSNAP** | **N** | 43 | 50 | |
| | | **Mean (SD)** | *5.3 (0.4)** | *4.1 (0.4)** | |
| **SDS Effect Size, Cohen's *d*** | **Treatment Effect (SE)** | | 0.43 (0.17) | 0.4 (0.18) | SMD (95% CI): 0.42 (0.17, 0.66) |

CAPS-5: Clinician-Administered PTSD Scale for DSM-5, CI: confidence interval, LSNAP: Lykos-specific non-assisted psychotherapy, MD: mean difference, MDMA-AP: MDMA-assisted psychotherapy, n: number, N: total number, RR: relative risk, SD: standard deviation, SDS: Sheehan Disability Scale, SE: standard error, SMD: standardized mean difference, vs.: versus

*Data were digitized.

†Responder was defined as ≥10-point decrease in CAPS-5.

‡Loss of diagnosis was defined as ≥10-point reduction in CAPS-5 and not meeting PTSD diagnostic criteria.

§Remission was defined as loss of diagnosis and a total CAPS-5 score of ≤11.

**Table D10. Safety Results[27,28,44,45]**

| Trial | | MAPP1 | | MAPP2 | |
|---|---|---|---|---|---|
| Arms | | MDMA-AP | LSNAP | MDMA-AP | LSNAP |
| N | | 46 | 44 | 53 | 51 |
| Timepoint | | 18 Weeks | | 18 Weeks | |
| AEs, n (%) | Muscle tightness | 29 (63)* | 5 (11.4)* | 31 (58.5) | 13 (25.5) |
| | Decreased appetite | 24 (52.2) | 5 (11.4) | 19 (35.8) | 5 (9.8) |
| | Nausea | 14 (30.4) | 5 (11.4) | 24 (45.3) | 11 (21.6) |
| | Hyperhidrosis (excessive sweating) | 9 (19.6)* | 1 (2.3) | 18 (34.0) | 3 (5.9) |
| | Feeling hot | 4 (8.7)† | 4 (9.1)† | 14 (26.4) | 6 (11.8) |
| | Feeling cold | 9 (19.6) | 3 (6.8) | 11 (20.8) | 3 (5.9) |
| | Restlessness | 7 (15.2) | 0 (0) | 8 (15.1) | 2 (3.9) |
| | Mydriasis (dilated pupils) | 7 (15.2) | 0 (0) | 6 (11.3) | 0 (0) |
| | Dizziness Postural (chronic dizziness) | 6 (13) | 2 (4.5) | NR | NR |
| | Bruxism (teeth grinding) | 6 (13) | 1 (2.3) | 7 (13.2) | 1 (2) |
| | Nystagmus (uncontrolled repetitive eye movement) | 6 (13) | 0 (0) | 7 (13.2) | 1 (2) |
| | Blood Pressure Increased | 5 (10.9) | 0 (0) | NR | NR |
| | Feeling Jittery | 5 (10.9) | 0 (0) | 8 (15.1) | 0 (0) |
| | Non-Cardiac Chest Pain | 5 (10.9)* | 1 (2.3) | NR | NR |
| | Dry Mouth | 5 (10.9) | 2 (4.5) | 9 (17) | 4 (7.8) |
| | Vision Blurred | 4 (8.7) | 1 (2.3) | 8 (15.1) | 0 (0) |
| | Visual impairment | NR | NR | 3 (5.7) | 0 (0) |
| | Pollakiuria (frequent urination) | 4 (8.7) | 1 (2.3) | NR | NR |
| | Intrusive Thoughts | 4 (8.7) | 0 (0) | NR | NR |
| | Vomiting | 4 (8.7) | 0 (0) | 4 (7.6) | 2 (3.9) |
| | Stress | 4 (8.7) | 0 (0) | NR | NR |
| | Musculoskeletal Pain | 4 (8.7) | 0 (0)* | NR | NR |
| | Pyrexia (fever) | 3 (6.5) | 1 (2.3) | NR | NR |
| | Chills | 3 (6.5) | 0 (0)* | 8 (15.1) | 1 (2) |

| Trial | | MAPP1 | | MAPP2 | |
|---|---|---|---|---|---|
| Arms | | MDMA-AP | LSNAP | MDMA-AP | LSNAP |
| N | | 46 | 44 | 53 | 51 |
| Timepoint | | 18 Weeks | | 18 Weeks | |
| | **Substance Use (cannabis)** | 3 (6.5) | 0 (0) | NR | NR |
| | **Micturition Urgency (urgent urination)** | 3 (6.5) | 0 (0) | NR | NR |
| | **Muscle Twitching** | 3 (6.5) | 0 (0) | NR | NR |
| | **Somnolence (drowsiness)** | 3 (6.5) | 0 (0) | NR | NR |
| | **Nervousness** | 3 (6.5) | 0 (0) | NR | NR |
| | **Paresthesia ("pins and needles")** | 5 (10.9)† | 3 (6.8)† | 10 (18.9) | 1 (2) |
| | **Chest Discomfort** | NR | NR | 9 (17) | 2 (3.9) |
| | **Tremor** | 6 (13)† | 3 (6.8)† | 6 (11.3) | 0 (0) |
| | **Palpitations** | 4 (8.7)† | 6 (13.6)† | 5 (9.4) | 1 (2.0) |
| | **Abdominal pain** | NR | NR | 2 (3.8) | 3 (5.9) |
| | **Abdominal discomfort** | 6 (13.0)† | 3 (6.8)† | 3 (5.7) | 3 (5.9) |
| | **Abdominal pain upper** | 5 (10.9)† | 4 (9.1)† | 5 (9.4) | 1 (2.0) |
| | **Diarrhea** | 2 (4.4)† | 5 (11.4)† | 1 (1.9) | 3 (5.9) |
| | **Asthenia (weakness)** | 7 (15.2)† | 4 (9.1)† | NR | NR |
| | **Crying** | 0 (0)† | 3 (6.8)† | NR | NR |
| | **Fatigue** | 14 (30.4)† | 14 (31.8)† | 14 (26.4) | 9 (17.7) |
| | **Influenza-like Illness** | 2 (4.4)† | 3 (6.8)† | NR | NR |
| | **Pain** | 4 (8.7)† | 1 (2.3)† | NR | NR |
| | **Temperature intolerance** | 4 (8.7)† | 2 (4.6)† | NR | NR |
| | **Upper respiratory tract infection** | 5 (10.9)† | 4 (9.1)† | 3 (5.7)† | 3 (5.9)† |
| | **Arthralgia (joint pain)** | 4 (8.7)† | 3 (6.8)† | 4 (7.6)† | 5 (9.8)† |
| | **Back pain** | 5 (10.9)† | 4 (9.1)† | 3 (5.7)† | 3 (5.9)† |
| | **Neck pain** | 2 (4.4)† | 4 (9.1)† | 3 (5.7)† | 7 (13.7)† |
| | **Pain in jaw** | 3 (6.5)† | 3 (6.8)† | 6 (11.3)† | 4 (7.8)† |
| | **Disturbance in attention** | 4 (8.7)† | 3 (6.8)† | 3 (5.7)† | 3 (5.9)† |
| | **Dizziness** | 9 (19.6)† | 5 (11.4)† | 15 (28.3)† | 8 (15.7)† |

| Trial | | MAPP1 | | MAPP2 | |
|---|---|---|---|---|---|
| Arms | | MDMA-AP | LSNAP | MDMA-AP | LSNAP |
| N | | 46 | 44 | 53 | 51 |
| Timepoint | | 18 Weeks | | 18 Weeks | |
| | **Headache** | 33 (71.7)† | 24 (54.6)† | 38 (71.7)† | 31 (60.8)† |
| | **Hypoesthesia (decreased sense of touch/sensation)** | 3 (6.5)† | 2 (4.6)† | 5 (9.4)† | 1 (2)† |
| | **Agitation** | 2(4.4)† | 3 (6.8)† | NR | NR |
| | **Anger** | 3 (6.5)† | 6 (13.6)† | NR | NR |
| | **Anxiety** | 15 (32.6) | 17 (38.6)† | 15 (28.3)† | 12 (23.5)† |
| | **Binge eating** | NR | NR | 0 (0) | 3 (5.9) |
| | **Depressed mood** | 5 (10.9)† | 4 (9.1)† | 5 (9.4)† | 6 (11.8)† |
| | **Depression** | 4 (8.7)† | 4 (9.1)† | NR | NR |
| | **Dissociation** | NR | NR | 3 (5.7)† | 0 (0)† |
| | **Emotional disorder** | 2 (4.4)† | 4 (9.1)† | 3 (5.7)† | 2 (3.9)† |
| | **Flashback** | 3 (6.5)† | 2 (4.6)† | NR | NR |
| | **Insomnia** | 20 (43.4)† | 13 (29.6)† | 19 (35.9) | 15 (29.4)† |
| | **Intentional self-injury** | 1 (2.2)† | 4 (9.1)† | NR | NR |
| | **Irritability** | 2 (4.4)† | 5 (11.4)† | 3 (5.7) | 2 (3.9)† |
| | **Nervousness** | 3 (6.5)† | 0 (0)† | NR | NR |
| | **Nightmare** | 7 (15.2)† | 7 (15.9)† | 4 (7.6) | 3 (5.9)† |
| | **Panic attack** | NR | NR | 3 (5.7) | 1 (2)† |
| | **Stress** | 4 (8.7)† | 0 (0)† | NR | NR |
| | **Suicidal Ideation** | 21 (45.6)† | 21 (47.73)† | 18 (34)† | 21 (41.2)† |
| | **Oropharyngeal Pain** | 2 (4.4)† | 3 (6.8)† | NR | NR |
| | **Feeling abnormal** | NR | NR | 5 (9.4)† | 2 (3.9)† |
| | **Body temperature change** | NR | NR | 5 (9.4)† | 0 (0)† |
| | **Thirst** | NR | NR | 4 (7.6)† | 1 (2)† |
| | **Gait disturbance** | NR | NR | 3 (5.7)† | 0 (0)† |
| | **COVID-19** | NR | NR | 4 (7.6)† | 4 (7.8)† |
| | **Heart rate increase** | NR | NR | 3 (5.7)† | 0 (0)† |

| Trial | | | MAPP1 | | MAPP2 | |
|---|---|---|---|---|---|---|
| Arms | | | MDMA-AP | LSNAP | MDMA-AP | LSNAP |
| N | | | 46 | 44 | 53 | 51 |
| Timepoint | | | 18 Weeks | | 18 Weeks | |
| | Myalgia (muscle ache) | | NR | NR | 7 (13.2)† | 4 (7.8)† |
| | Muscle spasm | | NR | NR | 4 (7.6)† | 0 (0)† |
| | Flushing | | NR | NR | 3 (5.7)† | 1 (2)† |
| TEAEs, n (%) | Total | | 46 (100)† | 44 (100)† | 53 (100)† | 49 (96.1) |
| | Serious | Total | 0 (0) | 2 (4.5) | 0 (0) | 0 (0) |
| | | Suicide attempts | 0 (0) | 1 (2.3) | NR | NR |
| | | Suicidal ideation resulting in self-hospitalization | 0 (0) | 1 (2.3) | NR | NR |
| | Severe | | NR | NR | 5 (9.4) | 2 (3.9) |
| | Leading to study discontinuation | | NR | NR | 0 (0) | 2 (3.9) |
| | TEAESI | | NR | NR | 6 (11.3) | 3 (5.9) |
| | Cardiac | | NR | NR | 7 (13.2) | 1 (2) |
| | Vascular | | NR | NR | 7 (13.2) | 2 (3.9) |
| | Psychiatric | Overall | NR | NR | 44 (83) | 37 (72.5) |
| | | Severe | NR | NR | 3 (5.7) | 2 (3.9) |
| Treatment-emergent AESIs, n (%) | Suicidality | Total | 3 (6.5) | 5 (11.4) | NR | NR |
| | | Suicidal ideation | 2 (4.3) | 3 (6.8) | 2 (3.8) | 1 (2) |
| | | Intentional self-harm in the context of suicidal ideation | 1 (2.2) | 0 (0) | NR | NR |
| | | Suicidal behavior (suicide attempts and preparatory acts) and self-harm | 0 (0) | 1 (2.3) | NR | NR |
| | | Suicidal behavior (preparatory acts), self-harm and suicidal ideation | 0 (0) | 1 (2.3) | NR | NR |

| Trial | | | MAPP1 | | MAPP2 | |
|---|---|---|---|---|---|---|
| Arms | | | MDMA-AP | LSNAP | MDMA-AP | LSNAP |
| N | | | 46 | 44 | 53 | 51 |
| Timepoint | | | 18 Weeks | | 18 Weeks | |
| | | Non-suicidal self-injurious behavior | NR | NR | 1 (1.9) | 1 (2) |
| | | Trichotillomania (urge to pull out hair) | NR | NR | 0 (0) | 1 (2) |
| | Cardiac events that could indicate QT prolongation | Total | 0 (0) | 1 (2.3) | NR | NR |
| | | Irregular heartbeats and palpitations | 0 (0) | 1 (2.3) | NR | NR |
| | Abuse potential for MDMA | | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

AE: adverse event, AESI: adverse event of special interest, LSNAP: Lykos-specific non-assisted psychotherapy, MDMA: 3,4-Methylenedioxymethamphetamine, MDMA-AP: MDMA-assisted psychotherapy, n: number, N: total number, NR: not reported, TEAE: treatment emergent adverse event, TEAESI: treatment emergent adverse event of special interest

*There is a discrepancy between publication and ClinicalTrials.gov data value. This value is from the publication.

†Data found only on ClinicalTrials.gov.

## D4. Ongoing Studies

**Table D11. Ongoing Studies**

| Title/Trial Sponsor | Study Design | Treatment Arms | Patient Population | Primary Outcome(s) | Estimated Completion Date |
|---|---|---|---|---|---|
| **MDMA-AP Long-Term Follow-Up Studies** | | | | | |
| A Multi-Site Open-Label Extension Study of MDMA-Assisted Psychotherapy for PTSD (MAPPUSX)<br><br>Lykos Therapeutics<br>NCT04714359 | Phase III, single-arm, open-label study<br><br>N~85<br><br>Locations: U.S., Canada, Israel | MDMA-assisted psychotherapy | Adults with PTSD who were previously enrolled in a Lykos parent study | -Change in PCL-5 (18 weeks) | November 2023 |
| Long-Term Safety and Effectiveness of MDMA-Assisted Therapy for PTSD (MPLONG)<br><br>Lykos Therapeutics<br>NCT05066282 | Phase IV, retrospective cohort study<br><br>N~400<br><br>Locations: U.S., Canada, Israel | MDMA-assisted therapy | Adults with PTSD who were previously enrolled in a Lykos parent study and received intervention in at least one experimental session | -CAPS-5 total severity score (at least six months since last experimental session) | September 2024 |
| **Other Trials** | | | | | |
| A Phase 2 Open-Label Treatment Development Study of MDMA-Assisted Cognitive Processing Therapy (CPT) for Post-traumatic Stress Disorder (PTSD)<br><br>Remedy (in collaboration with Lykos)<br>NCT05067244 | Phase II, single-arm, open-label study<br><br>N~10<br><br>Location: Canada | MDMA-assisted CPT psychotherapy | Adults with PTSD | -Change from baseline in CAPS-5 (visit 6, 3-4 weeks, 1 month, 3 months, 6 months) | June 2024 |
| MDMA-assisted Brief Cognitive Behavioral Conjoint Therapy for PTSD (MDMA-bCBCT) | Phase III, single-arm, open-label study | For dyads:<br><br>-bCBCT non-medicine sessions | Adult veterans with PTSD and their intimate partners without PTSD, in committed | -CAPS-5 (6 months post-treatment) | December 2024 |

| Title/Trial Sponsor | Study Design | Treatment Arms | Patient Population | Primary Outcome(s) | Estimated Completion Date |
|---|---|---|---|---|---|
| Dr. Leslie Morland, San Diego Veterans Healthcare System (in collaboration with Lykos Therapeutics)<br>NCT05979844 | N~16<br><br>Location: U.S. | (both partners) + MDMA medicine sessions (veteran partners only) | relationships for 12 months or longer | | |
| Study of Feasibility and Safety of MDMA-Assisted Group Therapy for the Treatment of PTSD in Veterans (MPG1)<br><br>Lykos Therapeutics<br>NCT05173831 | Phase II, single-arm, open-label study<br><br>N: NR<br><br>Location: U.S. | MDMA-assisted group therapy | Adult veterans with PTSD | -Change in CAPS-5 total severity score (3 months from first experimental session) | December 2024 |
| MDMA for AUD/PTSD Comorbidity (MDMA)<br><br>Carolina Haass-Koffler, Brown University<br>NCT05943665 | Phase II, single-arm, open-label study<br><br>N~18<br><br>Location: U.S. | MDMA-assisted psychotherapy (clinicians trained by Lykos Therapeutics) | Adult veterans with alcohol use disorder and moderate to severe PTSD for six months or longer | -Number of standard unit drinks (alcohol consumed) (18 weeks)<br>-CAPS severity score reduction (18 weeks) | January 2025 |
| MDMA for Co-occurring PTSD and OUD After Childbirth<br><br>University of New Mexico (in collaboration with Lykos)<br>NCT05219175 | Phase II, single-arm, open-label study<br><br>N~15<br><br>Location: U.S. | MDMA-assisted psychotherapy | Adults with opioid use disorder and moderate to severe PTSD for six months or longer | -CAPS-5 (4 weeks after 3rd experimental session) | April 2025 |
| MDMA-assisted Therapy Versus Cognitive Processing Therapy for Veterans With Severe Post-traumatic Stress Disorder<br><br>Patricia Suppes, Palo Alto Veterans Institute for Research<br>NCT05837845 | Phase II, randomized, unblinded study<br><br>N~30<br><br>Location: U.S. | -MDMA-assisted psychotherapy (clinicians trained by Lykos Therapeutics)<br><br>-CPT alone | Adult veterans with severe PTSD for six months, receiving services from VA Palo Alto, San Francisco, or NorCal Healthcare System | -Change in CAPS-5 total severity score (4 months post-baseline) | May 2025 |

| Title/Trial Sponsor | Study Design | Treatment Arms | Patient Population | Primary Outcome(s) | Estimated Completion Date |
|---|---|---|---|---|---|
| MDMA-Assisted Therapy for Veterans With Moderate to Severe Post Traumatic Stress Disorder<br><br>Stephen Robert Marder, VA Greater Los Angeles Healthcare System<br>NCT05790239 | Phase II, randomized, triple-blind study<br><br>N~40<br><br>Location: U.S. | -MDMA-assisted psychotherapy<br><br>-Low-dose D-amphetamine-assisted psychotherapy | Adult veterans with moderate to severe PTSD for at least six months, enrolled at a VA Healthcare Center in the Greater Los Angeles Area | -Change in CAPS-5 total severity score (14 weeks post-enrollment) | May 2025 |
| Study Comparing Two Versus Three Active MDMA-assisted Sessions in U.S. Military Veterans With Chronic PTSD (MPVA6)<br><br>Lykos Therapeutics<br>NCT04784143 | Phase II, randomized, open-label study<br><br>N=26<br><br>Location: U.S. | -Two sessions of MDMA-assisted psychotherapy<br><br>-Three sessions of MDMA-assisted psychotherapy | Adult veterans with moderate or greater PTSD | -Change in CAPS-5 total severity score for two-session group (3 months)<br>-Change in CAPS-5 total severity score for three-session group (4 months) | July 2025 |
| MDMA-assisted Massed Prolonged Exposure for PTSD (MDMA-PE)<br><br>Healing Breakthrough (in collaboration with Lykos Therapeutics)<br>NCT06117306 | Phase III, randomized, quadruple-blind trial<br><br>N~10<br><br>Location: U.S. | -MDMA-assisted prolonged exposure therapy<br>-Low-dose MDMA-assisted prolonged exposure therapy | Adult veterans with PTSD due to any military event | -CAPS-5 (4 months post-treatment) | January 2026 |
| Preliminary Effectiveness of Individual and Group MDMA-assisted Therapy for Israeli Veterans With PTSD and Moral Injury<br><br>HaEmek Medical Center, Israel (in collaboration with Lykos Therapeutics<br>NCT05732155 | Phase II, single-arm, open-label study<br><br>N~60<br><br>Location: Israel | MDMA-assisted therapy (individual and group experimental sessions) | Adult veterans of special forces undercover units in the Israel army, who have moderate or greater PTSD for at least six months | -Change in PCL-5 (up to 46 weeks) | June 2026 |

Sources: www.ClinicalTrials.gov (NOTE: studies listed on site include both clinical trials and observational studies)

AUD: alcohol use disorder, CAPS: Clinician-Administered PTSD Scale for DSM-5, MDMA: 3,4-methylenedioxymethamphetamine, N: total number, NR: not reported, OUD: opioid use disorder, PCL-5: Post-traumatic Stress Disorder Checklist for DSM-5, PTSD: Post-traumatic stress disorder, US, United States , VA: United States Department of Veterans Affairs

# D5. Previous Systematic Reviews and Technology Assessments

## Analysis of Phase II MDMA-AP Trials

**Table D12. Phase II Treatment Effect on CAPS Measurement[16,34,90,91]**

| Trial | CAPS* treatment effect size, between-groups Cohen's *d* |
|---|---|
| **MAPP1 & MAPP2 meta-analysis** | SMD (95% CI): 0.80 (0.49, 1.10) |
| **Tedesco et al. 2021** | SMD range (95% CI:) 1.58-3.83 (NR) |
| **Mithoefer et al. 2019** | SMD (95% CI): 0.8 (NR) |
| **Jerome et al. 2020** | SMD (95% CI): 1.58 (1.24, 1.91) |
| **Bahji et al. 2020** | SMD (95% CI): 1.3 (0.66, 1.94) |

CAPS: Clinician-Administered PTSD Scale, CI: confidence interval, SMD: standardized mean difference
*The Phase III MAPP1/2 trials utilized the CAPS-5 measure, while the Phase II trials utilized CAPS-4 measure. Tedesco et al. 2021 converted their CAPS-4 measure data to CAPS-5 data.

Several investigators performed systematic literature reviews and meta-analyses using 5-10 Phase II trials of MDMA-AP for the treatment of PTSD. Tedesco et al. 2021 performed a systematic review of 16 trials and a meta-analysis of 10 Phase II studies. Mithoefer et al. 2019 conducted a pooled analysis and Jerome et al. 2019 conducted an evaluation of six Phase II trials to understand the long-term benefits and safety of MDMA-AP for PTSD. Bahji et al. 2020 performed a systematic review and meta-analysis of five Phase II studies.

In the Tedesco et al. 2021 analysis (N=198), effect sizes of MDMA-AP from pre-treatment to follow-up ranged from 1.58-3.83;[91] further, they determined that participants in the MDMA-AP arm were more likely to demonstrate clinically significant responses compared to participants in the psychotherapy arm, including remission rates which ranged between 56-100%, and improvement on CAPS scores. The sustained effect of MDMA-AP had a large effect size (SMD: 0.81; 95% CI: 0.40, 1.23). Very few studies reported on adverse events, but side effects included diminished appetite, anxiety, headache, jaw tightness, and drug-related depression with suicidal ideation. Limitations included heterogeneity in MDMA dosage, design, number of experimental sessions, follow-up times, and prior or concurrent therapy.

Mithoefer et al. 2019 found in their analysis that active MDMA-AP treatment led to greater reductions in CAPS-IV scores compared to the control group (MMRM MD: -22.0; SE: 5.17; $p<0.001$), with an effect size of 0.8.[16] After two experimental sessions, more participants receiving MDMA-AP (54.2%) no longer met PTSD diagnostic criteria compared to the control group (22.6%), and similarly, MDMA-AP was associated with greater improvements in BDI-II scores. Safety assessments noted psychiatric TEAEs, including anxiety and depressed mood, and MDMA-associated AEs such as fatigue, jaw clenching, and nausea, but they were mostly mild to moderate. There were found to be no unexpected SAEs related to MDMA, with very infrequent and transient instances of suicide ideation.

Similar to the findings above, the long-term assessment from Jerome et al. 2020 reported significant reductions in CAPS-IV scores due to MDMA-AP (LSM: -44.8; SE: 2.82; d: 1.58; 95% CI: 1.24, 1.91)[34]. Additionally, from treatment exit to long-term follow-up (at least 12 months), the number of participants who no longer met PTSD diagnostic criteria increased from 56% to 67%. Among trials that administered the C-SSRS measure, there was a decrease in rate of lifetime positive ideation from baseline to LTFU.

Lastly, in the Bahji et al. 2020 systematic review and meta-analysis, MDMA-AP was associated with high rates of clinical response (RR: 3.47; (%% CI: 1.70, 7.06), remission (RR: 2.63, 95% CI: 1.37, 5.02), and PTSD symptom reduction (SMD: 1.30; 95% CI: 0.66, 1.94).[90] All studies reported no serious adverse events linked to MDMA, with the exception of one trial, that highlighted increased incidence of depressive symptoms and suicide ideation.

## D6. Heterogeneity and Subgroups

**Table D13. MAPP1 Dissociative Subtype Subgroup Results[27]**

| Trial | MAPP1 | | | |
|---|---|---|---|---|
| **Arms** | **MDMA-AP** | **LSNAP** | **MDMA-AP** | **LSNAP** |
| **Subgroup** | **Dissociative subtype** | | **Non-dissociative subtype** | |
| **Timepoint** | **18 Weeks** | | **18 Weeks** | |
| **CAPS-5 total score change from baseline, mean (SD)** | -30.8 (9) | -12.8 (12.8) | -23.6 (11.7) | -14.3 (11.2) |

CAPS-5: Clinician-Administered PTSD Scale for DSM-5, LSNAP: Lykos-specific non-assisted psychotherapy, MDMA-AP: MDMA-assisted psychotherapy

**Table D14. Covariate Results[27,28]**

| Analysis of Covariate Effects on Primary Results (CAPS-5) | | | | |
|---|---|---|---|---|
| | MAPP1 | | MAPP2 | |
| **Variable** | **p-value main effect** | **p-value interaction with Tx** | **p-value main effect** | **p-value interaction with Tx** |
| **Age (continuous)** | 0.2491 | 0.8291 | 0.3184 | 0.9878 |
| **Sex** | 0.6281 | 0.9376 | 0.0109* | 0.6136 |
| **Disabled (yes/no)** | 0.9883 | 0.4444 | 0.47 | 0.9821 |
| **Disease severity** | N/A | N/A | 0.7777 | 0.7473 |
| **COVID-19 (pre/during)** | 0.7701 | 0.9633 | NR | NR |
| **Prior SSRI Usage** | 0.6114 | 0.765 | 0.8217 | 0.0177* |
| **PTSD Duration** | 0.6688 | 0.3795 | 0.8323 | 0.8409 |
| **Dissociative subtype** | 0.035* | 0.0044* | 0.0709 | 0.9668 |
| **BDI≥23** | 0.1003 | 0.6373 | 0.0229* | 0.3298 |
| **ACE≥4** | 0.5198 | 0.5127 | 0.5239 | 0.2065 |

| Analysis of Covariate Effects on Primary Results (CAPS-5) | | | | |
|---|---|---|---|---|
| | MAPP1 | | MAPP2 | |
| **Variable** | **p-value main effect** | **p-value interaction with Tx** | **p-value main effect** | **p-value interaction with Tx** |
| **AUDIT≥5** | 0.4975 | 0.4071 | 0.9235 | 0.1028 |
| **DUDIT≥5** | 0.642 | 0.6441 | 0.4492 | 0.1969 |
| Site ID | NR | NR | 0.4384 | 0.2012 |
| Overnight stay/no stay | NR | NR | 0.7275 | 0.6077 |

ACE: adverse childhood experiences, AUDIT: Alcohol Use Disorders Identification Test, BDI-II: Beck Depression Inventory II, CAPS-5: Clinician-Administered PTSD Scale for DSM-5, DUDIT: Drug Use Disorders Identification Test, ID: identification, NR: not reported, PTSD: Post-traumatic stress disorder, SSRI: selective serotonin reuptake inhibitor, Tx: treatment

*Statistically significant.

# E. Long-Term Cost-Effectiveness: Supplemental Information

## E1. Detailed Methods

**Table E1. Impact Inventory**

| Sector | Type of Impact (Add additional domains, as relevant) | Included in This Analysis from […] Perspective? | | Notes on Sources (if quantified), Likely Magnitude & Impact (if not) |
|---|---|---|---|---|
| | | Health Care Sector | Societal | |
| **Formal Health Care Sector** | | | | |
| **Health Outcomes** | Longevity effects | X | X | |
| | Health-related quality of life effects | X | X | |
| | Adverse events | X | X | |
| **Medical Costs** | Paid by third-party payers | X | X | |
| | Paid by patients out-of-pocket | ☐ | ☐ | |
| | Future related medical costs | ☐ | ☐ | |
| | Future unrelated medical costs | ☐ | ☐ | |
| **Informal Health Care Sector** | | | | |
| **Health-Related Costs** | Patient time costs | NA | ☐ | |
| | Unpaid caregiver-time costs | NA | X | |
| | Transportation costs | NA | ☐ | |
| **Non-Health Care Sector** | | | | |
| **Productivity** | Labor market earnings lost | NA | X | |
| | Cost of unpaid lost productivity due to illness | NA | X | |
| | Cost of uncompensated household production | NA | ☐ | |
| **Consumption** | Future consumption unrelated to health | NA | ☐ | |
| **Social Services** | Cost of social services as part of intervention | NA | ☐ | |
| **Legal/Criminal Justice** | Number of crimes related to intervention | NA | ☐ | |
| | Cost of crimes related to intervention | NA | ☐ | |
| **Education** | Impact of intervention on educational achievement of population | NA | ☐ | |
| **Housing** | Cost of home improvements, remediation | NA | ☐ | |
| **Environment** | Production of toxic waste pollution by intervention | NA | ☐ | |
| **Other** | Other impacts (if relevant) | NA | ☐ | |

NA: not applicable

*Adapted from Sanders et al[92]

## Description of evLY Calculations

The equal value life year (evLY) considers any extension of life at the same "weight" no matter what treatment is being evaluated or what population is being modeled. Below are the stepwise calculations used to calculate the evLY.

1. First, we attribute a utility of 0.851, the age- and sex-adjusted utility of the general population in the US that are considered healthy.[93]
2. We calculate the evLY for each model cycle.
3. Within a model cycle, if using the intervention results in additional life years versus the primary comparator, we multiply the general population utility of 0.851 with the additional life years gained (ΔLY gained) within the cycle.
4. The life years shared between the intervention and the comparator use the conventional utility estimate for those life years within the cycle.
5. The total evLY for a cycle is calculated by summing steps 3 and 4.
6. The evLY for the comparator arm is equivalent to the QALY for each model cycle.
7. The total evLYs are then calculated as the sum of evLYs across all model cycles over the time horizon.

Finally, the evLYs gained is the incremental difference in evLYs between the intervention and the comparator arm.

## Target Population

**Table E2. Base-Case Model Cohort Characteristics**

| | **MDMA-AP (n=53)** | **LSNAP (n=51)** |
|---|---|---|
| Age, mean (sd) | 38.2 (11.0) | 40.0 (9.6) |
| Female, n (%) | 32 (60.4) | 42 (82.4) |
| *Race, n (%)* | | |
| Black or African American | 5 (9.4) | 3 (5.9) |
| White | 37 (69.8) | 32 (62.7) |
| Multiple | 6 (11.3) | 7 (13.7) |
| *Ethnicity, n (%)* | | |
| Hispanic or Latino | 17 (32.1) | 11 (21.6) |
| Dissociative subtype of PTSD, n (%) | 13 (24.5) | 11 (21.6) |
| Positive Lifetime Suicide Ideation, n (%) | 44 (83.0) | 47 (92.2) |
| Baseline CAPS-5 total severity score, mean (sd) | 39.4 (6.6) | 38.7 (6.7) |
| *Baseline PTSD severity, n (%)* | | |

| | MDMA-AP (n=53) | LSNAP (n=51) |
|---|---|---|
| Moderate (CAPS-5 score 28–34) | 13 (24.5) | 15 (29.4) |
| Severe (CAPS-5 score ≥35) | 40 (75.5) | 36 (70.6) |

CAPS-5: Clinician-Administered PTSD Scale for DSM-5, MDMA-AP: MDMA-assisted psychotherapy, n: number, PTSD: Post-traumatic stress disorder, LSNAP: Lykos-specific non-assisted psychotherapy, sd: standard deviation
*Source: Mitchell et al. 2023

# E2. Model Inputs and Assumptions

Key model inputs can be found in Table 4.2. Model inputs not included in the main report are described below.

## Model Inputs

*Non-Drug Costs*

Non-drug costs included health state costs for both arms of the model (Table E3) and separately costs associated with MDMA-AP sessions (Table E4). Resource use identified in claims data included outpatient care, inpatient care, antidepressant and other medication fills, and other mental health care. Davis et al. calculated the overall excess cost of PTSD to be $12,860.[5] However, their study did not provide a breakdown of these costs based on different severity levels of PTSD. Therefore, we assumed this cost was a weighted average of costs across severity categories. To determine these weights, we used the share of each severity level of PTSD within the general population.[62] To estimate the costs associated with each severity level, we relied on findings from Walker et al.,[63] who provided estimates of increased median costs adjusted by severity. For the asymptomatic state, we made the assumption that the cost of being asymptomatic would be half of the cost associated with the mild PTSD state. By utilizing the mean cost reported by Davis et al., along with the prevalence-based weights and the estimated relative costs of different severity categories from Walker et al., we estimated costs associated with each severity level of PTSD.

**Table E3. Health State Cost Severity Inputs**

| Health state | Share of PTSD in the U.S. population | Multiplier for increase in severity | Excess cost | Inflated to 2024 U.S. Dollars for model input |
|---|---|---|---|---|
| Asymptomatic | N/A | 50% | $4,270 | $4,830 |
| Mild | 30.2% | 100% | $8,540 | $9,670 |
| Moderate | 33.1% | 138% | $11,789 | $13,340 |
| Severe | 36.6% | 204% | $17,427 | $19,720 |

N/A: not applicable

**Table E4. Costs Associated with MDMA-AP Sessions**

| Resource use (number) | Description | CPT code | Number of therapists | CPT cost per hour | Cost per session | Total |
|---|---|---|---|---|---|---|
| 0.7 | Pregnancy test for women | NA | NA | NA | $121 | $85 |
| 1 | Psychological testing and evaluation | 96130 | 2 | $120 | $120 | $241 |
| 1 | Psychiatric diagnosis interview examination | 90792 | 2 | $219 | $219 | $438 |
| 3 | 90 min preparation session | 90837 | 2 | $147 | $221 | $1,324 |
| 3 | 8-hour MDMA session | 90837 | 2 | $147 | $1,177 | $7,059 |
| 9 | 90 min integration session | 90837 | 2 | $147 | $221 | $3,971 |

CPT: cognitive processing therapy, MDMA: 3,4-methylenedioxymethamphetamine

*Drug Acquisition Costs*

**Table E5. Drug Cost Inputs**

| Interventions | Administration | Unit | Placeholder Unit Price* |
|---|---|---|---|
| **MDMA-AP** | Oral | 3 sessions | $10,000 |

MDMA-AP: MDMA-assisted psychotherapy

*Placeholder unit price is a projected price from IPD Analytics. Payer & Provider Insights.[65]

*Productivity Costs*

Indirect costs were calculated using the same approach as direct medical costs as described in the non-drug costs section. Indirect cost estimates from Davis et al. included unemployment, productivity loss at work (presenteeism and absenteeism), caregiving, and premature mortality.[5]

**Table E6. Indirect Costs Associated with PTSD**

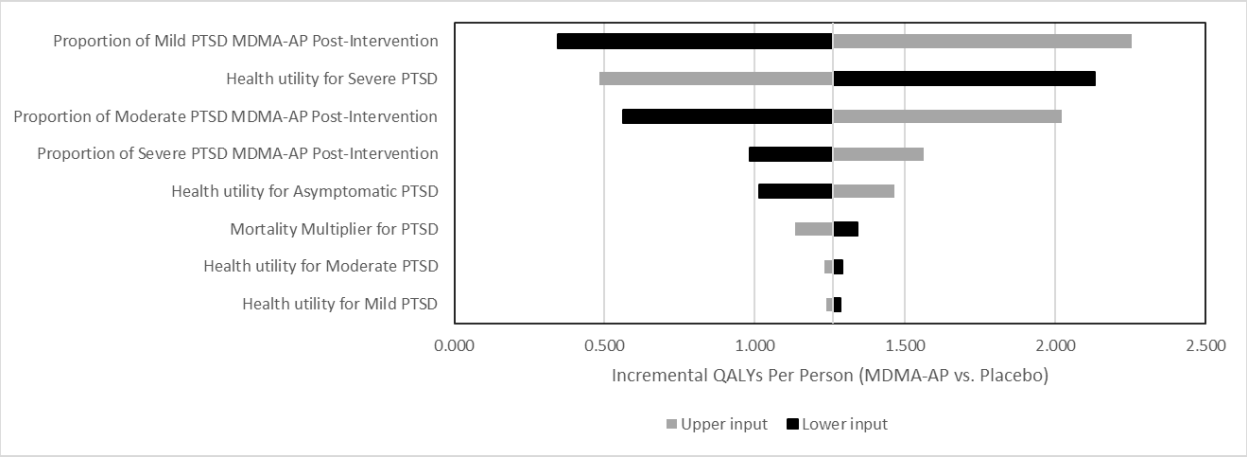
| Severity | Indirect Costs (mean per person per year) |
|---|---|
| Asymptomatic | $3,820 |
| Mild | $7,650 |
| Moderate | $10,560 |
| Severe | $15,600 |

# E3. Results

# E4. Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e., standard errors) or reasonable ranges to evaluate changes in outcomes associated with MDMA-AP versus placebo. Given the exploratory analysis estimated a dominant scenario (less costly, more effective), we instead present separate comparisons in terms of incremental changes in the numerator (e.g., total incremental costs) and incremental changes in the denominator (e.g., incremental QALYs and evLYs).

**Figure E1. Tornado Diagram: MDMA-AP versus Placebo on Incremental QALYs**




MDMA-AP: MDMA-assisted psychotherapy, PTSD: Post-traumatic stress disorder, QALY: quality-adjusted life year

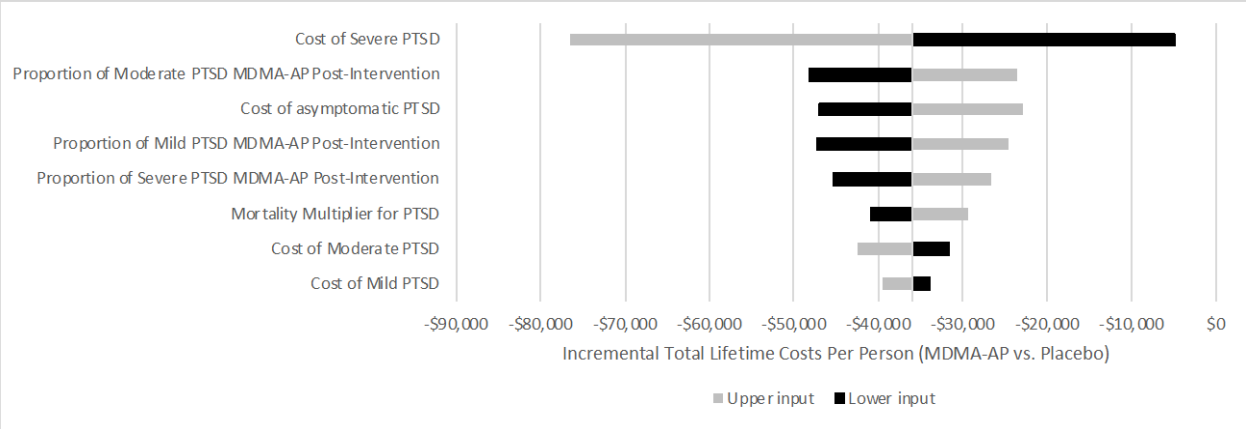
**Table E7. Tornado Diagram Inputs and Results for MDMA-AP versus Placebo on QALYs**

| Category | Lower Incremental QALY | Upper Incremental QALY | Lower Input* | Upper Input* |
|---|---|---|---|---|
| Proportion of Mild PTSD MDMA-AP Post-Intervention | 0.35 | 2.25 | 0.19 | 0.29 |
| Health utility for Severe PTSD | 2.13 | 0.48 | 0.37 | 0.82 |
| Proportion of Moderate PTSD MDMA-AP Post-Intervention | 0.56 | 2.02 | 0.16 | 0.24 |
| Proportion of Severe PTSD MDMA-AP Post-Intervention | 0.98 | 1.56 | 0.08 | 0.12 |
| Health utility for Asymptomatic PTSD | 1.01 | 1.46 | 0.85 | 0.94 |
| Mortality Multiplier for PTSD | 1.34 | 1.13 | 1.00 | 2.50 |
| Health utility for Moderate PTSD | 1.29 | 1.23 | 0.70 | 0.78 |
| Health utility for Mild PTSD | 1.29 | 1.24 | 0.79 | 0.87 |

CE: cost-effectiveness, MDMA-AP: MDMA-assisted psychotherapy, PTSD: Post-traumatic stress disorder, QALY: quality-adjusted life year

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

**Figure E2. Tornado Diagram: MDMA-AP versus Placebo on Incremental Costs**



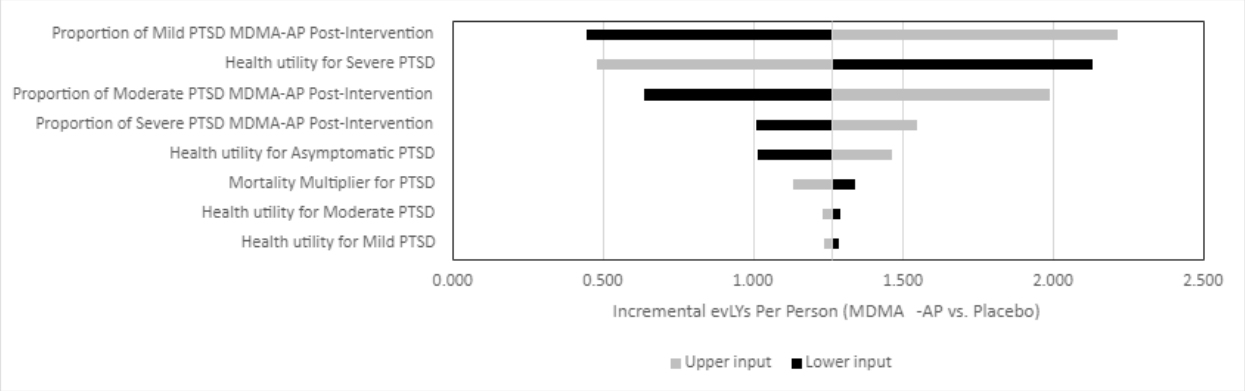

MDMA-AP: MDMA-assisted psychotherapy, PTSD: Post-traumatic stress disorder

**Table E8. Tornado Diagram Inputs and Results on Incremental Costs**

| Category | Lower Incremental Cost | Upper Incremental Cost | Lower Input* | Upper Input* |
|---|---|---|---|---|
| Cost of Severe PTSD | -$4,952 | -$76,483 | $11,271 | $30,492 |
| Proportion of Moderate PTSD MDMA-AP Post-Intervention | -$48,116 | -$23,616 | 0.16 | 0.24 |
| Cost of asymptomatic PTSD | -$47,003 | -$22,864 | $2,760 | $7,468 |
| Proportion of Mild PTSD MDMA-AP Post-Intervention | -$47,208 | -$24,658 | 0.19 | 0.29 |
| Proportion of Severe PTSD MDMA-AP Post-Intervention | -$45,381 | -$26,596 | 0.08 | 0.12 |
| | | | | |
| Mortality Multiplier for PTSD | -$40,884 | -$29,420 | 1.00 | 2.50 |
| Cost of Moderate PTSD | -$31,661 | -$42,426 | $7,624 | $20,627 |
| Cost of Mild PTSD | -$33,921 | -$39,545 | $5,527 | $14,952 |

CE: cost-effectiveness, MDMA-AP: MDMA-assisted psychotherapy, PTSD: post-traumatic stress disorder
*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

**Figure E3. Tornado Diagram: MDMA-AP versus Placebo on evLY**




evLY: equal value of life years, MDMA-AP: MDMA-assisted psychotherapy, PTSD: post-traumatic stress disorder

**Table E9. Tornado Diagram Inputs and Results for MDMA-AP versus Placebo on evLY**

| Category | Lower Incremental evLY | Upper Incremental evLY | Lower Input* | Upper Input* |
|---|---|---|---|---|
| Proportion of Mild PTSD MDMA-AP Post-Intervention | 0.45 | 2.22 | 0.19 | 0.29 |
| Health utility for Severe PTSD | 2.13 | 0.48 | 0.37 | 0.82 |
| Proportion of Moderate PTSD MDMA-AP Post-Intervention | 0.64 | 1.99 | 0.16 | 0.24 |
| Proportion of Severe PTSD MDMA-AP Post-Intervention | 1.01 | 1.55 | 0.08 | 0.12 |
| Health utility for Asymptomatic PTSD | 1.01 | 1.46 | 0.85 | 0.94 |
| Mortality Multiplier for PTSD | 1.34 | 1.13 | 1.00 | 2.50 |
| Health utility for Moderate PTSD | 1.29 | 1.23 | 0.70 | 0.78 |
| Health utility for Mild PTSD | 1.29 | 1.24 | 0.79 | 0.87 |

CE: cost-effectiveness, evLYs: equal-value life year, MDMA-AP: MDMA-assisted psychotherapy, PTSD: post-traumatic stress disorder

*Note lower input may reflect either upper or lower ICER value depending on the direction that the input has on the ICER output.

**Table E10. Results of Probabilistic Sensitivity Analysis for MDMA-AP versus Placebo**

| | MDMA-AP Mean | | Placebo Mean | Incremental |
|---|---|---|---|---|
| **Costs** | $229,000 | | $263,000 | -$34,000 |
| **QALYs** | 17.09 | | 15.87 | 1.22 |
| **evLYs** | 17.09 | 15.87 | 1.22 | |
| **Incremental CE Ratio** | Less Costly, More Effective | | | |

CE: cost-effectiveness, evLYs: equal-value life year, MDMA-AP: MDMA-assisted psychotherapy, QALY: quality-adjusted life year

# E5. Scenario Analyses

## Scenario Analyses

Scenario analysis 1 presents a modified societal perspective using lost productivity estimates available in Table E5. Scenario analysis 2 presents the cost-effectiveness results at a time horizon of 3 years. Scenario analysis 3 presents the cost-effectiveness results at a time horizon of five years.

**Table E11. Results for Scenario Analysis 1**

| Treatment | Exploratory Result | Scenario Analysis 1 | Scenario Analysis 2 | Scenario Analysis 3 |
|---|---|---|---|---|
| **MDMA-AP** | Less costly, more effective | Less costly, more effective | $143,000 per QALY | $66,000 per QALY |

MDMA-AP: MDMA-assisted psychotherapy, QALY: quality-adjusted life year

# E6. Heterogeneity and Subgroups

Given data limitations, we did not estimate subgroup analyses.

# E7. Model Validation

Model validation followed standard practices in the field. We tested all mathematical functions in the model to ensure they were consistent with the report (and supplemental Appendix materials). We also conducted sensitivity analyses with null input values to ensure the model was producing findings consistent with expectations. Further, independent modelers tested the mathematical functions in the model as well as the specific inputs and corresponding outputs.

Model validation was also conducted in terms of comparisons to other model findings. We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments.

## Prior Economic Models

The current model's structure was developed de novo. We identified two prior cost-effectiveness analyses (CEAs) concerning MDMA-AP for PTSD: [57,58] the Marseille 2020 study was constructed based on a pooled analysis of phase II trials, while the Marseille 2022 study specifically focused on a phase III trial, including only severe PTSD patients. In contrast, our evaluation draws upon the most recent latest phase III trial conducted by Mitchell 2023, which includes individuals with moderate-to-severe PTSD.

Participants underwent a protocol that included three 90-minute preparatory psychotherapy sessions, three eight-hour MDMA sessions, and nine 90-minute integrative psychotherapy sessions. Previous studies utilized varying treatment protocols. In Marseille 2020, participants had two to three non-drug therapy sessions followed by two eight-hour psychotherapy sessions with MDMA. In Marseille 2022, the treatment consisted of three non-drug 90-minute therapy sessions with MDMA. Following each experimental session, participants engaged in three 90-minute psychotherapeutic integration sessions.

There was a significant difference in how the comparator arms were defined in these models. Marseille 2020 and Marseille 2022 considered the control arm in the trial inappropriate for

representing the standard of care. Therefore, they assumed the comparator group would be the same as at baseline (as if patients had not received MDMA-AP). They argued that since spontaneous remission of symptoms is mostly limited to the initial years following diagnosis and considering that these patients had been living with PTSD for 14 to 16 years, it was unlikely that any improvement would occur without intervention. In contrast, our study evaluated the effectiveness of the comparator arm as the control arm in randomized trials. Observing improvements in patients on the placebo arm led us to conclude that including such improvements in the comparator arm was a more realistic approach. This discrepancy underscores a substantial divergence in methodological approaches and assumptions regarding the effectiveness of treatments and the selection of comparator groups.

Furthermore, the analytical approaches diverged in several other key aspects. Their model factored in the 'extreme' health state, while our model did not. This decision was based on the absence of data in the underlying trial regarding patients meeting the criteria for the extreme state (CAPS-5 score of 47+). Additionally, their study included a steady progression to more severe PTSD states after five years. We have not found any evidence substantiating continuous progression over the time horizon of our model. Instead, we included the possibility of retreatment within five years based on data showing that patients who achieved remission might need further treatment in this time period.

The updated study by Marseille 2022 incorporated utility values from the phase three trial published by Mitchell in 2021. These utility values were not originally provided in the trial publication but were included in the cost-effectiveness analysis. Our model adopted these estimates and utilized the same values. Nevertheless, we were unable to confirm the methodology used to derive these values.

In our model, mortality rates were not linked to the severity of the condition, unlike the other two studies where authors developed severity-adjusted mortality rates. Our study did not primarily consider varying probabilities linked to changes in the condition but rather emphasized that being asymptomatic lowers the risk of suicide. Given the lack of additional scientific evidence on severity-based mortality risk changes, our model factored in this aspect only.

After running various validation processes, we found a key difference in what influences our models. Our model focuses on health state costs and changes in quality of life, with mortality rates remaining consistent regardless of PTSD severity. In contrast, the prior models place greater emphasis on quality of life improvements and significant variations in mortality rates across different severity states.

# F. Potential Budget Impact: Supplemental Information

Given the "I" rating for the clinical evidence, the potential budget impact of MDMA-AP in this Draft Report should be considered as scenario analyses. These analyses were carried out to provide insight into the potential budgetary impact of MDMA-AP assuming that the results of the MAPP trials are accurate.

## Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential health care costs (including drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with MDMA-AP.

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated.[94,95] The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy. Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (Value Assessment Framework), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending.

For 2023-2024, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $735 million per year for new drugs.