

MDMA-Assisted Therapy for Post-Traumatic Stress Disorder (PTSD)

Draft Background and Scope

November 1, 2023

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.² 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.

PTSD affects approximately 3.5% of United States adults (about 7.7 million) every year.³ It is estimated that one in 11 people will be diagnosed with PTSD in their lifetime.⁴ The overall lifetime PTSD prevalence is 6.1% and it is higher in women than in men (8.0% vs. 4.1%).⁵ The lifetime prevalence of PTSD among US veterans is 6.9%. 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. 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.⁶

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. Commonly used psychotherapies include trauma-focused cognitive-behavioral therapy (CBT), exposure-based therapy, and eye movement desensitization and reprocessing (EMDR) therapy. For many patients, however, the current treatment options have been inadequate.

MDMA-assisted therapy (MDMA-AT) is a novel treatment for PTSD that combines psychotherapy with the administration of 3,4-methylenedioxymethamphetamine (MDMA). MDMA as a street drug is known as “ecstasy” or “molly”. MDMA affects multiple neurotransmitters in the brain, including serotonin, noradrenaline, and dopamine. 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 four to six hours. MDMA-AT was granted a breakthrough therapy designation by the Food and Drug Administration (FDA) in 2017. The Multidisciplinary Association for Psychedelic Studies Public Benefit Corporation (MAPS PBC) is expected to submit a new drug application for MDMA-AT late in 2023.

Stakeholder Input

ICER develops scoping documents with input from diverse stakeholders, including patients and their families, clinicians, researchers, and manufacturers of the agents of focus in this review. At the time of posting of this draft scope, we have received input from MAPS PBC and from clinical experts and have reviewed publicly available testimony from people with PTSD; additional input is being gathered. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

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 illness. Having the diagnosis of PTSD is a key first step into starting the therapy journey as it validates that what patients are going through is real and is not only “in their head”.

While psychotherapy is a cornerstone of treatment for PTSD, we heard about the shortage of available therapists and concerns that the intensive protocol used for MDMA-AT could exacerbate this shortage. We heard from clinical experts that while the results of studies of MDMA-AT have been dramatic, they remain uncertain about issues around what pieces of the therapy are required for success and about generalizability outside of clinical trials. Everyone we spoke with described concerns around functional unblinding of patients receiving MDMA. We also heard concerns about the safety of MDMA-AT, both for the patients receiving it and for the population more broadly if MDMA becomes more widely available.

Report Aim

This project will evaluate the health and economic outcomes of MDMA-AT for PTSD. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's [grey literature policy](#)).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (<https://osf.io/7awvd/>).

Populations

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
- History of prior SSRI use
- Sex
- Gender
- Race/ethnicity

Interventions

Our intervention of interest for this review is MDMA-assisted Therapy (MDMA-AT; MAPS PBC).

Comparators

We intend to compare MDMA added to MAPS PBC-specific manualized psychotherapy to psychotherapy alone as estimated by the placebo arm in clinical trials.

Data permitting, we also intend to compare MDMA-AT to other short-term trauma-focused psychotherapies commonly used for 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 effectiveness and evidence of harm will be derived from studies of any duration.

Settings

All relevant settings will be considered, with a focus on settings in the United States.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Society's goal of reducing health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost effectiveness of 3,4-methylenedioxymethamphetamine-assisted therapy (MDMA-AT) in patients with moderate to severe post-traumatic stress disorder (PTSD). We will compare MDMA-AT to usual care therapy and, data permitting, to other trauma-focused therapies. The model structure will be adapted from previously published models in PTSD.

The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than \$200,000 per QALY, and/or

when the result crosses the threshold of \$100,000-\$150,000 per QALY gained. The target population will consist of patients with moderate to severe PTSD who are eligible for MDMA-AT.

The model will consist of health states for PTSD severity (e.g. asymptomatic, mild, moderate, severe, and extreme PTSD) and death (including PTSD-related mortality and all-cause mortality), and an annual cycle length. We will assess outcomes over a lifetime horizon. In addition, cost-effectiveness will be estimated for shorter time horizons.

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

Health outcomes and costs will be dependent on time spent in each health state and direct medical costs. The health outcomes of each intervention will be evaluated in terms of the change in distribution across PTSD severity states following treatment completion compared with baseline, exacerbations avoided following treatment completion, 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 will be applied to each health state. Utilities will be derived from EQ-5D-DL surveys completed by participants in the published phase three trials that assessed MDMA-AT. The model will include direct medical costs of the intervention and patients with PTSD. Productivity changes and other indirect costs will be included in a separate analysis if available data allow. All costs will be inflated to 2023 US dollars. Results will be 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 clinical outcome avoided or gained). Additionally, data permitting, we will explore potential scenario analyses around subgroups of patients with common comorbidities that impact PTSD severity (e.g. dissociation, depression, and childhood trauma). Costs and outcomes will be discounted at 3% per year.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact, and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found [here](#).

Identification of Low-Value Services

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 additional resources in health care budgets for higher-value innovative services (for more information, see ICER's [Value Assessment Framework](#)).

These services are ones that would not be directly affected by MDMA-AT (e.g., need for ongoing psychotherapy), 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. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

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2. U.S. Department of Veterans Affairs. VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder Version 4.0. Published 2023. Accessed October 16, 2023.
3. Multidisciplinary Association for Psychedelic Studies (MAPS). Inverse: MDMA Steps Closer to FDA Approval as a Drug, but Now it Needs to Leap. <https://maps.org/2016/03/23/inverse-mdma-steps-closer-to-fda-approval-as-a-drug-but-now-it-needs-to-leap-2/>. Published 2016. Accessed March 26, 2021.
4. Nosta J. Treating PTSD at the Anatomic Source: The Amygdala. <https://www.psychologytoday.com/us/blog/the-digital-self/202305/treating-ptsd-at-the-anatomic-source-the-amygdala>. Published 2023. Accessed October 23, 2023.
5. 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.* 2016;51(8):1137-1148.
6. 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.* 2022;83(3).