REPORT AT A GLANCE: **POST-TRAUMATIC STRESS DISORDER**

JUNE 2024

KEY FINDINGS

Intervention	Evidence Rating	Health-Benefit Price Benchmark
MDMA-assisted psychotherapy (MDMA-AP)	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.

"PTSD can be a severe condition affecting nearly all aspects of an individual's life, and many current therapeutic options are insufficient for many people with PTSD. Despite two randomized trials of MDMA-AP, functional unblinding in the trials and additional concerns around trial design and conduct led to ICER concluding that the publicly available evidence is insufficient to assess the balance of benefits and harms. It was encouraging to learn that FDA is investigating such issues, including those brought to light at our Public Meeting."

– ICER's Chief Medical Officer David Rind, MD

THEMES AND RECOMMENDATIONS

- All stakeholders have a responsibility and an important role to play in improving the identification of people living with PTSD across diverse communities and in engaging with them in new ways to ensure that any effective new treatment option is introduced in a way that will help reduce health inequities.
- For any approved therapy using a psychedelic agent, the FDA should establish an expansive Risk Evaluation and Mitigation Strategies (REMS) program with components including tracking of adverse outcomes and which requires rigorous certification of all healthcare providers involved in treatment.
- There are many important evidence gaps in our understanding of the safety and effectiveness of MDMA-AP. Looking forward, clinical researchers and life science companies in this space should attend to research needed to help all stakeholders understand the appropriate place of psychedelic therapies in the care of people living with PTSD

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

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. 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%. PTSD disproportionally affects certain demographics including women, people from different racial and ethnic backgrounds and military veterans. The total economic burden for PTSD in the US surpassed $232.2 billion in 2018, encompassing costs beyond normal health care expenses.

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. MDMA is administered orally in a clinic setting. In 2017, The Food and Drug Administration (FDA) granted MDMA-AP a breakthrough therapy designation and priority review. An FDA advisory committee meeting on June 4, 2024, voted 9-2 that the available data did not show that MDMA-AP is an effective treatment in patients with PTSD, and 10-1 that the benefits of the treatment, along with the FDA’s proposed risk evaluation and mitigation strategy (REMS), did not outweigh its risks. A subsequent regulatory decision from the FDA is expected by August 11, 2024.

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-

Clinical Analyses

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 of the Final Evidence Report 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.

Economic Analyses

LONG-TERM COST EFFECTIVENESS & POTENTIAL BUDGET IMPACT

Given the "I" evidence ratings, the long-term cost-effectiveness and the potential budget impact analysis in the Evidence Report are only exploratory analyses that provide insights into costs, benefits, and short-term affordability 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 or drawing definitive conclusions on potential affordability concerns.

Public Meeting Deliberations

VOTING RESULTS

ICER assessed, and the independent appraisal committee voted on, the evidence of MDMA-AP for adults with a diagnosis of moderate-to-severe PTSD:

- A majority of panelists (14-1) found that current evidence is **not adequate** to demonstrate a net health benefit for MDMA-AP when compared to not treating with MDMA-AP.

- All panelists (15-0) found that current evidence is **not adequate** to demonstrate a net health benefit for MDMA-AP when compared to short-term traumas-focused psychotherapies.

Panel members also weighed potential benefits and disadvantages beyond the direct health effects and special ethical priorities. Voting highlighted the following as particularly important for payers and other policymakers to note:

- There is substantial unmet need despite currently available treatments.

- This condition is of substantial relevance for people from a racial/ethnic group that have not been equitably served by the healthcare system.

Consistent with ICER's process, because there is no firm estimate yet of a potential launch price for the treatment, the panel did not take a vote on the treatment's long-term value for money.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent, non-profit research institute that conducts evidence-based reviews of health care interventions, including prescription drugs, other treatments, and diagnostic tests. In collaboration with patients, clinical experts, and other key stakeholders, ICER analyzes the available evidence on the benefits and risks of these interventions to measure their value and suggest fair prices. ICER also regularly reports on the barriers to care for patients and recommends solutions to ensure fair access to prescription drugs. For more information about ICER, please visit www.icer.org.