Editorial

Response to ICER and the FDA Advisory Committee on MDMA Approval

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On May 14th, 2024, the Institute for Clinical and Economic Review (ICER) published an Evidence Report "Midomafetamine-Assisted Psychotherapy for Post-Traumatic Stress Disorder [1]" which stated that "the current publicly-available evidence for MDMA-AP is insufficient." The ICER MDMA report was one of the main pieces of evidence presented at a subsequent Federal Drug Administration (FDA) Advisory Committee meeting on June 4th, 2024. The Advisory Committee concluded 9-2 that the MAPP-1 and MAPP-2 trials did not prove the efficacy of MDMA-AP and 10-1 that the risks outweighed the benefits of MDMA-AP [2]. Both these votes are non-binding, but the FDA will take them into consideration at MDMA-AP's priority review session on August 11th, 2024. After the news broke, supporters of psychedelic medicine were rightfully disheartened, but before descending into despair, a critical analysis of the data that led the advisory committee to reach the conclusions it did must be undertaken.

All proponents of psychedelic medicine should read and analyze the ICER report in its entirety. Per ICER, it "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 [1]."

Additionally, ICER asks three fundamental questions of any intervention [3]:

- Based on the evidence, how much better is a new treatment at extending or improving patients' lives?
- What would a fair price be, based on the clinical evidence as well as patients' perspectives about the outcomes that are most important to them?
- And how can patients, clinical experts, and insurers translate the evidence into insurance coverage that ensures the best patient outcomes?

Before diving into the actual report, it is essential to recognize these motivations and intentions as they form the foundation for the report's structure and analysis. Comparative analysis of a novel intervention against the current standard of care is a worthy endeavor and, when done well, is an invaluable resource for the entire healthcare industry. However, attempting to determine a "fair price" undoubtedly slants the discussion away from the efficacy of the intervention and toward that of public policy. The FDA rightly does not concern itself with whether a drug will priced at a "fair price" but rather the trade-off between the risks and benefits of the proposed intervention based on the clinical data [4]. The price of a drug, whether deemed "fair" by those at ICER or elsewhere, is a decision that is best left to the market to determine rather than central planners who believe they can account for most or all of the value of an item in their models.

Turning now to the ICER report, the first thing of note is that no Psychiatrist or Psychologist was involved as an ICER Staff or Consultant nor in the modeling group. Being mindful of the appeal to authority

fallacy, having both a Psychiatrist and a Psychologist in the authorship would have added significant credibility, especially because MDMA is a novel psychiatric drug and MDMA-AP is a novel psychotherapy approach. The lack of familiarity with psychiatric and psychological interventions and the shortcomings of psychiatric clinical trials was highly evident when reading the report. It should be noted that one of the three expert reviewers was a Psychiatrist but disclosed that he is the inventor of a competing augmented reality intervention for PTSD management. No psychologists were reported as expert reviewers.

The following were the primary concerns identified in the ICER report regarding MDMA-AP:

- Ethical Concerns
- Trial Design and Conduct
- Safety Concerns
- Frequency of Benefits and Harms

Examination of these concerns in greater detail, from the most valid to the least valid, will follow.

Regarding ethical concerns this was the most concerning aspect of the report, specifically the misconduct and abuse of a clinical trial subject in 2015. The two therapists assigned to the patient deviated from the protocol during the clinical trial and allegedly engaged in a physical relationship with the patient after the trial was over. To their credit, the Multidisciplinary Association of Psychedelic Studies (MAPS), which sponsored the trials, reported this to Health Canada, the FDA, and IRBs and banned the therapist from all future trials. They also made significant changes to their policies, training practices, and reporting standards. Any time a patient is harmed by a practitioner, the processes and standards that allowed this to happen should be thoroughly evaluated, and substantial changes should be made to reduce the likelihood of an event like this happening again. However, before jumping to the conclusion that a breakthrough therapy should not approved, it is prudent to place this boundary violation in the context of the broader Psychotherapeutic enterprise. The MAPP-1 and MAPP-2 Trials collectively enrolled 194 total patients, only the patient above experienced a boundary violation for a rate of 0.5%. This rate should be compared to the rate of boundary violations within the general psychotherapy environment. A 2007 article [5] found the following: "Most research has involved self-report surveys of mental health professionals and has demonstrated a prevalence of 0.9–12% with a median figure of about 6%. Generally, male therapists are more involved in these violations than are female therapists with a ratio of about 3:1."

The ICER report also raised other ethical concerns, including research participants feeling pressured or encouraged to suppress adverse outcomes and overreport the positive attributes of MDMA-AP. However, while ICER claims they had firsthand and secondhand reports, they do not offer any other corroborating or substantive information. When pressed on this issue, ICER has responded by saying their refusal to make the public the source of the information "does somewhat decrease the transparency we would typically want in an ICER report" and that "We cannot be certain that these reports were accurate [6]." Taking all of this in totality, it is difficult if not impossible, to determine what is hearsay and what could be a credible piece of information. The FDA, through its standard monitoring programs, should be able to identify and thoroughly investigate these issues, but until such time that this information is validated, it should not be used as a rationale to prevent the approval of MDMA-AP. Lykos should have every right to address the criticism as well as note any particular credibility issues that any of the anonymous whistleblowers

might have, and the FDA can then weigh those arguments and make an informed decision.

Moving on to Trial Design and Conduct concerns, the ICER report takes particular aim at the use of the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) [7]. Again, this highlights the paucity of psychiatric and psychological involvement in the write-up of this report. As things currently stand, the CAPS-5 is the most well-validated scale to use for PTSD symptoms and is considered the gold standard for clinical trials in PTSD. The ICER report expressed the following concern: "We heard from multiple people that the CAPS-5 measures of improvement failed to capture participants overall response to MDMA-AP. ... 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." What ICER appears to be missing is that most patients can and do have multiple traumatic events, but in both research and therapeutic settings, the researcher must specify their aim before they begin the intervention or treatment. Therefore, only one index trauma or one specific series of traumatic events may be selected for research purposes or targeted in the initial therapeutic sessions. Commonly, patients will experience an initial worsening of index trauma symptoms early on in trauma therapy as they voluntarily confront past events. This is an extremely common phenomenon across all exposure therapies, and patients are often counseled that this will be the case. Trauma therapy can involve going through the worst moments of a patient's life with a fine-tooth comb, and reliving those experiences may be nearly as difficult as living through the event itself.

Additionally, as a patient progresses through the index trauma, symptoms specific to the index trauma, such as re-experiencing symptoms or avoidant behaviors, will improve. However, if other non-index-related traumas are present, these may occupy or contribute more to the trauma symptom burden. This likely occurs as a result of greater insight and the patient realizing just how much the traumatic events have impacted their lives.

It should be noted that this is not a drawback to the therapy but a necessary step in the healing process for the patient. Failure to adequately process trauma results in continued and often compounded symptom burden. As several of the therapists involved in the MAPP-1 and MAPP-2 trials wrote in response to these specific ICER complaints, "the accusation that it undermines the validity of the Phase 3 data supporting the use of MDMA-AP for PTSD could be leveled against any other clinical study using this outcome measure—which again, though flawed, is the gold-standard in the field of PTSD clinical research. We do not dispute that some participants may have experienced worsening psychological distress; however, secondary outcome measures (e.g., the Sheehan Disability Scale, the Beck Depression Inventory) and adverse event reporting (e.g., exacerbation of anxiety, suicidality, insomnia) would have captured that distress, even if it was not associated with the index trauma identified on the CAPS-5. Results from these secondary outcome measures did not show statistically significant worsening in the MDMA group; on the contrary, those results tended to favor active treatment with MDMA [8]."

Another primary concern raised by the ICER report surrounded the concept of functional unblinding, which means that patients and clinical trial staff could determine whether a patient was receiving MDMA or a placebo simply based on the effects of the drug. The adverse effects of the medications themselves mainly drive this. Furthermore, functional unblinding is almost

to be expected during a psychedelic clinical trial that uses an active drug vs. a placebo. While placebo-controlled randomized controlled trials are an excellent way to determine if specific interventions are, in fact, effective, they are not perfect for all therapeutic interventions, and psychedelic trials will likely need alternative trial designs to access efficacy [9], especially within psychopharmacologic trials where placebo responses are noted to be exceptionally high and variable. A recent systematic review and meta-analysis published in May 2024 [10] highlighted the potential impact that placebos could have across several psychiatric conditions.

It should be noted that these trials did not include non-placebo arms making it difficult to fully rule out regression to the mean or natural disease course. However, it fits into the more extensive discussion about placebo response to psychiatric medications. A separate May 2024 article [11] noted the following: "The third and perhaps most significant factor driving trial failures in psychiatry is the high and growing rates of placebo response. One systematic review of 252 antidepressant trials found a consistent placebo response rate today that is now between 35% and 40%." Additionally, there is no way to blind psychological interventions as both the patient and the clinician are aware of the intervention. Understanding these constraints on psychotherapy research and the placebo issues raises the question of why ICER and others on the advisory committee felt this was such a consequential piece of information. Combining a psychedelic drug with a psychotherapy protocol makes it almost impossible not to have at least some degree of functional unblinding.

Furthermore, the FDA was and is aware of this issue and still chose to greenlight the phase 3 trials. This is based on precedent for other psychopharmacology interventions, including clozapine [12] and esketamine [13]. Esketamine, being the most recently approved and a psychedelic-like agent in its own right, provided a road map that MDMA-AP followed by utilizing independent third-party raters. Independent raters worked exceptionally well for the eksetamine trials "[R]emote raters practically duplicated site-based findings in MADRS score reductions, yielding a 92.9% predictive value for matching treatment responses and remission rates [13]."

The third primary concern identified by the ICER report surrounded the adverse effects of MDMA and the long-term consequences of MDMA, specifically on the cardiovascular system. The only long-term data on MDMA's cardiovascular effects comes from observational studies or murine models. The observational data is predominately from patients who were abusing MDMA or what they presumed to be MDMA. Recreational MDMA cannot and should not be used as an appropriate comparator to pharmaceutical grade MDMA with a predetermined dose-response curve with only 2-3 dosages being given about one month apart. Given its stimulant-like qualities, a suitable comparator for MDMA may be stimulant medications used in the treatment of ADHD. While these medications are typically taken daily or at least multiple times per week, they still do show the potential for longer-term cardiovascular disease. A recent article from November 2023 found the following: "[L]ong-term exposure to ADHD medications was associated with an increased risk of CVDs, especially hypertension and arterial disease [14]." While there may be other cardiovascular adverse effects such as valvular disease, arrhythmia, or heart failure, these will likely not appear in the short term of a clinical trial but rather will require diligent monitoring over the long term. The lack of long-term data on these issues,

however, should not serve as sufficient rationale to preclude approval. The Risk Evaluation and Mitigation Strategy programs can require advanced cardiovascular screenings and monitoring prior to and during MDMA-AP treatment, and similar to Clozapine, long-term monitoring interventions could be instituted as well. However, like stimulant medications, a risk-benefit discussion between a physician and a patient should occur, and shared decision-making should follow.

Finally, regarding the frequency of benefits and harm concerns, the ICER reports make nonspecific and veiled comments stating:

> "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 [1].”

PTSD is a highly debilitating condition where up to 50% of patients do not adequately respond (a 50% reduction in symptom burden) to psychotherapeutic interventions [15], and only 20-30% of patients on psychopharmacologic agents achieve complete remission of symptoms [16]. Couple that with the necessity to take the medication every day and have continual exposure to antidepressants and their accompanying side effects and then compare that MDMA-AP, which reported a 46.2% rate (loss of PTSD diagnosis and CAPS-5 score <12) roughly 15-25% better than the standard of care antidepressant therapies and in total 71.2% of patients no longer met diagnostic criteria for PTSD. The contrast is incredibly striking, given that these results were after 2 or 3 MDMA dosing sessions and approximately 15 psychotherapy sessions.

Even if a regression to the mean of the effect sizes reported in the MAPP-1 and MAPP-2 trials is allowed, MDMA-AP still shows significant benefits over the current standard of care. As Dr. Thomas Sowell said, "There are no solutions, there are only trade-offs." This idea is at the crux of psychedelic research. Outside of the regrettable and unacceptable boundary violations that occurred with a single patient in the trial and possible but as of yet unsubstantiated concerns regarding biased reporting and influencing of study participants, there is no perfect or ideal form of a randomized controlled trial for the purposes of investigating the efficacy of a psychedelic compound. While other researchers have tried to utilize lower dosages of a psychedelic substance as a control instead of an inactive placebo to combat functional unblinding, this does not guarantee successful blinding and also introduces the possibility that even a microdose of a substance can exert a therapeutic effect. Finally, concerning safety, there exists a continuum from acceptable side effects to life-threatening ones. All MDMA-AP trials have shown that when pharmaceutically manufactured MDMA is taken in a therapeutic environment, it has transient side effects that are generally acceptable. Long-term effects must be assessed in a post-marketing environment, and extrapolations from recreational MDMA studies are confounded by a lack of quality

control for the medications and the likely use of supra-therapeutic dosages. Recreational MDMA observational studies can point long term monitoring in a general direction in regard to the area of focus in the post-marketing analyses.

Additionally, the risk of MDMA must be appropriately weighed against the risks of continued antidepressant, antipsychotic, anxiolytic, and other pharmacotherapy used in the treatment of PTSD. Daily usage of multiple medications, often for years in the case of severe refractory cases, results in a significant burden to patients and raises health care costs. If a medication can he most severely ill with 2 or 3 administrations and decrease or eliminate the need to take medications daily and indefinitely with limited acute and intermediate side effects, the choice for most patients and providers is evident. Hopefully, the FDA will not lose the metaphorical forest for the trees as they attempt to parse out the data on MDMA-AP. While there are valid concerns, especially about boundary violations, the anonymously reported hearsay and vague indirect critiques leveled against the trial either must be substantiated or set aside. Taking anonymously sourced claims or assuming facts not in evidence is a fool's errand, but going a step further and using that information to discredit multiple studies showing significant benefits for patients with PTSD above and beyond those of the current standard of care would truly prove George Orwell correct when he said: "Some ideas are so stupid that only intellectuals believe them."

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