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New York Law Journal

What's Next for MDMA?

Amid clinicians, researchers and congressional lawmakers urging the FDA to approve MDMA for PTSD despite a negative vote by the FDA's advisory committee, the authors ask: What's next for MDMA?

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August 8, 2024

When making regulatory decisions about a drug, the U.S. Food and Drug Administration (FDA) often relies on advisory committees to provide independent advice. (U.S. Food & Drug Admin., *Learn About FDA Advisory Committees* (Apr. 23, 2024), https://www.fda.gov/patients/learn-about-fda-advisory-committees).

Advisory committee members typically include scientific experts as well as members of the public, representatives of industry and consumers/patients. The votes and recommendations of the committee are nonbinding, and the FDA is responsible for making the final decision regarding the drug.

On June 4, 2024, the FDA held a Psychopharmacologic Drugs Advisory Committee meeting (the Advisory Committee Meeting) to discuss the New Drug Application (NDA) submitted by Lykos Therapeutics for midomafetamine (MDMA) for the treatment of post-traumatic stress disorder (PTSD). (U.S. Food & Drug Admin., *Meeting of the Psychopharmacologic Drugs Advisory Committee Meeting Announcement* (June 4, 2024), https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-meeting-time-and-public-participation-information-june-4-2024-meeting-psychopharmacologic).

Credit: Angelica Corneliussen/Adobe Stock

The nine-hour meeting included briefings from the FDA and the drug sponsor, Lykos Therapeutics, as well as public comments. It concluded with a negative vote by the advisory committee members: a 9-2 vote that the available findings did not show MDMA to be effective for PTSD and a 10-1 vote that the potential benefits of MDMA do not outweigh the potential risks.

Key Issues Addressed

The FDA's Advisory Committee Meeting addressed the following key issues:

• Functional Unblinding and Expectation Bias: Two significant issues discussed were the impacts of functional unblinding — where participants are able to recognize whether they received the medication or placebo — and expectation bias in the data. These factors can potentially influence the study outcomes and are common concerns in studies involving psychoactive medications.

•Durability of Effect: The Committee raised concerns about the durability of the therapeutic effects of MDMA and the interpretability of follow-up evaluations. This involves questioning whether the benefits of the drug are sustained over time.

• Safety Profile: There was limited information on the cardiac safety profile and limited clinical laboratory data, such as liver function testing. The Committee also noted the lack of data on effects such as euphoria or elevated mood, which could inform abuse potential.

•Therapist Misconduct: Allegations of therapist misconduct were highlighted, including one instance in a phase 2 trial and a public allegation in a phase 3 trial. These issues underscore the risks involved in the therapeutic setting.

• Public Comments: During the public comment period, some PTSD patients highlighted the crucial need for effective PTSD treatments and described their healing experience with MDMA-assisted therapy.

• Influencing Patient Reporting: A report by the nonprofit group, Institute for Clinical and Economic Review (ICER), alleged that "[c]oncerns 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." (Reem A. Mustafa et al., *MDMA-Assisted Psychotherapy for Post-Traumatic Stress Disorder: Effectiveness and Value; Evidence Report. Institute for Clinical and Economic Review*, at 2 (May 14, 2024), https://icer.org/wp-content/uploads/2023/11/PTSD_Revised-Report_For-Publication_05142024.pdf). During the Advisory Committee Meeting, the FDA noted that they are investigating the allegations in the ICER report, but could not share details due to the ongoing nature of their investigations. (Advisory Committee Meeting, *supra*).

The negative vote by the Advisory Committee appears to have surprised many in the psychedelic space. As discussed below, following the Advisory Committee Meeting, additional pleas for FDA approval of the medication emerged, including a consensus statement issued by 23 prominent researchers and clinicians, and a bipartisan effort by congressional lawmakers. (Consensus Statement, *Experts Endorse MDMA-assisted Therapy for PTSD Re: Lykos Therapeutics NDA #215455, Midomafetamine (MDMA) for use in the treatment of PTSD* (July 7, 2024), https://www.scientiststatementonptsd.com/).

Since advisory committee votes and recommendations are non-binding, it is unclear whether the FDA will ultimately grant approval of this medication by the Prescription Drug User Fee Act deadline of Aug. 11, 2024.

Two publications by Daval and colleagues, which evaluated the relationships between advisory committee votes and FDA regulatory actions, may offer insight to those wanting to make a prediction about the likelihood of FDA approval of MDMA. (C. Joseph Ross Daval et al., *Association of Advisory Committee Votes With US Food and Drug Administration Decision-Making on Prescription Drugs, 2010-2021*, JAMA Health Forum, 2023 July;4(7):e231718 and C. Joseph Ross Daval et al., *Unwanted Advice? Frequency, Characteristics, And Outcomes Of*

Negative Advisory Committee Votes For FDA-Approved Drugs, Health Aff (Millwood), 2022 May; 41(5):713-721).

Expert Consensus Statement

On July 7, 2024, 23 researchers and clinicians published a consensus statement online urging FDA approval of MDMA and discussed their rationale based on urgency, efficacy and safety. (Consensus Statement, *supra*). According to the authors, the statement represents a professional assessment of published phase 3 clinical trial data, the Institute for Clinical and Economic Review's report identifying issues with the clinical trial data, Lykos Therapeutics' brief for the Advisory Committee Meeting, and the Committee's deliberations. Some of the members disclosed receiving support/funding from Lykos and/or having worked on Lykos-sponsored projects.

Urgency. The consensus statement highlighted the existing mental health crisis and the urgent need for more effective PTSD therapy. It noted that 13 million Americans suffer from PTSD, current treatments for PTSD are unsuccessful for reaching remission in over half of treated patients, and the suicide rate for U.S. military veterans is over 17 suicides per day. (*Id.*).

Efficacy. The consensus statement stated that the phase 3 clinical trials "have shown substantial evidence of efficacy" and that the "consistency of results" across study sites and patient subgroups "provides additional confidence in the reliability of the primary finding." (*Id*. at 1-2).

Regarding the concerns about functional unblinding and expectancy effects in the phase 3 trials, the authors noted that these are "common issues" when studying psychoactive medications and that they believed "these concerns do not rise to a level that would call the main clinical trial findings into question." (*Id*. at 2).

Safety. MDMA-assisted therapy has been shown to be "generally safe and well tolerated" in clinical trials, with "no serious adverse events indicative of cardiovascular or hepatic risk in the phase 3 trials." (*Id*. at 2-3). The authors also noted the relatively short course of drug exposure comprising only three MDMA treatment sessions and suggested that any remaining safety concerns can be addressed through safety surveillance and post-approval studies.

Regarding psychotherapy, the authors acknowledged that MDMA "can increase" the risks present with psychotherapy and noted "one instance of harmful therapist misconduct in a phase 2 trial of MDMA and a public allegation of harmful therapist misconduct in a phase 3 trial." (*Id*. at 3). They explained that after approval, the delivery of psychotherapy "will likely be governed by a combination of state licensing boards, payers, and professional associations." (*Id*. at 3).

Consensus Statement Conclusions

The consensus statement advocated for FDA approval of MDMA for PTSD alongside appropriate safeguard and post-approval monitoring. The authors concluded:

"While we agree with many of the issues raised by the FDA advisory committee, given the data we have reviewed and the urgency of the need, our assessment is that the benefits of midomafetamine-assisted therapy outweigh the risks and that midomafetamine is now approvable. The use of midomafetamine-assisted therapy should include a Risk Evaluation and Mitigation Strategy (REMS) that can be adjusted as real-world safety and efficacy data emerge." (*Id*. at 3).

Press Conference

On July 10, 2024, four congressional lawmakers, Representatives Lou Correa (D-CA), Jack Bergman (R-MI), Morgan Luttrell (R-TX) and Jimmy Panetta (D-CA) held a press conference urging FDA approval of MDMA and participated in a Heroic Hearts Project ceremony where 150,000 military dog tags were displayed on the U.S. Capitol grounds to represent the number of

veterans who died from suicide since 9/11. (Heroic Hearts Project, *Bipartisan Congressional Press Conference on New Therapies for Veteran PTSD/ Suicide*, YouTube (July 10, 2024), https://www.youtube.com/watch?v=yS8ODLJT7FI&t=24s).).

Rep. Bergman, a three-star general marine veteran, expressed his disappointment and frustration with the advisory committee's negative vote on MDMA-assisted therapy for PTSD. Rep. Correa, cofounder along with Rep. Bergman of the Congressional Psychedelics Advancing Therapy Caucus, remarked that "[w]e owe it to our veterans to give them the medicines that they need" and gave the message: "FDA do your job[;] take care of our veterans[;] save veterans from suicide." (*Id*.). Rep. Luttrell, a former Navy SEAL, called for FDA to "recognize . . . the science." (*Id*.). Rep. Jimmy Panetta (D-CA), also a veteran who served in Afghanistan, highlighted the "disturbing dilemma" of veteran suicide and promoted FDA approval of MDMA treatment. (*Id*.).

Lykos Therapeutics' Planned Additional Oversight

On Aug. 1, 2024, Lykos announced it is taking additional steps to ensure oversight for MDMA-assisted therapy, if it gains FDA approval. (PR Newswire, *Lykos Therapeutics Announces New Initiatives and Measures for Additional Oversight for Midomafetamine-Assisted Therapy, if FDA Approved* (Aug. 1, 2024), https://www.prnewswire.com/news-releases/lykos-therapeutics-announces-new-initiatives-and-measures-for-additional-oversight-for-midomafetamine-assisted-therapy-if-fda-approved-302211749.html#:~:text=SAN%20JOSE%2C%20Calif.%2C%20Aug,%2Dassisted%20therapy%22)%20for%20the). This includes instituting an independent advisory board consisting of "external experts in corporate and medical ethics, innovation, psychiatry, and military and veteran health," to inform the medication's launch including therapy training, ethics and health care integration. (*Id.*). In addition, upon initial launch, Lykos plans to work with only select centers with strong levels of oversight and collaborate with other institutions on therapy training.

Historical Perspective

Daval and colleagues evaluated the relationship between FDA advisory committee votes from 298 human drug advisory committee meetings from 2010-2021 and FDA regulatory actions. (Daval 2023, *supra*). The authors reported that as of November 30, 2022, the FDA had approved 142 of the 147 drugs (97%) that had received a positive vote by the advisory committees and had declined to approve 40 of the 60 drugs (67%) that had received a negative vote. In other words, the FDA almost always took regulatory action consistent with the advisory committees when they voted for approval, but diverged from the advisory committees' votes one-third of the time when the advisory committees voted against approval.

The time between advisory committee votes and FDA approvals varied: a median of 74 days for drugs with positive votes compared to 700 days for those with negative votes. The authors discussed that not all instances of FDA drug approval following a negative vote by the advisory committee were necessarily representative of the FDA simply overruling the advisory committee. They explained that many of the drug approvals happened years after the advisory committee's vote, when new evidence may have emerged in support of approval.

In an accompanying commentary to the study, Genevieve Kanter postulates that the findings from the Daval 2023 study suggest that perhaps the FDA is not necessarily asking the advisory committees "Should we approve this drug?," but is instead asking "What is preventing this drug from being approved right now?" (Genevieve P. Kanter, *The Real Question the FDA Is Asking Its Advisory Committees*, JAMA Health Forum, 2023 July;4(7):e231234).

In another publication, Daval and colleagues reported that, between 2010-2021, the FDA approved a drug that received negative votes by an advisory committee about once a year. (Daval 2022, *supra*). For the 10 approved drugs that had originally received a negative vote, the authors reported that advisory committee concerns included insufficient data for eight of the 10 drugs, safety and efficacy concerns in six of the 10 drugs, and surrogacy endpoint not translating to clinical effect in three of the 10 drugs.

The authors also included a breakdown of yes and no votes for the 10 approved drugs that had originally received a negative vote. No clear pattern is apparent, with at least four of the 10 drugs showing a similar pattern to that of the 9-2 and 10-1 negative votes MDMA received. For instance, aducanumab received zero yes, 10 no, and one uncertain votes and was approved in 2021; flibanserin received zero yes and 11 no votes and was approved in 2015; olaparib received two yes and 11 no votes and was approved in 2014; and florbetapir received three yes votes and 13 no votes and was approved in 2012.

Going against the advisory committee votes is not without risk of controversy, as illustrated by the FDA's approval of the Alzheimer's medication aducanumab. Although the drug received zero yes, 10 no, and one uncertain votes regarding convincing evidence of efficacy, the FDA approved the drug based on factors not discussed during the advisory committee meeting and was criticized by some in the medical community for this action. (*Id*.).

Predictions

Many stakeholders in the psychedelic space, including drug developers, researchers, clinicians, health care organizations and patients, are eagerly awaiting FDA's decision, expected by Aug. 11, 2024. The publications discussed above by Daval and colleagues illustrate that FDA approval following a near unanimous negative vote by an advisory committee is not unprecedented, leaving open the possibility for MDMA approval.

Even if the FDA denies approval, it may request additional research, potentially leaving the door open for future approval. The FDA may also potentially choose to institute strict safeguard and post-approval monitoring as suggested by the consensus statement.

How and what the FDA decides will undoubtedly hold lessons for other psychedelic medications in development. In addition, the discussions held during the advisory committee meeting and lessons learned from Lykos Therapeutics' drug development process will help shape the future of medicinal psychedelic research.

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