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May 23, 2024

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Psychopharmacologic Drugs Advisory Committee
U.S. Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: [Docket No. FDA-2024-N-1938] Psychopharmacologic Drugs Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments--Midomafetamine Capsules

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Dear Chairman Rajesh Narendran,

On behalf of the American Psychiatric Association (APA), the national medical specialty society representing over 38,900 psychiatric physicians and their patients, we thank you for the opportunity to respond to the request for comments regarding Midomafetamine Capsules (MDMA) from the Psychopharmacologic Drugs Advisory Committee. APA supports research and therapeutic discovery into psychedelic agents provided they are conducted with the same scientific integrity and regulatory standards applied to other emerging therapies in medicine.

Promising preliminary research involving psychedelics for the treatment of serious and disabling conditions such as posttraumatic stress disorder (PTSD) has stimulated growing interest in the therapeutic potential of these agents. APA is well aware of the unmet need for treatment of patients with PTSD as evidenced-based therapies and the fact that the U.S. Food and Drug Administration (FDA) approved medications for PTSD do not result in remission from this disorder in the majority of patients. However, APA cautions that decisions should not be made based on headlines, but rather with unbiased evidence that meets the scientific integrity and regulatory standards that patients and medical providers expect. FDA approval based on this important principle is imperative in the consideration of removing MDMA as a Schedule I controlled substance, and its impact on future uses.

Furthermore, all decisions must be made in the narrow scope of the research available. Conclusions that can be drawn from studies of recreational use are limited by many confounds. This especially limits the extent to which evidence related to recreational use can be extrapolated to therapeutic use.¹ There is also a need for more data on long-term follow-up among participants receiving MDMA, as well as use among diverse groups of patients.

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¹ In Press with the American Journal of Psychiatry
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Current State of Research

The scientifically and ethically sound design of psychedelic research is complicated by several unique features of psychedelic experience. MDMA is difficult to blind (for both researchers and participants). Because the effects of MDMA are acute, intense, and idiosyncratic, it can be relatively easy for participants and researchers to recognize whether they have received the placebo or active drug, as shown by the available data from the Phase III trial article published in *Nature Medicine* (75% participants in the placebo with therapy group were certain or thought they received placebo).^{2,3} “Functional unblinding” may have been more likely in the Phase III trials reported as approximately 40% of participants had prior experience with MDMA. In many pharmacological trials, individuals with prior exposure are excluded from participation. The advisory committee must consider whether the current regulatory framework for clinical trials for psychedelics is ensuring the highest quality results or if it is creating bias in expectancy effects.

Expectancy effects among research participants can influence outcomes. Patients entering psychedelic clinical trials have likely been non-responders to conventional treatment modalities and read the headlines touting psychedelic therapies, creating high expectations for dramatic symptom relief. The cultural enthusiasm about psychedelics thereby risks causing a self-fulfilling cycle, wherein high expectations lead to artificially inflated results.⁴ Similarly, expectancy effects may influence study therapists.

In carefully controlled research settings, the safety profiles of MDMA and psilocybin have been encouraging. However, the FDA needs to be mindful about generalizing results of clinical trials to populations that have traditionally been excluded from research. To enhance diversity and equity, more work needs to be done to engage marginalized populations in psychedelic research.

The clinical trials incorporated therapy with MDMA as part of the treatment. APA cautions that the comprehensiveness of psychedelic therapist training programs can impact the outcome of clinical trials. In certain settings, the psychotherapy training is intensive, often including over 100 hours of specialized didactic and clinical experiences.⁵ In addition, the Phase III MDMA-assisted therapy trials before the FDA involved approximately 84 hours of psychotherapist time, considerably greater than the time allocated in most randomized controlled trials of other better studied trauma-focused (TF) therapies such as TF-Cognitive Behavior Therapy, Prolonged Exposure or Eye Movement Desensitization and Reprocessing (EMDR). As individuals under the influence of MDMA are thought to be in a more vulnerable, suggestible state, the study design has involved a male and female co-therapy model for safety. If psychedelics are made available outside of research settings, there is a risk that the quality of psychotherapeutic support will fall as incentives to cut costs become more relevant. Many psychotherapeutic modalities follow a pattern of rigorous adherence to protocols in research settings followed by relaxation of strict standards once they are deployed more broadly.⁶

² American Psychiatric Association, Resource Document on Ethical and Practice Implications of Psychedelics in Psychiatry (2022) <https://www.psychiatry.org/getattachment/998071b6-138e-40d1-a482-e7b8e85d4f90/Resource-Documents-Psychedelics-in-Psychiatry.pdf>

³ [MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial | Nature Medicine](#)

⁴ American Psychiatric Association, Resource Document on Ethical and Practice Implications of Psychedelics in Psychiatry (2022) <https://www.psychiatry.org/getattachment/998071b6-138e-40d1-a482-e7b8e85d4f90/Resource-Documents-Psychedelics-in-Psychiatry.pdf>

⁵ American Psychiatric Association, Resource Document on Ethical and Practice Implications of Psychedelics in Psychiatry (2022) <https://www.psychiatry.org/getattachment/998071b6-138e-40d1-a482-e7b8e85d4f90/Resource-Documents-Psychedelics-in-Psychiatry.pdf>

⁶ Brujniks, S.J.E., Franx, G. & Huibers, M.J.H (2018). The implementation and adherence to evidence-based protocols for psychotherapy for depression: The perspective of therapists in Dutch specialized mental healthcare. *BMC Psychiatry* 18(1). <https://doi.org/10.1186/s12888-018-1768-x>

To mitigate these potential consequences, any FDA approval of MDMA must be accompanied by rigorous regulations, strict prescribing and dispensing controls, comprehensive patient education, and ongoing monitoring and surveillance systems. Investment in research to further elucidate the neurotoxic and cardiotoxic potential of MDMA, the long-term effects, potential for abuse and optimal therapeutic protocols for MDMA-assisted psychotherapy is also essential. These studies should incorporate comprehensive neuroimaging, sensitive neurocognitive measures, neuroendocrine challenges, and long-term follow-up assessments.

Adolescents

APA is particularly concerned about the vulnerability of adolescents and young adults due to the ongoing development and maturation of the human brain through young adulthood. Exposure to substances that cross the blood brain barrier such as psychedelic agents risk the derailment of this development and maturation. Right now, very little is known about the effects of these substances on youth, including long-term psychological and physiological effects, reinforcing potential, sex differences in psychedelic responses, and the impact of childhood trauma.⁷ Some research indicates that certain psychedelics, particularly dissociative, and MDMA, may produce reinforcing or aversive effects that differ between adults and adolescents.⁸ Adolescents may be at elevated risk of being taken advantage of while in an altered state of consciousness. They may also be less able to manage challenging content that emerges during the psychedelic experience, placing them at increased risk of negative outcomes. The potential risk of reinforcing effects in youth further underscores their heightened vulnerability. Given these considerations, careful measures must be taken to ensure adolescents' safety should psychedelic therapies be offered to this population. The expected benefits would have to be high to justify the potential risks.⁹ We also encourage the Advisory Committee to consider future research needs for pediatric populations in terms of safety, efficacy, and tolerability. APA understands that non-medical/recreational MDMA is not the same as the pharmaceutical grade therapeutic, the same cannot be said for the perceived safety and effectiveness that vulnerable populations may be able to access of non-medical/recreational forms of MDMA or pharmaceutical MDMA without appropriate medical supervision for safety.

As the Advisory Council reviews the evidence, APA encourages the members to consider if the research is too limited and whether guardrails must be incorporated for public safety. It is crucial to prioritize patient safety and public health, ensuring that any new treatment for PTSD does not inadvertently lead to adverse consequences for individuals and society as a whole. Thank you for your review and consideration of these comments. If you have any questions, please contact Brooke Trainum (btrainum@psych.org), Director, Practice Policy.

Sincerely,



Saul M. Levin, M.D., M.P.A., FRCP-E, FRCPsych
CEO and Medical Director

⁷ American Psychiatric Association, Resource Document on Ethical and Practice Implications of Psychedelics in Psychiatry (2022) <https://www.psychiatry.org/getattachment/998071b6-138e-40d1-a482-e7b8e85d4f90/Resource-Document-Psychedelics-in-Psychiatry.pdf>

⁸ Bates MLS, Trujillo KA. Use and abuse of dissociative and psychedelic drugs in adolescence. *Pharmacol Biochem Behav.* 2021 Apr;203:173129. doi: 10.1016/j.pbb.2021.173129. Epub 2021 Jan 28. PMID: 33515586.

⁹ American Psychiatric Association, Resource Document on Ethical and Practice Implications of Psychedelics in Psychiatry (2022) <https://www.psychiatry.org/getattachment/998071b6-138e-40d1-a482-e7b8e85d4f90/Resource-Document-Psychedelics-in-Psychiatry.pdf>