AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY

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August 25, 2023

Lauren K. Roth
Associate Commissioner for Policy
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Re: Comments for Psychedelic Drugs: Considerations for Clinical Investigations Guidance for Industry (FDA-2023-D-1987)

Submitted Electronically

Dear Ms. Roth:

The American Academy of Child and Adolescent AACAP is the professional home to more than 10,000 child and adolescent psychiatrists, fellows, residents, and medical students with a mission to promote the healthy development of children, adolescents and families through advocacy, education, and research. On behalf of the physicians we represent, and the children and youth they serve, we appreciate the opportunity to provide comments on the draft document *Psychedelic Drugs: Considerations for Clinical Investigations-Guidance for Industry.* First, we note that the draft guidance for clinical trials does not specify an age range, and as such, does not provide guidance relevant to the pediatric population. There is a clear need for pediatric guidance, as explained below.

AACAP's comments have been developed after close consultation with members who have expertise in this area, especially Gail A. Edelsohn, MD, MSPH, MBE, currently affiliated with the Community Care Behavioral Health Organization, a component of the University of Pittsburgh Medical College Insurance Services Division. She has held past academic

appointments at Johns Hopkins, Thomas Jefferson University, and most recently as volunteer faculty at Lewis Katz School of Medicine at Temple University. Dr. Edelsohn has also co-authored an article on ethical issues in pediatric psychedelics research and treatment. [i]

Anticipated Pediatric Clinical Trials

Children and adolescents are also significantly burdened with many of the conditions psychedelics researchers are targeting in adults. The lifetime prevalence of PTSD among adolescents aged 13–18 years is 5% (in adults the prevalence of PTSD is 3.6%) (National Institute on Mental Health 2022). An estimated 3.2 million adolescents aged 12–17 had at least one major depressive episode, with a past-year prevalence of 13.3% (in adults 18–25 years, the prevalence of depression is 17%) (National Institute on Mental Health 2022). The National Survey on Drug Use and Health (2019) found 414,000 adolescents had alcohol use disorder. According to the Center for Disease Control and Prevention (2022), about one in 54 children has autism spectrum disorder (ASD).

The call to expand clinical research to youth younger than 18 years is inevitable given that youth suffer from the same psychiatric conditions that have been the focus of research in adults, such as post-traumatic stress disorder (PTSD), treatment resistant depression (TRD), alcohol use disorder, ASD. The existing medications for PTSD, depression, and TRD have not been found to be very effective in the pediatric population, and the potential benefit of psychedelics for minors is significant. Once psychedelic drugs gain Food and Drug Administration approval for adults, the Pediatric Research Equity Act (PREA) will apply. The October 2021 Annual Meeting of the American Academy of Child and Adolescent Psychiatry (AACAP) hosted a comprehensive presentation that reviewed the use of psychedelics in treatment and research and discussed the regulatory and ethical implications and the implications for the pediatric population. This presentation was well attended and suggests there will be pediatric use of psychedelics immediately after approval. Therefore, pediatric guidance for clinical investigations involving psychedelics should be developed and included.

Assent and Parental/Guardian Permission to Participate and Enhanced Disclosure

The current draft guidance states "The informed consent should clearly describe that subjects may experience changes in perception, cognition, and judgment that persist for many hours, as well as increased vulnerability and suggestibility during the treatment session." The ineffable experience produced by psychedelics makes assent, parental permission, and disclosure challenging. Factors such as the minor's age, emotional status, cognitive ability, capacity to

process unusual experiences, and language development should be reviewed by parents/guardians when considering granting permission to participate. Psychedelic agents are uniquely different from other psychotropic drugs, as in addition to the experience changes listed above, there is the potential for personality changes, shifts in fundamental values, and re-exposure to trauma. It is not known how the personality changes attributed to psychedelics will impact the developing personalities for minors. Guidance should address the need for developmentally age-appropriate enhanced disclosure and the assent process.

The literature of psychedelics has emphasized the importance of psychological make up, and life situation at the time of exposure to psychedelics including the social factors, circumstances, and environment including those present during the drug administration. Parents/guardians will need to be apprised of the additional support and dedicated time required to support the minor throughout the clinical research trial in light of the minor's psychological mindset.

Each psychedelic drug has its own safety profile, physiological and psychological effects, and risks. Information included in the permission to participate should acknowledge the unknown risks and that side effects may present differently in minors. AACAP would like to advocate for a Risk Evaluation and Mitigation Strategy for these clinical investigations to ensure the benefits outweigh the risks.[ii]

Screening for Minors

In addition to the considerations listed under C. Clinical Pharmacology (145-170), thorough review of family and personal medical and psychiatric history, including trauma and substance use history, is recommended. Careful adherence to eligibility and exclusion criteria will be critical as researchers may encounter pressure to enroll vulnerable youth who may not meet study criteria in response to heightened demand for new treatment options.

Use of Touch During Psychedelic Sessions

Reassuring non sexualized touch such as handholding with permission may occur during psychedelic administration. Therapeutic touch should be explained and reviewed carefully as to where on the body it may occur and the purpose of the touch when obtaining assent and parental/guardian permission. Individuals with histories of physical or sexual trauma, a diagnosis of PTSD, may be uncomfortable with touch. Those with ASD may require more time to review and discuss prior to concluding the assent and permission process.

Diversity, Equity, Inclusion

In general, clinical trials of psychedelics have not included racially and ethnically diverse individuals. The development of culturally sensitive treatments is linked to the inclusion of racially and ethnically diverse youth.

Psychological Support or Psychotherapy in Combination with Investigational Drugs

The current draft notes the complexity of assessing effectiveness and "...the contribution of the psychotherapy component to any efficacy observed with psychedelic treatment has not been characterized (301-303)." Clinical trials of MDMA and psilocybin have included supportive psychotherapy pre-drug administration, during administration of psychedelic and integrative sessions post administration. For clinical trials involving minors, given the unique psychological effects of psychedelics, the administration of psychedelics to youth in the absence of supportive therapy raises the issue of potential increases in harm and potentially diminished benefit. We suggest that the indication specify a combination of psychotherapy and drug.

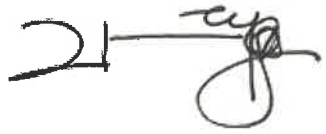
Public Health Effects

Many drugs are used off label in the pediatric population, and it is highly likely that would be the case for psychedelics once approved for adults. The public health risks are considerable with regards to misuse, overdose, and increased adverse effects. Ingestions presenting in emergency settings and underground practices promoting psychedelic use beyond the evidence base provide a glimpse of potential harm, not only to the public, but their potential to have a chilling effect on continuing research, as psychedelic researchers have warned (Yaden DB, Yaden ME, Griffiths, RR 2021. JAMA Psychiatry 78 (5):469-70).

AACAP would welcome the opportunity to work with the FDA to develop guidelines for clinical investigations that would target specific populations, such as the pediatric population. AACAP would also welcome participation in any psychoeducational materials for minors and families, with attention to underrepresented and minoritized groups. Once again, AACAP appreciates the opportunity to provide comments on the draft guidance.

We are hopeful to see our recommendations reflected in the final guidance on clinical investigations of psychedelic drugs. Should you have questions, you may contact Karen Ferguson, Deputy Director of Clinical Practice at kferguson@aacap.org.

Sincerely,



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[i] Project MUSE - Past Is Prologue: Ethical Issues in Pediatric Psychedelics Research and Treatment (jhu.edu))
[ii] Psychedelics as Therapeutics—Potential and Challenges | Depressive Disorders | JAMA Psychiatry | JAMA Network