Summary. We, the undersigned academic scientists and representatives of organizations involved in treatment development for substance use disorders and professional therapeutic societies, are writing to express our support for expanded federal and private sector investments in clinical studies examining the potential of the class of psychedelic and dissociative medications for the treatment of various psychiatric conditions. In doing so, we also emphasize that the small number of highly controlled clinical studies of psychedelics that have been performed to date are insufficient to support their safety for widespread clinical use. In some instances, inaccurate claims have prompted state and local governments to decriminalize or legalize public use of psychedelics, which might lead to harmful unsupervised use before efficacy and safety are firmly established. The full therapeutic benefits of these drugs are still being established and it is premature to make sweeping statements about their benefits without additional careful research.

Researchers at prominent academic institutions have conducted small rigorous studies of clinician-monitored administration of psychedelics, most including guided psychosocial therapy – an approach increasingly referred to as "psychedelic-assisted therapy". These studies have shown promise in relieving existential distress in patients who have cancer, and in treating various mental health conditions including substance use disorders, depression, anxiety, and post-traumatic stress disorder (PTSD). In 2017, 3,4-methylenedioxymethamphetamine (MDMA) was granted a Breakthrough Therapy (BT) designation by the Food and Drug Administration (FDA) for MDMA-assisted psychotherapy to treat PTSD. The BT designation for MDMA for PTSD was followed by a BT designation for psilocybin for treatment-resistant depression in 2018, and then for another sponsor's psilocybin product for major depression in 2019. BT designation is a regulatory process designed to expedite the development and review of drugs intended to treat a serious condition, and that may demonstrate substantial improvement over available therapies. As per FDA's guidance to industry[1], a drug that receives BT designation is eligible for all Fast Track designation features, intensive guidance from FDA on the drug development program, and organizational commitment involving FDA senior managers.

These early studies suggest that psychedelics may demonstrate effectiveness for some psychiatric disorders under tightly controlled clinical research conditions. However, various press and media reports, private sector investors, and grassroots advocates are premature in pronouncing the benefits of psychedelics. There is insufficient evidence at this time to support claims that psychedelics are panaceas for a multitude of (yet unstudied) psychiatric disorders.

Although the early clinical studies appear to show the therapeutic promise of this class of drugs, large-scale studies have not yet been conducted in real-world settings, which is critical for establishing their widespread therapeutic potential. A few cautionary notes:

- First, full-scale Phase 3 clinical trials for safety and efficacy have only been completed for the Multidisciplinary Association for Psychedelic Studies (MAPS) MDMA product for PTSD; Compass Pathways' Phase 3 study of a psilocybin product for treatment-resistant depression is ongoing. No product has yet been approved by the FDA for these indications. Thus, we urge the public and other stakeholders to temper claims about which disorders can be safely and effectively treated until the appropriate research is conducted. Additional randomized clinical trials are the standard, expected practice, and are necessary to replicate the current promising findings and to better understand potential risks of these potent compounds prior to widespread approvals. This has been emphasized by Professors Yaden and Griffiths, two prominent leaders in the field of psychedelic-assisted therapies at Johns Hopkins University, who stated "additional studies will be required to better understand the mechanisms by which psychedelics exert their therapeutic effects, ideal dosing schedules, selection of the most effective compounds, and optimal clinical management."[2]

[1] See FDA's summary of BT therapies as at https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/frequently-asked-questions-breakthrough-therapies

[2] David Yaden, Mary Yaden, Roland Griffiths, "Psychedelics in Psychiatry—Keeping the Renaissance from Going Off the Rails," JAMA Psychiatry, 2021: 78(5):469-470

- Second, most of the clinical trials conducted to date involved administration of psychedelics delivered in conjunction with psychotherapy that may vary depending on the specific drug and disorder, and all occurred in a controlled clinical environment designed to maximize patient safety, especially as they relate to appropriate clinical management of adverse events, and to optimize health benefits. Borrowing from previous development of therapeutics for similar disorders, the best therapeutic outcomes, with reduced risks to patient safety, occur when psychedelic compounds are taken under medical supervision and in a controlled clinical setting. Existing evidence suggests that safety risk increases with an increase in dose. All of the prospective clinical studies utilized carefully considered inclusion criteria and excluded individuals with a history of psychotic disorders, bipolar disorder, or current substance use disorders due to safety concerns. Drs. Griffiths and Yaden have written that "the safest and most effective psychedelic treatment protocols will likely be those that integrate existing evidence-based interventions and psychotherapies."[2]

- Third, the psychedelic compounds administered in recent and current clinical trials are of pharmaceutical grade with pre-specified dosing conditions. These studies were conducted under Investigational New Drug applications that were rigorously evaluated before being approved by the FDA. According to FDA Controlled Substance Staff and experts in a recent peer-reviewed publication: "…***it should be stressed that the safety established in clinical studies with a formulation containing a classic psychedelic does not extend to the safety of a drug obtained from illicit channels, which will be of unknown identity, quality and composition." (Calderon et al. 2023) Calderon and colleagues caution that when psychedelics are "used recreationally in uncontrolled circumstances, there may be a different safety profile because of differences in dose, drug quality, individual pre-existing conditions (e.g., history of psychotic disorder, bipolar disorder, current substance use disorder), or use of the drug in combination with alcohol and other drugs."[3] [emphasis added]***

Based on clinical trial results to date, we are encouraged to see that psychedelic compounds have demonstrated potential benefits for the treatment of a variety of disorders, as reviewed in a recent special issue of *Neuropharmacology,* based on the 2021 NIH Psilocybin Speaker series (see Belouin et al. 2023[4] addressing the potential promises, risks, and conditions important to ensure safe and effective use). The ongoing preliminary studies serve as the foundation for additional public- and private-sector funding. Larger registration clinical trials intended for FDA approvals, followed by rigorous regulatory review, are needed to actualize the potential for psychedelics to be used as new and effective treatments for a range of psychiatric disorders in order for this class of medications to be integrated into accepted medical practice.

Another concern is the potential for what Dr. Griffiths refers to as "blowback"[5] and what the journalist Michael Pollan calls "irrational stigmatization"[6] which occurred just a half century ago from the broad-based recreational unrestricted use of unregulated psychedelics. As Michael Pollan has written, "it would be a shame if the public is pushed to make premature decisions about psychedelics before the researchers have completed their work.

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[3] Silvia Calderon, Katherine Bronson, Chad Reissig, Joshua Lloyd, Steven Galati, Dominic Chiapperino, "Considerations in assessing the abuse potential of psychedelics during drug development," Neuropharmacology, Volume 224, 15 February 2023

[4] Sean Belouin, Dan Xi, Ann Berger, David Shurtleff, Farah Zia, "National Institutes of Health psilocybin research speaker series: State of the science, regulatory and policy landscape, research gaps, and opportunities," Neuropharmacology, Volume 230, 1 June 2023

[5] David Yaden, James Potash, Roland Griffiths, "Preparing for the Bursting of the Psychedelic Hype Bubble," JAMA Psychiatry, 2022;79(10):943-944

[6] Michael Pollan, "Michael Pollan: Not So Fast on Psychedelic Mushrooms," The New York Times, May 10, 2019

There is, too, the risk of inciting the sort of political backlash, that, in the late 1960s, set back research into psychedelics for decades."[7]

Further, what is missing from the conversation is the disincentives to public- and private-sector investment in the development of psychedelic compounds that would likely result from widespread recreational use of psychedelic compounds. These investments would result in rigorous scientific testing that would culminate in FDA approval of safe and effective medications for treating a variety of health conditions. Allowing our policies to precede science may prevent us from ever realizing the full potential of these compounds and premature and unregulated use of this class of drugs for untested mental and physical conditions may amplify adverse side effects that ultimately could undermine their availability, mirroring what we saw in the 1960s and 1970s.

The research and evidence base for this class of drugs is growing and receiving new support from federal agencies. In May 2023, the National Institute on Drug Abuse (NIDA) announced three new requests for research proposals for psychedelic research, medicine development, and policy (e.g., see https://grants.nih.gov/grants/guide/rfa-files/RFA-DA-24-028.html). This is promising because philanthropy support has been vital but is not nearly large enough for all the research that must be done to verify safe and effective doses and indications. National Institutes of Health (NIH) funding can ensure that vital research will be conducted to fill gaps not being addressed by medicine developers and provide checks and balances. Ideally, there will be some degree of coordination or at least cooperation in these efforts as can be provided by public-private sector types of initiatives that have been so effective in other areas of medication development.

To conclude, as members of the scientific and clinical communities, we encourage the continued investment of private sector and NIH-funded research on the potential therapeutic benefits of psychedelics and urge policymakers and the public to engage critically with purported claims about psychedelics in the media and to seek out credible, evidence-based sources of information regarding the relative risks and benefits of psychedelics, which are still being established empirically. Efforts to decriminalize or legalize unrestricted recreational use of psychedelics before due diligence research has been completed could significantly undermine the public's understanding of these products as safe and evidence-based therapeutics.

[7] Michael Pollan, How to Change Your Mind: What the New Science of Psychedelics Teaches Us About Consciousness, Dying, Addiction, Depression, and Transcendence, Random House LLC, 2018