UNITED STATES DISTRICT DEPARTMENT OF JUSTICE

Drug Enforcement Administration

In the Matter of **Scheduling 4-OH-DiPT, 5-MeO-AMT, 5-MeO-MiPT, 5-MeO-DET, and DiPT**	**Docket No. 22-15**

STATEMENT OF DR. LYNNETTE A. AVERILL

My name is Dr. Lynnette A. Averill. I am an Associate Professor, a clinical research psychologist, and a practicing psychologist. My primary academic appointment is in the Menninger Department of Psychiatry and Behavioral Sciences at Baylor College of Medicine in Houston, TX and I maintain a faculty appointment at Yale School of Medicine and the US Department of Veterans Affairs National Center for PTSD – Clinical Neurosciences Division and Michael E. DeBakey VA Medical Center. My CV is **M&TX 62** and a list of my publications is **M&TX 52**.

I offer this opinion as an expert in clinical psychology, psychopharmacotherapy, and neuroscience – specifically stress- and trauma-related pathology, novel, rapid-acting interventions including ketamine and psychedelic medicines, and the underlying neurobiology of treatment response and drug mechanisms. Some of my comments and opinions have appeared in my other statements and publications, which are cited in this document. These opinions are my own and do not necessarily reflect the policy or position of Baylor College of Medicine, Yale School of Medicine, or the US Department of Veterans Affairs. I speak for myself only and do not speak as a representative of any of these institutions.

Background

I am the daughter of a US Marine Corp Veteran who served in Vietnam and who, over 35 years ago, died by suicide after a long struggle with PTSD, substance use and ineffective treatments. I don't remember much about my father—I was three years old when he passed—but I grew up aware of the effects of war, trauma, and chronic stress on the people who experience these things firsthand as well as on their family, friends, and communities who experience so much of this in tandem. Growing up, I was always struck by the extent of impact stress and trauma have on the human experience and how even our best treatments are not enough for so many struggling with the repercussions. Of course, across the past 35 years, we have made significant advancements in our understanding of PTSD and other related conditions and in our ability to treat them. However, the prevalence of these conditions and the rates of suicide, severe addiction, and other concerns including homelessness, unemployment, domestic violence, etc. are clear evidence we have urgent need to further expand the tools in our prevention and intervention armamentarium.

Throughout my career, I have published dozens of papers in peer-reviewed scientific journals on subjects relating to mental health broadly, with a focus on PTSD, depression and suicidality, ketamine and psychedelic therapy, and Veteran issues specifically.

I also am a Co-Founder or Reason for Hope, a non-profit whose mission is to prevent deaths of despair by helping to develop and advocate for the policy and legal reforms needed to facilitate safe and affordable access to psychedelic medicine and assisted therapies. Along with myself, the organization is led by retired Marine Three-Star Lieutenant General Martin Steele, retired Army Brigadier General and psychiatrist, Stephen Xenakis, MD, and Brett Waters, Esq.

I have testified in support of legislative action calling for the advancement of psychedelic research and the access of interventions to individuals in desperate need while we await FDA

approval. I recently served as a subject matter expert for HB1802 in Texas, which supports and funds a clinical trial of psilocybin for Veterans with PTSD. I also served as a subject matter expert for Connecticut's Psilocybin Workforce, established during their last legislative session with the intent of helping guide the state's preparation for the expected FDA approval and subsequent roll-out of select psychedelic medicines. Relatedly, I testified in support of HB-5396 in Connecticut, which increases access to psychedelic therapies through the FDA's Expanded Access program for Veterans, first responders and front-line healthcare workers. Finally, I have served as a subject matter expert for special briefings to legislative subcommittees in New Hampshire and Maine as they considered bills relating to psychedelic medicine and assisted therapies.

Exhibits

M&TX 4 is an article entitled *Investigational drugs for assisting psychotherapy for posttraumatic stress disorder (PTSD): emerging approaches and shifting paradigms in the era of psychedelic medicine* of which I am lead author. The article describes the current mental health crisis and the limitations of current approved treatments in treating PTSD. It explains the serendipitous discovery of the rapid-acting antidepressant effect of ketamine, a Schedule III anesthetic, approximately two decades ago has prompted a paradigm shift in neuropsychiatry and novel drug development and how psychoplastogens (i.e., fast-acting pharmacotherapeutics) like ketamine, MDMA, psilocybin, 5-MeO-DMT, and potentially other tryptamine substances which rapidly promote structural and functional neural plasticity have great potential to provide fast-tracked, robust improvements in stress- and trauma-related symptoms. Finally, it discusses the urgent need to advance these interventions, to support further study and investigation, to consider ways (including expanded access programs) to accelerate the access of selected interventions with a significant body of evidence (i.e., MDMA and psilocybin) to those in desperate need, and to

carefully consider how, as a society, we can best roll-out these interventions to support reasonable, safe, and equitable use.

M&TX 14 and **M&TX 58** are papers I co-authored entitled *Psychedelic Treatment for Trauma-Related Psychological and Cognitive Impairment Among US Special Operations Forces Veterans* and *Psychedelic treatment for co-occurring alcohol misuse and post-traumatic stress symptoms among United States Special Operations Forces Veterans* respectively. Both articles describe surveys of Veterans that used two Schedule I drugs, ibogaine or 5-MeO-DMT (a tryptamine) – treatment was completed in an established clinic outside the US where these medicines are not regulated. **M&TX 14** provides preliminary results to support clinical trials to investigate the safety and efficacy of ibogaine and 5-MeO-DMT for those suffering with psychological and cognitive symptoms. Special Operations Forces Veterans (SOFV) in this study reported rapid, robust and durable improvements across a range of symptoms including PTSD, depression, anxiety, substance use, suicidality, cognitive impairment and symptoms of traumatic brain injury (TBI). Participants also reported these experiences were highly impactful and meaningful even experiences beyond the symptom improvements. In **M&TX 58**, the aim was to assess whether psychedelic treatment with these drugs was associated with reductions of alcohol use and PTSD symptoms among SOFV engaged in high-risk drinking. The study showed rapid and significant decreases in alcohol use and PTSD symptoms among a clinical sample of SOFV, consistent with prior studies showing that MDMA, a Schedule I substance and mixed-monoaminergic entactogen and psychedelic, has been shown to produce significant PTSD symptoms and psilocybin, a serotonergic psychedelic and Schedule I substance has been shown to promote rapid and robust improvements across a range of symptoms including in depression, anxiety, and alcohol use.

M&TX 60 is an article by Captain Sean J. Belouin of the U.S. Public Health Service and Jack E. Henningfield entitled "*Psychedelics: Where we are now, why we got here, what we must do*" published in November 2018 in Neuropharmacology. In the article, the authors provide a brief historical context for psychedelic drug research, its modern rise, fall, reemergence, and the importance of finding pathways through the complex legal, policy, and social barriers, to effectively research the potential medicinal applications of previously maligned psychedelic compounds. The article explains how LSD and other psychedelic substances were once heralded as potential treatments for a variety of serious mental health disorders including anxiety, depression, schizophrenia, war time stress reactions, alcoholism and other substance use disorders, and that many leading researchers in psychiatry and the emerging fields of neuropharmacology and neuropsychopharmacology conducted research into these psychedelic substances. It further explains how patterns of abuse emerging with LSD in the 1960s and the "counterculture" contributed to an emerging unfavorable reputation among numerous political and medical leaders. It further discusses a "rapidly growing awareness, anticipation, and hope for the potential of several psychedelic drugs to become medically approved for various psychiatric disorders," citing almost a dozen studies from the past 10 years. **M&TX 60** at 4.

Current Therapies Fall Short in Addressing Today's Mental Health Crisis

We stand at an inflection point in history. We have recently observed the 20-year anniversary of 9/11 and 20 years of sustained combat, the longest in US history, with far reaching global involvement/impact. Approximately 20 US Veterans die by suicide each day and a recent report suggests military suicides are four times higher than deaths in war operations post-9/11.[1]

[1] Thomas Howard Suit, I., High suicide rates among United States service members and Veterans of the post-9/11 wars 20 yeas of War; A costs of war research series 2021: p. 1-35.

Globally, a suicide epidemic and opioid crisis rage on relatively unabated. Political, social and civil unrest and related acts of violence and hate crimes are significantly heightened and widely covered across all news and media outlets. Across the world, there are many pockets of refugees and asylum seekers are who suffering significant stress and trauma, and many more who continue to suffer inside their home countries. These startling realities are only further compounded by being more than 2 years into a globally shared traumatic stressor, the COVID-19 pandemic and related mental health implications both due to the illness itself as well as the various financial, employment, housing, and other crises occurring in parallel. The recent withdrawal from Afghanistan and the current Russian invasion of Ukraine heightens the stress and trauma burden further, and in 2022 we have seen near daily mass shootings and other acts of violence. As individuals, and as a country, we are desperate for effective ways of managing stress and trauma. I agree with Captain Beloin and Henningfield's assessment that "[c]ontinued decline in mental health poses an existential strategic threat within the United States whose impact is now being fully recognized." **M&TX 60** at 6.

The mental health crisis of today is unlike anything we have known before. The NIMH estimates the total costs associated with serious mental illness, including those disorders that are severely debilitating and affect about 6 percent of the adult population, to be in excess of $300 billion per year. **M&TX 60** at 7. The unfortunate reality of today's mental health crisis highlights the limited effective pharmacologic treatments in our toolbox for stress and trauma-related concerns such as PTSD, depression, and suicidality. There are only two FDA-approved medications indicated for PTSD, both selective serotonin reuptake inhibitors (SSRIs) and the landscape of effective treatment is even bleaker for suicidal thoughts and behaviors.

These traditional medications may work very well for a restricted population, but they have significant limitations.[2] Even when optimally delivered, 40% of the patients do not respond to SSRIs, and only about 20% to 30% achieve remission, and the magnitude of the difference from placebo ranges from 10% to 20%.[3] The rates of non-response or partial response to these medications among combat-exposed individuals, particularly those with chronic PTSD, are comparable or worse to those of civilian patient populations.[4] In working with Veterans and civilians with PTSD and other chronic stress issues for years, I saw that the number of patients who had a phenomenal response to talk therapy or SSRIs (either as individual interventions or in combination) were relatively few and far between. Further, even when traditionally available SSRIs are effective, they are slow acting. These antidepressants have a delayed onset of action, meaning it can take weeks to months before patients experience clinical benefit. This latency period increases the risk for suicide and self-harm as well as other destructive behaviors.

Treatment guidelines for PTSD have designated psychotherapy as the first line of intervention given the limited efficacy of SSRIs. After psychotherapy (sometimes multiple rounds), PTSD often remains with high rates of psychiatric and medical comorbidity and significantly impacted quality of life. The attrition rate among gold-standard psychotherapy outcome studies ranges has been as high as 55.8% and nonresponse can be as high as 50%. Although SSRIs and talk therapy remain critically important and beneficial interventions, given their limitations and the magnitude of the mental health crisis, they are simply not enough.

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[2] Averill, L.A., et al., Investigational drugs for assisting psychotherapy for posttraumatic stress disorder (PTSD): emerging approaches and shifting paradigms in the era of psychedelic medicine.
[3] *Id.*
[4] *Id.*

I agree with Captain Beloin and Mr. Henningfield's assessment that "our mental health prevention and treatment programs, including regulatory and policy initiatives, collectively have not decreased the trajectory for a battery of mental health disorders being reported annually" and that, despite these initiatives, mental health disorders "continue to increase over the time periods where data continues to be collected." **M&TX 60** at 7.

Psychedelic Therapies May Offer Safer Treatments and Better Results

Mounting evidence suggests fast-acting therapeutics rapidly promote structural and functional neural plasticity and have great potential to provide fast-tracked, robust improvements in stress- and trauma-related symptoms. This class of drugs includes ketamine (Schedule III) as well as MDMA, psilocybin, and 5-MeO-DMT, and many other drugs regarded as Schedule I hallucinogens.

Evidencing the need to study these Schedule I hallucinogens, within the past five years, FDA's Center for Drug Evaluation and Research (CDER) has granted a Breakthrough Therapy Designation to two Schedule I drugs: MDMA and psilocybin. MDMA has received this designation for PTSD and psilocybin for both major depressive disorder and treatment-resistant depression. The FDA's Breakthrough Therapy Designation is intended to expedite the development and review of drugs for serious or life-threatening conditions in which clinical evidence suggests the novel drug may demonstrate significant improvement over available interventions for a given clinical endpoint.

Much of what the scientific community thought long ago has been called into question, if not refuted, by research and clinical trials over the past decade. For example, psychedelic medicines do not appear to be habit forming and generally are safer than many other prescription and non-prescription drugs. This research generally shows that this class of drugs has the unique

potential to offer relief and healing to individuals who have been failed by current treatments and that psychedelic medicines work more rapidly than traditionally available treatments, more robustly, are safe, and have few lasting side effects. In addition, beyond PTSD, my and other's research has shown that psychedelic treatments may be effective at reducing alcohol misuse disorder in Veterans. **M&TX 58** at 7

In my opinion, from a scientific and medical perspective, relying on an evaluation of the evidence that is a decade old (2012) is highly troubling in any case and especially so in an area with such rapidly advancing and expanding evidence.[5] Neither current empirical research nor clinical anecdotes support abuse potential of psychedelics as a major concern and certainly rapidly growing evidence, reported from premier academic organizations across the world suggests great potential medical benefit of these interventions and a high degree of safety. Indeed, when considering the cost benefit analysis against the low potential for abuse relative to the risk of continuing with ineffective treatments, the incredible distress experienced by those struggling with ineffectively treated symptoms, the day-to-day life lost, and ultimately the lives lost – there is no comparison to be made.

Importantly, much of the healing that comes from the use of psychedelic medicines in therapy comes from experiences that have deep personal meaning. There is evidence from trials across a constellation of symptoms, that psychedelic medicine works because of the psychedelic experiences in the form of a "full system shut down and restart" giving a window of opportunity to do some rewiring in the brain, allowing for shifts away from maladaptive cognition evaluations,

[5] I have read, reviewed, and agree with the statements made by Dr. Brett Giroir in his declaration and can attest to its authenticity. **M&TX 65**. I too express no opinion as to whether the specific substances at issue in these hearings are or will prove to be medically and scientifically useful.

enhanced insights and shifting perspectives about one's own self, others, and the world. These experiences are therapeutically relevant and likely contribute to mood or behavioral changes after taking a psychedelic. It is highly unlikely that rodents would have similar experiences, reinforcing the limitations of rodent-to-human comparisons with the class of psychedelic substances. While rodents can absolutely experience stress and trauma, we have no way of capturing or understanding what, if any, may be their experience with very human elements that are significantly impacted by these experiences such as one's belief systems, past experiences, the compounding effects of chronic trauma, marginalization and systemic issues, experiences with guilt, shame, demoralization, forgiveness of self or others (or lack thereof), meaning and purpose, connection, environmental factors, and so on.

In my experience, traditionally available medications and talk therapy often – though not nearly often enough – can do a good job at helping people avoid death. And while avoiding death, avoiding suicide, is an absolute win, for many this avoidance is only to the point of tolerance, tolerating living another day or another week, while still questioning if life is really worth living and not seeing much hope or meaning. While, of course, not the case for everyone (nothing is a one size fits all), I have heard time and time again in my research, clinical, and advocacy work that intervention with psychedelic medicines not only supported the avoidance of death in many cases, these interventions provided a foundation from which people were able to build lives they truly wanted to be living – lives in which they found connection with themselves, others, and the world, and had a sense of meaning and purpose. These outcomes are very different – tolerating versus thriving. I want to stress that these very transformative experiences are not the expectation and that many do not experience such a highly robust outcome following intervention with a psychedelic medicine and assisted therapy; however, I will note that I have never had my own patients nor

heard of anyone else's comment that SSRI treatment was one of the most meaningful experiences of their life.

Lesser Studied Analogues of Schedule I Substances May Produce Safer Treatments and Better Results

Despite the FDA CDER designating MDMA and psilocybin breakthrough therapies, there is an urgent need to expand research beyond these two compounds to the entire class of drugs traditionally regarded as psychedelics or "hallucinogens." As discussed above, contemporary evidence does not support the notion that these drugs present significant danger or public health risks—certainly when compared to other drugs such as prescription opiates and methamphetamine. Equally important, psychedelic medicines and assisted therapies are not a "one size fits all," not a panacea, and not a miracle cure. There are some who these interventions are not appropriate for, not safe for, and/or some who will not have a significant improvement in symptoms. This is the case for all interventions across all fields of medicine – there is never a "one size fits all."

Although evidence suggests these breakthrough therapies are safe and effective, they only begin to address today's mental health crisis. Current psychedelic therapies are intensive interventional treatments, have 6 to 8 hours of duration that require medical monitoring during that period, which raises important questions and concerns about scalability and affordability (conversations are happening in many settings to address these). There are concerns that MDMA may not be appropriate for patients undergoing concurrent SSRI treatment. To date, patients seeking to use MDMA to treat PTSD will need to discontinue SSRI treatment well in advance of MDMA therapy, which presents its own serious risks to those patients. There are plans to evaluate the safety of continued SSRI treatment with MDMA; however, the findings of these studies are far in the future. Identifying medicines that may be safe and appropriate for use concurrently with SSRIs is critical work. There is also a need for psychedelic medicine with a lessened psychedelic

and/or cardiovascular/physiological experience, which would likely translate to reduced costs for care and burden on providers as patients may not need as much monitoring and support that accompanies current first-generation psychedelic therapies such as psilocybin and MDMA.

In addition, the focus of psychedelic therapies to date has been on treating mental conditions such as depression, end of life anxiety, PTSD, and more recently substance use and addiction. Given their mechanisms of action, psychedelic compounds also show promise in addressing other brain-based conditions such as traumatic brain injury, headache, stroke, and even Alzheimer's disease. There remains an urgent need to address these conditions with further research.

In particular, research suggests serotonin 2A agonist psychedelics hold potential in combatting opioid and other substance use disorders. In the paper entitled *Persisting Reductions in Cannabis, Opioid, and Stimulant Misuse After Naturalistic Psychedelic Use: An Online Survey* (**M&TX 18**) researchers reported that out of 444 responders to an anonymous, retrospective self-report data survey, over 70% of participants (331) reported that they had greatly reduced or quit using their primary substance following a psychedelic experience. Although 95.7% of surveyed individuals met SUD criteria before the reference psychedelic experience, only 27.3% met criteria for a SUD in the time since the reference psychedelic experience. These findings are consistent with findings from other prior surveys that report reductions in tobacco and alcohol consumption following psychedelic use. Participants also reported less severity of anxiety and depression symptoms after the reference psychedelic experience when compared with other attempts to reduce their substance use. And the participants endorsed changes in life priorities or values, including an increased belief in their ability to abstain, and an increased ability to delay gratification. The

researchers conclude that serotonin 2A psychedelics may hold considerable potential as novel therapeutics in treating various substance use disorders.

Similarly, in the paper *Classical hallucinogens in the treatment of addictions* (**M&TX 10**) the authors discuss the toll of substance use disorders in the United States—over half a trillion dollars lost per year—and that the evidence suggests hallucinogens hold considerable promise in the treatment of addiction, particularly given the limited efficacy of current treatments. The paper further explains that classic hallucinogens have a safe profile when compared to other abused drugs such as opioids and stimulants, and how these hallucinogens can be safely administered with medical supervision. Further, there is growing interest in the role of ibogaine in the treatment of opioid dependence. **M&TX 10** at 7.

For these aforementioned reasons, in the past several years, the study of hallucinogenic substances outside of psilocybin and MDMA has dramatically increased in both the academic community and private sector/naturalistic settings. There is a vast scientific need to build this body of literature from all angles and a vast market need to identify new drugs that promote rapid structural and functional neural plasticity and rapid and robust improvements across a range of symptoms.

I am informed that some of the Five Tryptamines that are subject to these proceedings may produce similar effects to these breakthrough therapies with fewer side-effects or shorter duration. A drug that can produce MDMA like effects in modest doses and may be able to work alongside treatment with SSRIs is highly important to investigate. If the medical and scientific evidence supports this, such a drug could, in theory, address a gap in first-generation in the breakthrough MDMA therapy: the fact that it cannot work on patients undergoing SSRI treatment and the risks of those patients discontinuing SSRI treatment. To illustrate the point, I recently co-authored a

research paper entitled *Clinical Evidence for the Use of Methylone in the Treatment of PTSD: A Case Series with Long-Term Follow-Up*. Methylone is a drug that is structurally related to MDMA that has similar but milder effects and a shorter duration of action. We examined the clinical experience with 21 patients treated with one or more oral doses of methylone for PTSD in a naturalistic setting. Methylone was well-tolerated over a broad dose range and produced acute and enduring improvements in PTSD symptoms, without any notable lasting adverse effects. All patients achieved at least minimal improvement following treatment, with 17 achieving "much" or "very much improved" ratings on the Clinical Global Impressions Scale. Notably, no adverse events occurred in patients receiving concomitant SSRI therapy, which is noteworthy because as discussed above, MDMA-therapy typically requires patients to taper off of these medications. If future research supports the conclusion that methylone can produce rapid-acting and robust symptom improvement in treatment refractory PTSD, it may prove to be an important and urgently needed addition to the therapeutic armamentarium as a drug with "softer" effects than MDMA.

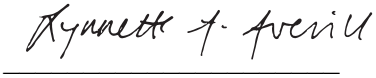
In my opinion, as a researcher and clinician in this area, placing drugs that have a low relative potential for abuse, have little to no demonstrated actual abuse over more than a decade period, and may be useful in research with potential medical benefit, including a likelihood to address shortcomings in the first-generation psychedelic medicine in Schedule I, is a mistake from a public health perspective and creates a risk to the public health. It is well-documented and has been my experience and that of many colleagues that the regulatory barriers associated with using Schedule I substances in research are formidable. They can delay and sometimes halt, the advancement of scientific and medical research. Dr. Nora Volkow, for example, the Director of the National Institute of Drug Abuse, (NIDA) recently stated at an event hosted by the National Academies of Sciences, Engineering and Medicine entitled "Exploring Psychedelics &

Entactogens to Treat Psychiatric Disorders," that she is personally reluctant to take up research initiatives involving Schedule I substances due to these restrictions and these have "slowed down the process enormously."

I agree with Captain Beloin and Henningfield's assessment that "[r]esearch is essential to provide the solid science foundation to identify and address the risks, benefits, and conditions that promote the safe use of psychedelic substances" and that more than ever, the research community needs "to investigate these substances which include how they should be integrated with behavioral and other evidenced based therapies to provide safe and effective interventions for PTSD, addiction, depression, and/or anxiety and possibly other mental health disorders." **M&TX 60** at 8. Given this, imposing regulatory restrictions that significantly slows down the clinical and scientific research into drugs that can provide us with a greater understanding of this class of medicines and which may have a potential to address shortcomings in the current mix of psychedelic therapies, even for a few months, creates risks to the public health and endangers the lives of those who may not respond or who may not be suited to first-generation psychedelic medicines. And it does all of those individuals who are struggling with ineffective traditionally available interventions (and their families, friends, and communities) who are desperate for effective therapies a significant disservice. At this time in history, I think we are hard pressed to find anyone who is not at least a little impacted by the stress and trauma of the past decade (and beyond) – either themselves or a loved one. At this time, adding barriers to research and treatment development is a disservice to all – and likely one that will cost additional lives and carry immense economic burden.

I certify under penalty of perjury that the foregoing is true and correct.

Executed on 7/15/22



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