On the proposed Schedule 1 classification of 2,5-dimethoxy-4-iodoamphetamine (DOI) and 2,5-dimethoxy-4-chloroamphetamine (DOC)
Docket No. DEA1156
Regarding § 1316.47 Request for Hearing

Executive Summary

Psychedelic drugs such as psilocybin have enjoyed a marked increase in media and scientific attention within the last decade for potential treatment of psychiatric disorders such as post-traumatic stress disorder (PTSD), anxiety, obsessive-compulsive disorder (OCD), treatment-resistant depression and substance use disorders (Tullis, 2021; Sanders, 2021; Vargas et al., 2021, Johnson et al. 2017, Bogenschutz et al 2022). Yet, many of these psychedelics act through a wide variety of receptor systems, and the exact identity, localization, and downstream mechanisms of the molecular targets that account for their therapeutic efficacy is an active area of research. DOI and DOC are invaluable research tools to study these receptor systems and their roles in therapeutic effects because, unlike more conventional psychedelic drugs such as psilocybin, DOI and DOC are highly selective for serotonin 2 receptors (5-HT_2). Activity at these receptors are thought to be the primary mechanism underlying subjective psychedelic drug effects as well as therapeutic benefit in clinical studies of psychiatric disease (Jaster & Gonzalez-Maeso, 2023; Ling et al., 2021). Importantly, psychedelics are among the least harmful and least likely to be abused of all recreational drugs, considering their sporadic use patterns, non-reinforcing effects and rapid tolerance to the hallucinations and subjective effects (de la Fuente Revenga et al. 2022). Their low abuse potential paired with their clear medical benefits in clinical trials calls into question the legitimacy of their current Schedule 1 status (Nutt et al., 2020).

Actual or Relative Abuse Potential

Psychedelics have been long characterised for their unusual effects on sensory perception and subjective experiences. Until the last ten years, psychedelics have not been fully investigated utilising modern methodology or institutional review board regulations for their own use liability or ability to reduce drug use in both clinical and preclinical models.

While the CSA uses drug discrimination as an *in vivo* test to assess drug use liability in comparison to known “drugs of abuse”, the core of drug discrimination is to evaluate the stimulus similarity between a test novel chemical entity and a reference agent. While psychedelics like DOI and DOC do substitute for DOM, LSD and psilocybin this is due to their shared pharmacology at the 5-HT_2 receptors (Glennon et al. 1982). In recent years, other measures that are more widely accepted tests of drug use include self-administration, intracranial self-stimulation and food versus drug choice operant responding (Spanagel, 2017). In these more rigorous measures, DOI and some analogs have been shown to be non-reinforcing and to reduce reinforcing effects of other drugs.

For example, DOM decreased heroin self-administration in non-human primates but did not alter food responding (Maguire et al. 2013), DOI depresses intracranial self-stimulation in rats which is opposite to other drugs like heroin, cocaine and amphetamines which all stimulate responding

(Jaster et al. 2022), and DOI was found to decrease ethanol preference in a conditioned place preference and two-bottle choice model (Oppong-Damoah et al. 2019). Further, DOI was found to have dose-dependently decreased motivation for fentanyl seeking and decreased low-cost and total fentanyl consumption, which was evidenced to be dependent on 5-HT_{2A} activation (**Fig. 1** taken from Martin et al. 2021).

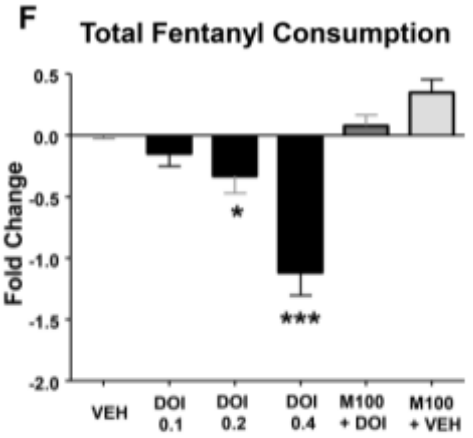

Figure 1. Decrease in fentanyl consumption shown as Log2 fold-change for each drug condition relative to the log-average of all vehicle sessions. Martin, 2021. Effects of 5-HT2A Receptor Stimulation on Economic Demand for Fentanyl after Intermittent and Continuous Access Self-Administration in Male Rats. *Addiction Biology*, 2021;26(3).

Most recently, DOI was found to accelerate natural extinction of opioid preference using a mouse conditioned place preference model (Jaster et al. 2024, unpublished).

To this end, if the same logic is applied to drug discrimination, all these compounds may produce non-reinforcing effects and potentially attenuate use of other substances and therefore do not fall into the “high potential for abuse” category. With this consideration, the proposed reclassification of DOI and DOC into Schedule I of the CSA would be inappropriate solely based on the “high potential for abuse” and no “medicinal value,” as there is a growing body of evidence that contradicts this opinion.

Danger to Self and Public Health

Between 2015 and 2019, DOC was associated with only *three* fatal complications, and *zero* involving DOI (Drug Enforcement Agency, 2022). These numbers pale in comparison to lives claimed by opioids, which are typically Schedule 2 compounds that killed 47,000 Americans by overdose in 2018 alone (Chandler et al., 2020). Further, case reports found in which DOC was attributed to death included the use of other compounds. For example, the presence of DOC was negligible (< 10 ng/mL in cardiac blood sample), but buprenorphine, cocaine and cannabis metabolites were also present complicating the cause of death (Lelievre et al 2022).

Importance as a Scientific Tool and Impact of Schedule 1 Classification

DOI was synthesised by the pioneering biochemist Alexander Shulgin, who was himself a consultant and researcher for the DEA (Nutt et al., 2020). Because commonly used psychedelics like psilocybin and LSD had been classified as Schedule 1 drugs in 1970, DOI and DOC have represented legal and accessible research chemical alternatives to working with traditional psychedelics that had been widely used for “psycholytic therapy” in the 1960s.

Since 2012, DOI has been utilised in approximately 1,200 research articles in leading journals such as Cell, Nature, and Science (Tullis, 2021). This number has only grown in the last two years. Due to its relative ease of accessibility and exceptional pharmacological profile, scientists have gravitated towards DOI and DOC as benchmark compounds in psychopharmacotherapy research. Further, DOI and its phenylethylamine analogs are being studied for chronic pain and

as anti-inflammatory agents (Nichols, 2022), making them an important tool to understand and develop better and less addictive pain medications than opioids.

The proposed Schedule 1 classification of DOI and DOC significantly reduces their accessibility as research chemicals for basic science research which is essential for novel drug development and understanding of conditions like pain, substance use and neuropsychiatric diseases. While laboratories may apply for a Schedule 1 DEA Licence, it is well understood amongst the scientific community that the financial barriers and bureaucratic red tape associated with obtaining a Schedule 1 licence and conducting research with these compounds amounts to a nearly prohibitive roadblock for many laboratories (Andreae, 2016). As such, many laboratories may simply choose not to apply for a Schedule 1 Licence, and abandon projects within this sector. Thus, the proposed reclassification of DOI and DOC will significantly hamper and deter medical research, and delay the development of future pharmacotherapeutics for treating a variety of neuropsychiatric, substance use and inflammatory disorders. All of this promising research relies on complete characterization of the 5-HT_2 receptors' function.

Conclusion

Activation of the 5-HT_2 receptors is a common mechanism of action for all serotonergic psychedelic drugs and is likely necessary for their profound emotional, cognitive, and sensory effects, as well as their therapeutic effects. The profound effects of psychedelics on end-of-life anxiety, treatment-resistant depression, and substance use disorders have been extensively reported upon in the scientific literature (Griffiths et al., 2016. Tullis, 2021, Davis et al., 2020, Jaster & Gonzalez-Maeso 2023). See **Fig. 2** taken from Tullis et al 2021.

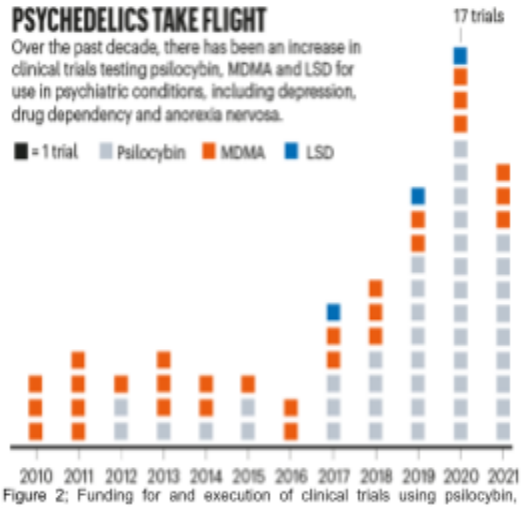

Figure 2; Funding for and execution of clinical trials using psilocybin, MDMA, and LSD for psychiatric research in humans have steadily increased over the last decade, peaking in 2020. Tullis, 2021. How ecstasy and psilocybin are shaking up psychiatry. *Nature*, *589*(7843), 506-510.

The process to obtain a Schedule 1 licence is long, arduous, and burdensome for many laboratories that want to work with such substances. Due to DOI and DOC's value to scientific research and relative lack of abuse, it does not follow scientific or logical reasoning to place it into Schedule 1 category. It is morally wrong to impede the efforts of scientists working to develop therapeutics that could prevent suicide, eliminate PSTD in combat veterans, break the cycle of drug addiction, and alleviate intrusive thoughts and compulsive symptoms in patients with conditions that do not respond to currently available drugs (Sellers & Leiderman, 2018).

The DEA should not move to reclassify DOI and DOC as Schedule 1 compounds. As we know, this practice promotes the development of untested analogues that may be more dangerous than the compounds they mimic. The cycle of designing analogues to bypass DEA regulations is a well-established phenomenon (Koh et al., 2018), and reclassifying DOI and DOC will lead

down the same road. The synthetic cannabinoid, AM-2201, became more prevalent following the DEA's scheduling of cannabinoid JWH-018. The two compounds are nearly identical, yet small changes can circumvent the DEA's scheduling (Crews, 2013). The chemical changes may lead to unexpected metabolic products which are more harmful to the consumer than the well-established safety profile of Δ^9-THC. Similar development of untested analogues may ensue if DOI and DOC are moved to schedule I.

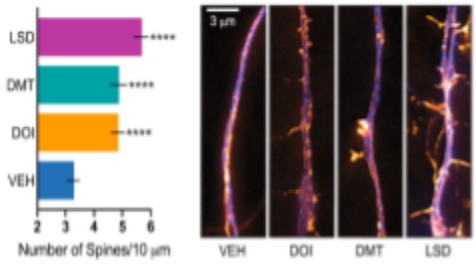

Figure 3: DOI and classic psychedelics like DMT and LSD swiftly promote the growth of dendritic spines, possibly acting as plastinogens to exert their rapid therapeutic effects in animal models of psychiatric disease.. Ly et al., 2018. Psychedelics promote structural and functional neural plasticity. Cell reports, 23(11), 3170-3182.

Lastly, classical and non-classical psychedelics like psilocybin and MDMA respectively, are coming down the FDA regulatory pipeline and these drugs will soon enter the consumer marketplace (MAPS 2023, FDA 2019). This resurgence in interest in psychedelic therapy is in no small part due to the data generated from basic science research using phenethylamines such as DOI to elucidate $5HT_2$ receptor pharmacology and actions on structural and synaptic plasticity (de la Fuente Revenga et al. 2021; Desouza et al. 2021; Ly et al. 2018). See **Fig. 3** taken from Ly et al. 2018.

It is of interest to all parties involved that we achieve a scientific understanding of the mechanisms of action of these compounds, which will be widely used in psychiatric settings within a matter of years (Nutt & Carhart-Harris, 2021).

Recommendations

1) Maintain DOI and DOC current non-scheduled status to expedite research into the **5-HT_2** receptors and their influence on disease states and chronic pain.

2) Establish a new framework to remove Schedule 1 DEA licensing requirements for any laboratories with a Schedule II licence, allowing them to study Schedule 1 substances. In the context of DOI and DOC, the DEA's own position is that the drugs do not appear "on the streets" via illegal dispersal from scientific research laboratories (Drug Enforcement Agency, 2023), so this modest allowance is unlikely to increase the amount of illegally trafficked DOI/DOC.

Lindsey Galbo, PhD (Integrative Physiology and Pharmacology, Wake Forest University); 2020-2021 American Society for Pharmacology and Experimental Therapeutics (ASPET) Policy Fellow, Co-Chair of the Scientific Policy Council for Students for Sensible Drug Policy. Founding President of Students for Sensible Drug Policy at Wake Forest School of Medicine. Lindsey currently studies the behavioural pharmacology of alcohol and cocaine, and investigating novel pharmacotherapies for treating alcohol abuse.

Elijah Z. Ullman, PhD Candidate (Molecular and Systems Pharmacology, Emory University), Co-Chair of the Scientific Policy Council for Students for Sensible Drug Policy. Founding President of Students for Sensible Drug Policy at Colorado State University. Elijah currently

studies the molecular pharmacology underlying conductance-modification of the NMDA Receptor and dynamics of the ion channel pore.

Alaina M. Jaster, PhD (Pharmacology and Toxicology, Virginia Commonwealth University); Dissertation focused on the molecular and neural circuits involved in DOI and psilocybin's effects in preclinical models of opioid-reward. Member of the Scientific Policy Council for Students for Sensible Drug Policy. Member of Trainee Editorial Board for *Psychedelic Medicine*, a scientific journal focused specifically on basic and clinical research of psychedelics. Founder and host of *Your Brain on Science,* a podcast and website focused on bringing psychedelic science to the public.

Tyler G. Ekins, PhD (Neuroscience, Brown University), Postdoctoral Research Fellow, University of Michigan, Michigan Psychedelic Center Collaborator. Tyler studies the acute and sustained effects of 5-HT_2 receptor agonists/psychedelic drugs on neuronal electrophysiology.

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