**UNITED STATES DISTRICT DEPARTMENT OF JUSTICE**

**Drug Enforcement Administration**

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

## STATEMENT OF DR. DAVID NUTT

My name is David Nutt. I am a neuropsychopharmacologist that specializes in the research of drugs that affect the brain and conditions such as addiction, anxiety, and sleep.

I currently serve as the Edmond J Safra chair in Neuropsychopharmacology and director of the Neuropsychopharmacology Unit in the Division of Brain Sciences at Imperial College London. I am also currently the chairman of Drug Science, a non-profit I founded in 2010 to provide independent, evidence-based information on drugs. Previously, I was a member of the UK Committee on Safety of Medicines and President of the European Colleges of Neuropsychopharmacology and the European Brain Council. I am a Fellow of the Royal College of Physicians, Royal College of Psychiatrists and the Academy of Medical Sciences. **M&TX 49** is my CV. **M&TX 48** is a list of publications listing me as an author or co-author.

I am offering this opinion as an expert in neuropharmacology (how drugs work in the brain) and drug abuse. Many of the opinions expressed herein echo or reproduce statements from papers I have authored or co-authored including **M&TX 1**, **M&TX 29, M&TX 30, M&TX 31, M&TX 32, M&TX 37, M&TX 59**. These opinions are my own and do not necessarily reflect the institutions I work for or am affiliated with.

## Background

I have worked as a neuropharmacologist and in the field of drug abuse for more than forty years. I started work as a clinical scientist and medical researcher after graduating from Downing College, Cambridge in 1972.

Previously I was a member and Chair of the Advisory Committee on the Misuse of Drugs (ACMD – 1998-2009), i.e., the UK government's chief drug adviser. I was asked to resign after discussing how alcohol and tobacco were more harmful than many illegal drugs, particularly psychedelics, a belief I held and currently hold to be consistent with research evidence as opposed to political considerations. I was dismissed from my post for challenging the evidential base for the UK drugs laws, and other members of the committee resigned in protest.

I have also been a member of the HEFCE/NHS Senior Lecturer Selection Panel and of the MRC Neuroscience Board. I served as the medical expert on the Independent Inquiry into the UK Misuse of Drugs Act (2000 Runciman report). I was the clinical scientific lead on the 2004/5 UK Government Foresight initiative "Brain science, addiction and drugs" that provided a 25-year vision for the area of science and public policy.

In 2010, the Times Eureka science magazine included me as one of the 100 most important figures in British Science, and the only psychiatrist.

I currently lead the Centre for Psychedelic Research at Imperial College London, which has a research team of about three dozen post-docs, students, fellows, and interns. The Centre also collaborates with almost two dozen other individuals across many countries. At the Centre, I have helped conduct a number of clinical trials with psychedelic compounds.[1]

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[1] For example, see **GX 3** at 921-930, Carhart-Harris, Robin et al. "Trial of Psilocybin versus Escitalopram for Depression." *The New England journal of medicine* vol. 384,15 (2021): 1402-1411. doi:10.1056/NEJMoa2032994

I am the Chief Scientific Officer of Awakn, Inc., a life sciences company researching, developing, and commercializing therapeutics to treat addiction with a near-term focus on Alcohol Use Disorder (AUD) and a medium-term focus on behavioral addictions. Awakn is currently investigating the use of Ketamine and MDMA to treat AUD and other new chemical entities for substance and behavioral addictions.

I edited the Journal of Psychopharmacology for over two decades and act as a psychiatry drugs advisor to the British National Formulary. I have published over 500 original research papers, a similar number of reviews and books chapters, 8 government reports on drugs and 36 books, including Drugs: Without the Hot Air, which won the Transmission Prize in 2014. I have written extensively on drugs of abuse, including amphetamine[2], alcohol[3], DMT[4], MDMA[5],

[2] Heal, David J et al. "Amphetamine, past and present--a pharmacological and clinical perspective." *Journal of psychopharmacology (Oxford, England)* vol. 27,6 (2013): 479-96. doi:10.1177/0269881113482532

[3] Nutt, David et al. "Alcohol and the Brain." *Nutrients* vol. 13,11 3938. 4 Nov. 2021, doi:10.3390/nu13113938

[4] Timmermann, Christopher et al. "DMT Models the Near-Death Experience." *Frontiers in psychology* vol. 9 1424. 15 Aug. 2018, doi:10.3389/fpsyg.2018.01424

[5] Nutt, David J, and Harriet de Wit. "Putting the MD back into MDMA." *Nature medicine* vol. 27,6 (2021): 950-951. doi:10.1038/s41591-021-01385-8

ketamine[6], psilocybin[7], cannabis[8], LSD[9], benzodiazepines,[10] GHB[11], opioids[12], and "designer drugs"[13]. I have also written extensively on topics such as opioid dependence,[14] drug dependence,[15] antidepressants,[16] and addiction.[17]

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6 Singh, Ilina et al. "Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight." *The lancet. Psychiatry* vol. 4,5 (2017): 419-426. doi:10.1016/S2215-0366(17)30102-5

7 Lebedev, Alexander V et al. "Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin." *Human brain mapping* vol. 36,8 (2015): 3137-53. doi:10.1002/hbm.22833

8 Schlag, Anne Katrin et al. "Medical cannabis in the UK: From principle to practice." *Journal of psychopharmacology (Oxford, England)* vol. 34,9 (2020): 931-937. doi:10.1177/0269881120926677

9 Sanz, Camila et al. "The entropic tongue: Disorganization of natural language under LSD." *Consciousness and cognition* vol. 87 (2021): 103070. doi:10.1016/j.concog.2020.103070

10 Baldwin, David S et al. "Benzodiazepines: risks and benefits. A reconsideration." *Journal of psychopharmacology (Oxford, England)* vol. 27,11 (2013): 967-71. doi:10.1177/0269881113503509

11 Gonzalez, Alejandro, and David J Nutt. "Gamma hydroxy butyrate abuse and dependency." *Journal of psychopharmacology (Oxford, England)* vol. 19,2 (2005): 195-204. doi:10.1177/0269881105049041

12 van Amsterdam, Jan et al. "Ranking the harm of non-medically used prescription opioids in the UK." Regulatory toxicology and pharmacology : RTP vol. 73,3 (2015): 999-1004. doi:10.1016/j.yrtph.2015.09.014

13 McNabb, Carolyn B et al. "Single chemical entity legal highs: assessing the risk for long term harm." Current drug abuse reviews vol. 5,4 (2012): 304-19. doi:10.2174/1874473711205040005

14 Fonville, Leon et al. "Functional evaluation of $NK_1$ antagonism on cue reactivity in opiate dependence; An fMRI study." *Drug and alcohol dependence* vol. 221 (2021): 108564. doi:10.1016/j.drugalcdep.2021.108564

15 Nutt, David J. "The role of the opioid system in alcohol dependence." *Journal of psychopharmacology (Oxford, England)* vol. 28,1 (2014): 8-22. doi:10.1177/0269881113504017

16 Artigas, Francesc et al. "Mechanism of action of antidepressants." *Psychopharmacology bulletin* vol. 36 Suppl 2 (2002): 123-32.

17 Nutt, David J et al. "The dopamine theory of addiction: 40 years of highs and lows." *Nature reviews. Neuroscience* vol. 16,5 (2015): 305-12. doi:10.1038/nrn3939; Daglish, Mark R C, and David J Nutt. "Brain imaging studies in human

I was awarded the John Maddox Prize from Nature/Sense about Science in 2013 for courage in standing up for science and evidence.[18] The British Association of Psychopharmacology awarded me its Lifetime Achievement Award in 2016.

## Research from the 1950s and 1960s

I am deeply familiar with and have written extensively about the extensive body of research from the 1950s and 1960s that reported largely positive effects and a lack of adverse clinical effects with psychedelics. Briefly, I will summarize that research.

Much of this early research with psychedelic or hallucinogenic compounds focuses on LSD. Without the recent advances of neuroscience technologies such as PET and MRI, the effects of hallucinogens the brain remained largely unknown. Nonetheless, by 1961, a large body of research and clinical science incorporating over 1000 papers, including over 40,000 participants, showed largely positive effects and a lack of adverse effects to hallucinogen use. (See **M&TX 1, M&TX 37** at 2**.**) Some considered it a major breakthrough treatment.

The research showed great therapeutic potential to LSD, particularly to treat substance abuse. I generally agree with a statement in a recent letter from the U.S. Department of Health and Human Services:

> NIH-supported research in the 1950s and 1960s investigated the potential beneficial effects of psychedelic drugs, especially LSD. These revealed promising effects in mood disorders and addiction, but were conducted prior to the development of modern ethical standards and human subjects protections, adopted by the Department of Health and Human Services in the 1970s. More recent psychedelics research studies have also seen the adoption of more rigorous experimental designs; advanced methodologies in non-invasive brain imaging, medicinal chemistry, and other areas; and a more critical approach to measuring outcomes and eliminating potential confounds. In addition to minimizing risks to study participants, these

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addicts." *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* vol. 13,6 (2003): 453-8. doi:10.1016/j.euroneuro.2003.08.006

[18] Other awardees of the John Maddox Prize include Anthony Fauci (2020)

> advances in ethics and methodology are enabling current investigators in the psychedelics field to gain a better understanding of both the safety and efficacy of emerging psychedelic therapies.[19]

For example, a recent meta-analysis showed that LSD of the older research showed that the effectiveness of LSD to treat alcoholism was as great as that of any other treatment of alcoholism since.[20] The study included from more than 500 participants. More recent research confirms the potential usefulness of psychedelic compounds in treating substance abuse. Specifically, some research shows an inverse correlation between psychedelic use and substance abuse, and that psychedelic compounds administered with psychotherapy are potentially effective and durable substance abuse interventions.[21]

Although some of these early studies were of relatively high scientific quality, because of the lack of appropriate controls, small numbers of participants, inappropriate statistical analyses, and lack of follow-up, few if any could be extrapolated into proof of safety and efficacy that would meet FDA approval standards. **M&TX 37** at 2.

As I discuss further below, our understanding psychedelics have come a long way since the first wave of clinical experimentation. While their potential range of psychological and psychiatric, as well as physiological risks remains to be fully understood, the physiological safety

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19 June 15, 2022 Letter from Joshua Gordon and Nora Volkow to Sen. Brian Schatz (https://s3.documentcloud.org/documents/22076083/response-from-nimh-nida-re-psychedelics-research-061522.pdf).

20 See **M&TX 1** at 1, **M&TX29** (citing Krebs T, Johansen P-O (2012) LSD for alcoholism: a meta-analysis of controlled trials. *J Psychopharmacol* 26: 994 – 1002).

21 See, for example, Pisano VD, Putnam NP, Kramer HM, Franciotti KJ, Halpern JH, Holden SC. The association of psychedelic use and opioid use disorders among illicit users in the United States. Journal of Psychopharmacology. 2017;31(5):606-613. doi:10.1177/0269881117691453.

of psychedelics is by now relatively well established and are one of the safest known classes of Central Nervous System drugs. I agree with Nichols (2016) (**GX 15** at 54), which explains:

> For decades, the media have largely portrayed psychedelics as extremely dangerous drugs; in fact, the classic serotoninergic psychedelics are generally considered very physiologically safe, certainly compared with opiates and psychostimulants.

The evidence discussed in Nichols (2016) establishes that most psychedelics, such as LSD and psilocybin "can be safely used under supervision," do not lead to addiction or dependence, and are not considered to be reinforcing. Indeed, not only is there no evidence that psychedelics have addictive properties, but the balance of evidence is that these compounds have *anti*-addictive properties. **M&TX 59** at 2, **M&TX 37** at 4.

From a physiologic standpoint they are in fact one of the safest known classes of central nervous system affecting drugs. Serotonergic hallucinogens do not directly affect dopaminergic systems, a pharmacology that appears essential for nearly all drugs that can engender dependence. Psychedelics do not cause addiction, and no overdose deaths have occurred after ingestion of typical doses of LSD, psilocybin, or mescaline. There are no known deaths, for example, attributable to a direct toxic effect of LSD. Research since the 1970s has found no or weak evidence that psychedelics are hazardous with respect to somatic health. The fast build-up of tolerance that minimizes the risk of dependence, and a lack of withdrawal symptoms has been repeatedly shown in the literature. **M&T 37** at 4 (citing studies).

## Drug Control, the Safety of Hallucinogens, and Abuse Potential

In the 1960s and 1970s, international drug treaties and drug control laws put the promising research on psychedelics to a halt.

By the 1960s, non-medical experimentation with psychedelic compounds, particularly LSD, led to an extreme media overreaction with sensationalized representations of hallucinogenic

substances. These encouraged governments to enact bans on LSD (and related psychedelic drugs such as psilocybin -magic mushrooms) so ending this period of scientific research. **M&TX 37** at 2. The banning of LSD, for example, appeared to be largely driven by political concerns — including that American youths were using it and as a result some declined to fight in Vietnam. The ban was justified by claims of harms such as people dying while trying to fly or having enduring psychotic experience, many of which were never proven.

Although LSD certainly causes hallucinations, more recent research shows that the risks and harms were greatly exaggerated. The most recent scientific evidence shows that LSD and other psychedelics are less harmful and have a lower potential for abuse than nearly every other class of controlled substances, including stimulants, opiates, cannabinoids and benzodiazepines.

Nonetheless, initial classifications decisions according to these laws in the 1960s and 70s were made in view of misunderstandings of the science and without the benefit of more modern science that allows a proper understanding of their pharmacologies and toxicologies. These classifications, including those under the Controlled Substances Act, appear to be unclear, inconsistent, and made for political rather than health-related reasons.

For example, in the 1960s, many believed that psychedelics were considered to have high abuse potential simply because there were frequent reports of their use. **M&T 37** at 3. Our understanding of problematic hallucinogen abuse is much different today and more nuanced. Hallucinogen Use Disorder (HUD) is described in DSM-V as a problematic pattern of hallucinogen use leading to clinically significant impairment or distress, and not all use of hallucinogenic substances meets this description, and only a problematic of behavior resulting from hallucinogenic use warrants a HUD diagnosis. **M&T 37** at 3.

A contemporary diagnosis of HUD is extremely rare. A recent study a prevalence of twelve-month and lifetime hallucinogen *use* among adults 18 and older in the US was 0.6% and 9.3% and that prevalence of twelve-month and lifetime HUD were 0.05% and 0.6%. The study showed that no association between hallucinogen use and HUD and increased disability or social isolation, and that hallucinogen use does not constitute a major public health risk.[22]

Another misnomer is toxicology. A prevailing public belief about psychedelics or hallucinogens is that they are neurotoxic. **M&T 37** at 7. Some early research from the 1960s and 1970s suggested hallucinogen use damaged chromosomes. **M&T 37** at 7 (citing studies). In many cases, these studies have been refuted or retracted. **M&T 37** at 7. Most researchers today do not consider classic hallucinogens such as LSD or psilocybin to be toxic, even in high doses. **M&T 37** at 7 (citing studies).

The initial decision to list psilocybin, LSD, or other serotonergic as Schedule I drugs as drugs having a "high potential for abuse" does not appear to be based on a careful consideration of their physical or psychological harms or the scientific evidence. And because research was interrupted so early, the methods and tools were not available to examine the neurobiological basis for the safety and efficacy of LSD and other related hallucinogenic compounds were not available. Based on a more recent understanding of science—particularly advances in the past 10 years—there is almost no relation between the harms of a range of psychoactive drugs and their legal status.

Today, there are accepted safety protocols for the use of hallucinogens under medical supervision. **M&TX 57** is a paper by Matthew Johnson, William Richards, and Roland Griffiths

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[22] Shalit, Nadav et al. "Epidemiology of hallucinogen use in the U.S. results from the National epidemiologic survey on alcohol and related conditions III." Addictive behaviors vol. 89 (2019): 35-43. doi:10.1016/j.addbeh.2018.09.020.

of Johns Hopkins entitled *Human Hallucinogen Research: Guidelines for Safety* cited in **M&T 37**. The Johnson paper provides guidance for the safe administration of high doses of hallucinogens—guidance that has been accepted as permitting the safe use of hallucinogens under medical supervision. The article explains that there is no evidence of neurotoxic effects with classical hallucinogens, but that physiological symptoms such as dizziness, weakness, tremors, nausea, drowsiness, paresthesia, blurred vision, dilated pupils may occur. These symptoms, however, are typically "unimpressive." **M&TX 57** at 6. I concur with the paper's assessment that hallucinogens are not typically drugs of dependence. **M&TX 57** at 7. The main risk with hallucinogen use is psychological, as the paper describes, a "bad trip" or anxiety, fear/panic, dysphoria, and/or paranoia that may accompany use. **M&TX 57** at 7. As the article further explains, these risks can largely be mitigated by appropriate supervision and/or prepared conditions surrounding use, including the selection of appropriate monitors/guides and having a trained supervisor present. **M&TX 57** at 11-19.

As an investigator, I have participated in and conducted numerous clinical trials with hallucinogens, and I know that, in general, they can be safely used under medical supervision. I am listed, for example, as one of the authors of a trial of psilocybin versus escitalopram (Lexapro) for depression. **GX 3** at 921-930. The study involved the use of psilocybin under medical supervision. There were no serious adverse events reported. When consumed in standard doses, psychedelics have generally been shown to be physiologically safe in humans. **M&T37** at 7.

The safety profile of these substances is often misunderstood. A good example of a deeply misunderstood substance is MDMA. In the 1980s, MDMA and related compounds were placed into Schedule I both in the United Kingdom and United States. It was once thought that MDMA had a relatively high fatal toxicity. A recent analysis showed that the publicly held view that is

incorrect. For twenty years, the only paper on MDMA published in a leading scientific journal was one purporting to show dopaminergic brain damage.[23] The article was later retracted after it emerged that the investigators had used methamphetamine by mistake.[24] Today, MDMA in conjunction with psychotherapy has been designated by FDA as a breakthrough therapy for PTSD due to its unique ability to enhance empathy and trust and reduce the brains responses to threats. **M&TX 59** at 4-5 (discussing MDMA's potential usefulness as treatment for PTSD).

In the Background section, DEA's 8-factor analysis notes that the abuse of hallucinogens can lead to "a variety of adverse health effects, such as paranoia, agitation, depression, and violent outbursts, towards self and others." **GX 11** at 2. The sole paper cited for this statement, the Carbonaro (2016) paper (cited in **M&T 37** at 5), does not study hallucinogens generally, but cites results from an anonymous internet survey conducted by researchers of a non-diverse population of past use of psilocybin mushrooms. Although I do not dispute that abusing certain hallucinogens may have adverse health effects – that is true of most of not all psychoactive compounds – it is difficult to extrapolate a conclusion about hallucinogens generally let alone the specific compounds at issue in this proceeding from Carbonaro (2016) (**GX 15** at 515).

Importantly, I understand that there is little meaningful way to revisit the initial abuse and safety findings made almost 50 years ago based on an incomplete (or outdated) understanding of the science and political considerations. And a Schedule I classification is "self-fulfilling": once a drug or substance is classified into Schedule I, research on therapeutic uses and refutation of harms is severely impeded. As the Beloin and Henningfield article suggests (**M&TX 60** at 9), an

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[23] Ricaurte, George A et al. "Severe dopaminergic neurotoxicity in primates after a common recreational dose regimen of MDMA ("ecstasy")." Science (New York, N.Y.) vol. 297,5590 (2002): 2260-3. doi:10.1126/science.1074501

[24] https://www.science.org/doi/10.1126/science.301.5639.1479b?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

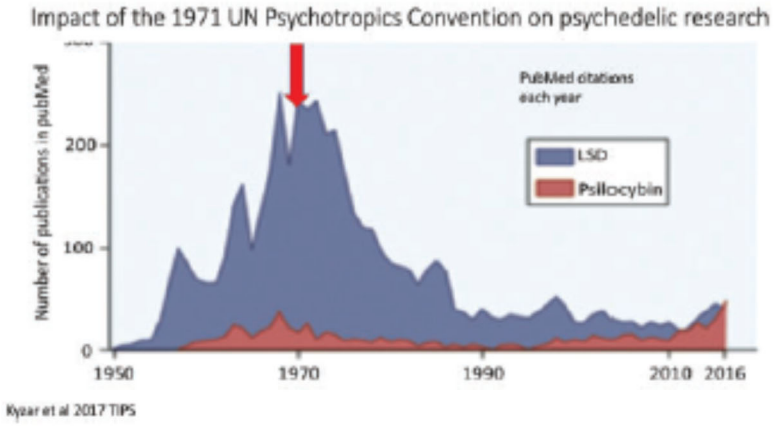
unintentional scientific medical bias evolved due over the past approximately one-half century due to the Schedule I legislative classification of having "no currently accepted medical use." That classification contributed to a multi-decade long deterring of clinical research, and an almost total cessation of its funding, such that few clinical studies have been finalized to date. With stalled clinical research, the stated premise "drugs with no currently accepted medical use" may have subtly and unintentionally institutionalized itself into a scientific medical norm.

In one case, abuse potential has been rigorously revisited. I am aware of **M&TX64**, a paper by Matthew Johnson and other researchers assessing the abuse potential of medical psilocybin, a Schedule I substance, according to the eight factors of the CSA. Psilocybin is a compound I have clinically studied as well. Psilocybin is tryptamine. **M&T 37** at 4 (citing **M&TX 64**). The Johnson paper notes, among other items, that research has shown psilocybin to have weak reinforcing effects, is not toxic, and does not show physiological dependence or withdrawal symptoms. One study showed psilocybin had a lower risk of dependence than caffeine. **M&T 37** at 4. Using the Addiction Research Centre Inventory, the authors found a major difference between the abuse potential of psychedelics, as compared with other substances that carry a high risk of compulsive pattern of repetitive use and abuse.

Obtaining permissions to study Schedule I substances takes a significant amount of time, costs significant amounts of money, and subjects the license holder to regular administrative reviews. **M&TX 59** at 3. As a result, many researchers and small businesses that would like to work on these substances and develop new medicines lack the resources to do so. Even researchers who use only sub-hallucinogenic doses must comply with these regulations. For example, in a trial of psilocybin for patients with cancer in the United States, researchers were required to ensure that the few milligrams of substance were weighed daily by two people to protect against theft.

Moreover if an investigator can obtain all the necessary approvals and licenses to study a Schedule I drug, the problem then becomes that obtaining the pharmaceutical substance, because these substances are not available from most chemical manufacturers because they are Schedule I substances. Those that do supply these substances can charge exorbitant prices, for example, $12,000 per gram for psilocybin. **M&TX 59** at 3. Until recently, no company was committed to manufacturing medical grade psychedelics. **M&TX 31** at 4.

It is therefore not surprising then that Schedule I classifications also operate as a powerful deterrent to grant-giving bodies. Below, for example, is a graph showing the impact of worldwide Schedule I classifications number of publications in PubMed (**M&T30** at 4):




Laws relating to Schedule I drugs thus have had a deleterious impact on the progress of neuroscience research and treatment development. Although the therapeutic potential and academic value of studying these drugs is clear, further investigation has been hampered and continues to be hampered by the hurdles and costs that often unnecessary regulations impose. Perhaps more important for the neuroscience community is the fact that human brain studies on phenomena such as hallucinations and consciousness and the role of the 5HT2A receptor have been massively impeded by these regulations.

Although governments often maintain that current drug regulations do not prevent research because some people have been able obtain licenses, for at least the reasons I just explained, there has been a de facto severe censorship on research into many psychoactive drugs over the past 50 years. The one exception has been government sponsored studies focused on identifying negative (for example, brain-impairing) properties of psychoactive drugs.

These initial classifications therefore make it exceptionally difficult to refute the initial half-century old finding of a "high potential for abuse," which was based on incomplete and in many cases, inaccurate science.[25] The science has progressed—albeit far slower than it should—due to persistence and despite these formidable obstacles. And that science shows that many hallucinogenic Schedule I compounds do not have a high potential for abuse—certainly and unambiguously when compared to far more dangerous substances in other schedules, such as opiates and stimulants.

For example, in 2010, along with Leslie A King, Lawrence D Phillips, I weighed the relative harms of twenty different drugs using a technique called multi criteria decision analysis. **M&TX 32**. I consider this to be the most detailed, transparent, and objective measure of drug harms that has ever existed. We convened a group of 30 experts to look at all the harms that drugs produce. The group returned thousands of harms that could be condensed into 16 variables, 9 of which harmed the user and 7 of which harmed society. Social, psychological, and physical harms were all accounted for. Drugs were scored out of 100 points, and the criteria were weighted to indicate their relative importance (**M&TX 32** at 5). The results of the study are shown below.

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[25] Nutt, David J et al. "Effects of Schedule I drug laws on neuroscience research and treatment innovation." *Nature reviews. Neuroscience* vol. 14,8 (2013): 577-85. doi:10.1038/nrn3530

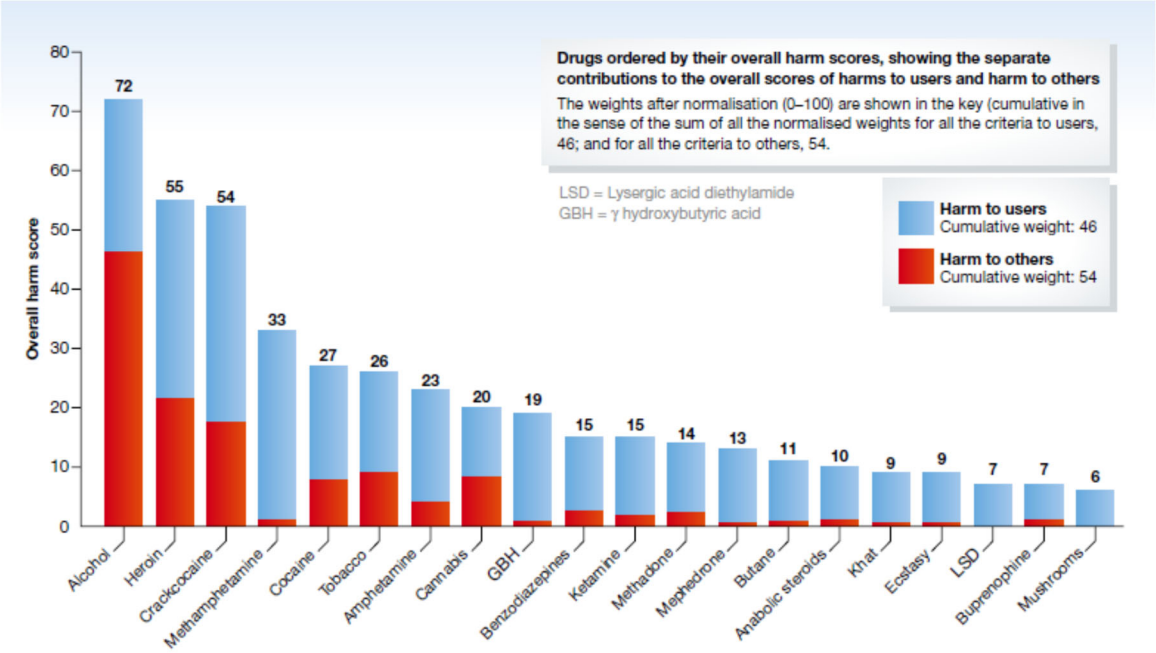


**Figure 1.** The relative harms of twenty different drugs from [12].

The overall weighted scores are shown below (**M&TX 32** at 7):

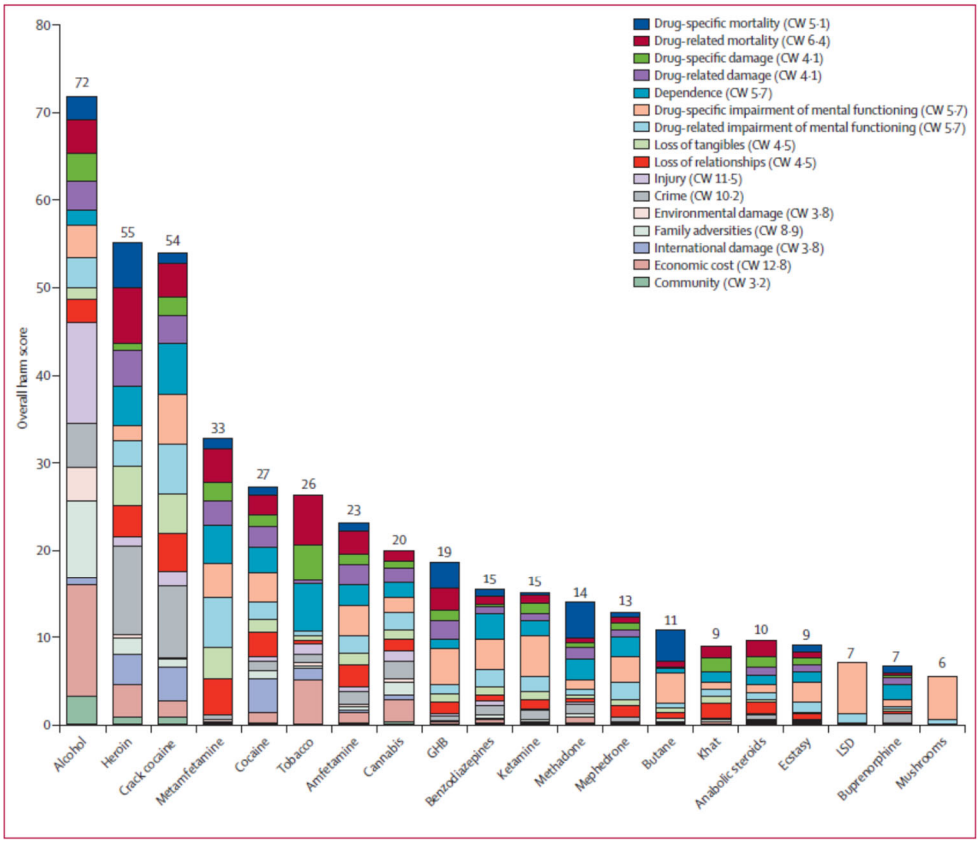


*Figure 4:* **Overall weighted scores for each of the drugs**

I note that in the case of LSD and mushrooms—two serotonergic hallucinogenic substances and tryptamines that, of the substances studied, may be the most comparable to the substances at issue in this case—nearly all harm comes from drug specific mental impairment and not drug specific or related mortality. Using a grant from the European Commission, we replicated the study using 30 European experts from 20 different countries and obtained similar results.

These studies confirm that the harms of heroin, crack cocaine, methamphetamine, and cocaine cause greater harm to society and to users. Benzodiazepines also cause greater harm. In contrast, hallucinogenic substances such as LSD and psilocybin mushrooms neither present public health risks nor present much harm to others. They present mild harms to users.

In sum, we know more about controlled mind-altering drugs or substances today when compared to fifty years ago. The widespread perception that because a substance is currently classified as a Schedule I drug, it necessarily poses a significant danger to humans still exists among lawmakers and the public. But this perception is generally incorrect. The scientific and medical evidence of today shows that there is a tenuous relationship between the harms of drugs and their legal classifications. We know more about their potential for medical benefit and harm to individuals and society—and relative potential for medical benefit and harm when comparing controlled drugs. And if an initial classification of a substance was a mistake based on incomplete or grossly misunderstood science, then a subsequent classification predicated on the initial classification is no less a mistake. Drugs placed in the most restrictive schedules often pose more harm to individuals and society than drugs in less restrictive schedules. The most up-to-date science unequivocally shows that hallucinogens such as LSD and psilocybin mushrooms have a low potential for harm to the individual and society, both in relative and absolute terms.

## Recent Advances in the Scientific Understanding of Hallucinogens and the Importance of Research

In 2014, I wrote that in the "fifty years since the enactment of these laws, there has been little new research despite remarkable advances in neuroscience technologies such as PET and MRI that would allow a greater understanding than of its actions than were possible in the 1950s." **M&TX 29** at 2. Since that time, in the past decade, research on these compounds has been re-established and accelerated by a few groups around the world, culminating in new centers for psychedelic research at Imperial College London, Johns Hopkins University, New York University, UC Berkeley, Yale University, Mount Sinai, Icahn School of Medicine, UT Austin Dell Medical School, and the University of Wisconsin.

Today, neuroscientists apply modern brain imaging techniques such as positron emission tomography (PET), single photon emission computer tomography (SPECT), magnetic resonance imaging (MRI), electroencephalogram (EEG), and magnetoencephalography (MEG) to the study of these drugs in the laboratory, allowing for new and valuable understandings about their brain mechanisms including neuro-correlates of their unique psychological effects.[26]

For example, figure 1 from the article I co-authored *Psychedelic Psychiatry's Brave New World* (**M&TX** 31 at 2) shows the Three Levels of Activity of Psilocybin. The type of imaging used to produce these images and understanding was not available in 1970.

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[26] For example, Carhart-Harris, Robin L et al. "Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms." *Scientific reports* vol. 7,1 13187. 13 Oct. 2017, doi:10.1038/s41598-017-13282-7; Roseman, Leor et al. "Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression." *Neuropharmacology* vol. 142 (2018): 263-269. doi:10.1016/j.neuropharm.2017.12.041.

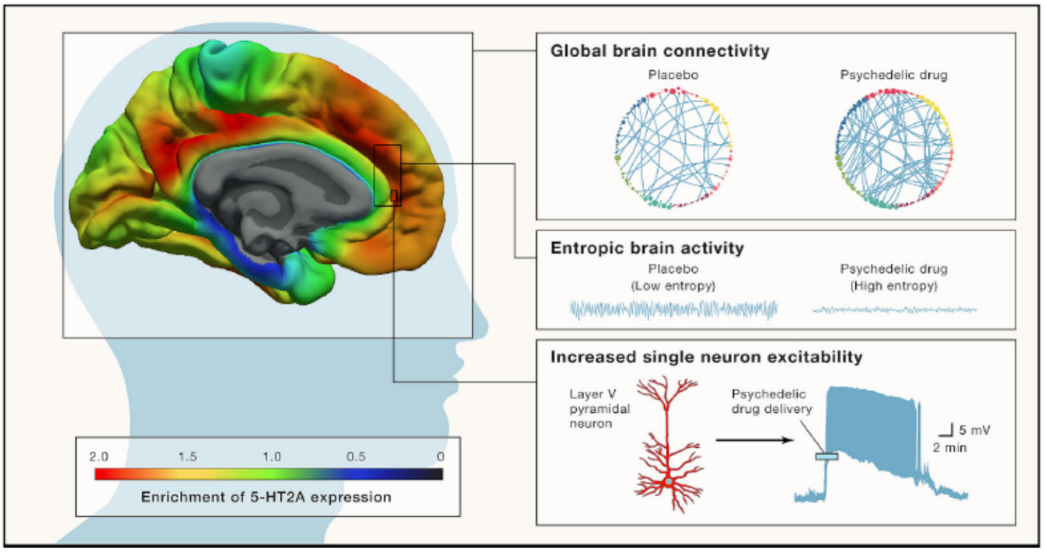


**Figure 1. The Three Levels of Activity of Psilocybin**
Psilocybin, along with other serotoninergic psychedelics, acts to stimulate 5-HT2A receptors in the cortex, particularly layer 5 pyramidal cells. This leads to massive depolarization and thence rapid repeated firing of these neurons (lower inset). Because these neurons are responsible for organizing cross-cortical integration, this activity results in a profound alteration of cortical signaling. Both magnetoencephalography and electroencephalography measures reveal a major loss of typical rhythmical activity, resulting in a state of extreme desynchronization or enhanced entropy (middle inset). Also, these layer 5 neurons mediate the "top down" perceptual and cognitive predictions (so called "priors"), which form the basis of normal brain processing. Thus, under psychedelics the brain "escapes" from its usual tightly constrained and predictable ways of working; this leads to a global increase in connectivity (top inset) that allows new insights into past behavior, memories, actions, feelings, and beliefs. These in turn can lead to therapeutic changes in conditions such as depression and addiction, which are driven by dysfunctional brain processing. Average density map for 5-HT2A receptor adapted from Beliveau et al. (2017).

Most of this groundbreaking research with psychedelics has taken place in the past decade. This neurobiological research is being supplemented large-scale epidemiological studies as well as clinical or experimental research. This modern, state-of-the-art research is beginning to show why psychedelic drugs, in connection with therapy, show promise in treating mental disorders. Current treatments (such as antidepressants) suppress symptoms by protecting against psychological stressors that perpetuate depression but often do not directly address the underlying biopsychosocial causes. In contrast, psychedelic therapies create a therapeutic window opened via the effects of the drugs to facilitate insight and emotional release and, with psychotherapeutic support, a subsequent healthy revision of outlook and lifestyle. For example, in addictions, the object of addiction takes on the role of negative thinking in depression, driving behavior that is specific, narrow, and rigid; addicts ruminate on relief afforded by the object, how to get it, how to pay for it, and so on.

In *Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies*, **M&TX1**, we systematically reviewed 10 post-millennium psychedelic-assisted therapy studies (16 papers) for mental health indications, with a total of 188 patients being dosed with the hallucinogenic compounds psilocybin, LSD or ayahuasca/DMT. Several points are notable. There were no reports of any serious cardiovascular adverse events in any of the trials. For the ayahuasca trials, the most common side effects reported vomiting (52%), nausea (32%), and transient anxiety (23%). In the psilocybin trials, the most common side effects reported among this group were transient anxiety/fear (27%), headache (22%), and nausea/purging (12%). In the LSD trials, the most frequent adverse events were illusions (72.7%), feeling cold (45.4%), and a feeling of abnormality (40.9%). Overall, across all reported trials, the side effects were mild and transient. No severe adverse events were reported.

Although our understanding of hallucinogen abuse has dramatically improved, their potential range of psychological and psychiatric, as well as physiological risks remains to be fully understood. Nonetheless, several points have been established. Withdrawal symptoms typically do not occur with hallucinogens. Psychedelic or hallucinogenic use does not conform to the profile of clinical features representing other types of drug dependencies, for example, opioid dependence. **M&T 37** at 3. Drugs having hallucinogenic properties are not reliably self-administered in animal studies. **M&T 37** at 4. Very few hallucinogen users experience an inability to cut down or control use, a key indicator of dependence. The vast majority of hallucinogen users do not transition to hallucinogen dependence. Research has repeatedly shown that psychedelics do not cause dependence or compulsive behavior. **M&T 37** at 4 (citing studies). The effects of psychedelics are not universally euphoric (and can be dysphoric), tolerance develops quickly, which tolerance cannot be overcome by dose escalation. **M&T 37** at 4.

For these reasons, in 2018, SAMHSA ranked psychedelic use at the bottom in terms of their dependence risk. **M&TX 31** at 4. [27] In comparison to other recreational drugs, psychedelics rank as the lowest in the United States, with 1.9 emergency department visits per 100,000 in 2011. This is consistent with the 2017 SAMHSA rankings. **M&T37** at 10. There is little evidence of an association between psychedelic use and mental health problems. **M&T37** at 6. The main risk of psychedelic use is a "bad trip" or challenging experience. **M&T37** at 5.

Despite major advances in psychedelics research, there is a lot we still do not know. For the reasons I have explained, pharmacological treatments for psychiatric disorders have been painfully slow. Most medicines used today are derivatives of drugs discovered in the 1950s through serendipity and refined through pharmacological modifications. Further research is needed to examine the efficacy and safety of psychedelic drugs for mental illnesses and substance use disorders, including the effects of repeated exposure and potential interactions with existing treatments. For this reason, placing more psychedelics into Schedule I—including those that show potential to be useful therapies—not only impedes science, but presents a risk to the public health.

Unlike other classes of drugs, psychedelics have a particularly important role in science and medicine because they can induce unique and specific changes in consciousness that can be instrumental in the treatment of mental illnesses, substance abuse disorders, emotional dysregulation, and other brain-based conditions. There have been studies, for example, showing efficacy of psilocybin in alcoholism and tobacco dependence. **M&TX 31** at 1 (citing (Rucker et al., 2018)).

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[27] https://www.samhsa.gov/data/sites/default/files/cbhsq-reports/NSDUHDetailedTabs2017/NSDUHDetailedTabs2017.htm#lotsect1pe

Beyond the production of new medicines, psychedelics and hallucinogenic substances are critically important in research to understand how the brain activity. (See, for example, **M&TX 31** at 2-4, describing how psychedelic substances have provided essential insights into the 5-HT2A receptor.) The placement of these compounds into Schedule I (and any other hallucinogenic compound that shows little signs of actual abuse) thus presents a risk to the public health because it could interfere with research that could provide insight into the neurobiological mechanisms underlying neurobiological disorders.

As an example, consider buprenorphine. Buprenorphine is a prescription drug used as replacement therapy to treat opioid dependance. The development of this treatment has proven instrumental in addressing the opioid epidemic. But buprenorphine pharmacotherapy is only possible because research on opioids has substantially improved our understanding of the brain mechanisms of addiction allowing for new treatments for heroin addiction.

The legal justification regulating drugs is to reduce harms. Yet paradoxically, when infrequently abused drugs that are similar to other drugs of abuse and useful in research are hastily restricted or banned, we increase the risk to society by impeding the very research that could allow us to better understand the mechanisms and develop improved treatments for drug abuse. If we understood the effects of hallucinogenic drugs better, we might be able to develop and deploy analogues that maintain therapeutic potential but have fewer adverse effects. Indeed, I understand that at least one of the substances at issue in this proceeding is an analogue that may maintain the therapeutic potential of FDA breakthrough therapies but have fewer adverse effects.

The Eight Factor analysis notes that the tryptamine substances at issue elicit pharmacological effects similar to other Schedule I substances like LSD, which the analysis claims has "high abuse potential." **GX 11** at 5. But as I have explained, as a scientific matter, although

"high abuse potential" may have described a common or popular understanding of certain hallucinogens in 1970 when the Controlled Substances Act was enacted, that conclusion does not remain true today based on rigorous science. Contemporary research indicates that most hallucinogens do not have a high abuse potential. Certainly, they do not have an abuse potential that is equal to or greater than other controlled substances such as opiates, stimulants, or benzodiazepines.

Without a pattern of actual abuse, based on today's scientific understandings and evidence, a finding that a drug or substance has similar pharmacological effects to LSD or psilocybin, to the extent it says anything, is evidence that a drug has a *low* potential for abuse, or at least *lower* potential for abuse when compared to more dangerous and addictive drugs such as stimulants like cocaine, opiates, or benzodiazepines.

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

Executed on 7/_14_/22

**Dr. David Nutt**