EMBO reports

Mind-altering drugs and research: from presumptive prejudice to a Neuroscientific Enlightenment?

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The Enlightenment was a philosophical, intellectual and cultural movement of the late 17th century that stressed reason, science and freedom of thought over dogma, blind faith and superstitious deism. One of the driving forces of the Enlightenment was the oppression of research and original thought imposed by the Catholic Church. The most extreme example was when astronomers were told that they could not study the universe in case they challenged conventional wisdom. In 1616, the Church banned the writings of Copernicus who had revealed for the first time that the Earth revolved around the Sun and not the other way round as the Church had been teaching. They also threatened Galileo with death unless he desisted in his research on the same topic and recanted his findings. This ban on knowledge lasted for 150 years, and it is probably the worst example of scientific censorship in history.

> *"... current DEA regulations in the USA make it impossible for federally funded researchers to study medicinal cannabis or even the effects of its liberalisation"*

Over the past 50 years, a similarly far-reaching censorship has affected neuroscience and clinical research though it is hardly being discussed and indeed may not be known of by most researchers. This particular censorship was enacted by the United Nations (UN) in 1961 and 1971 by putting a range of mind-altering drugs into Schedule 1 of controlled substances: this is the highest level of control. This decision has efficiently ceased research into these drugs to the detriment of researchers; worse still, many thousands of patients have been denied potential new medicines.

The basis for this ban is the Single Convention on Narcotic Drugs of 1961, an international treaty that prohibits the production, trade and use of specific drugs except under a licence. As of 2013, it has 184 state signatories. Many mind-altering drugs are controlled under the Single Convention, which includes different schedules of restrictions (Table 1). Some of these drugs are in Schedule 1 on the grounds that they have no medicinal value. It means that researchers need a special and expensive licence to work with cannabis or MDMA, but not for using heroin or cocaine. Clearly, there is no rational or scientific basis to this distinction, and it is exactly the opposite of what one would predict from previous assessments of harms (Fig 1).

The ostensible reason for this strict control is the recreational use of these drugs, particularly by young people. The controls are supposedly designed to reduce their harms, although in many cases, these harms

Table 1. The legal status of narcotics under the UN single convention

UN Schedule 1 drugs	UN Schedule 2 drugs	Non-scheduled but illegal in many countries	Legal drugs (in most countries)
Psychedelics for example LSD, psilocybin and mescaline	Heroin morphine and many other full agonist opioids	Ketamine and analogues	Alcohol
MDMA and analogues	Cocaine	GHB and related GABA agonists	Tobacco/nicotine products
Cannabis THC and many of its analogues	Amphetamines including met-amphetamine	Khat and related cathinones	Caffeine

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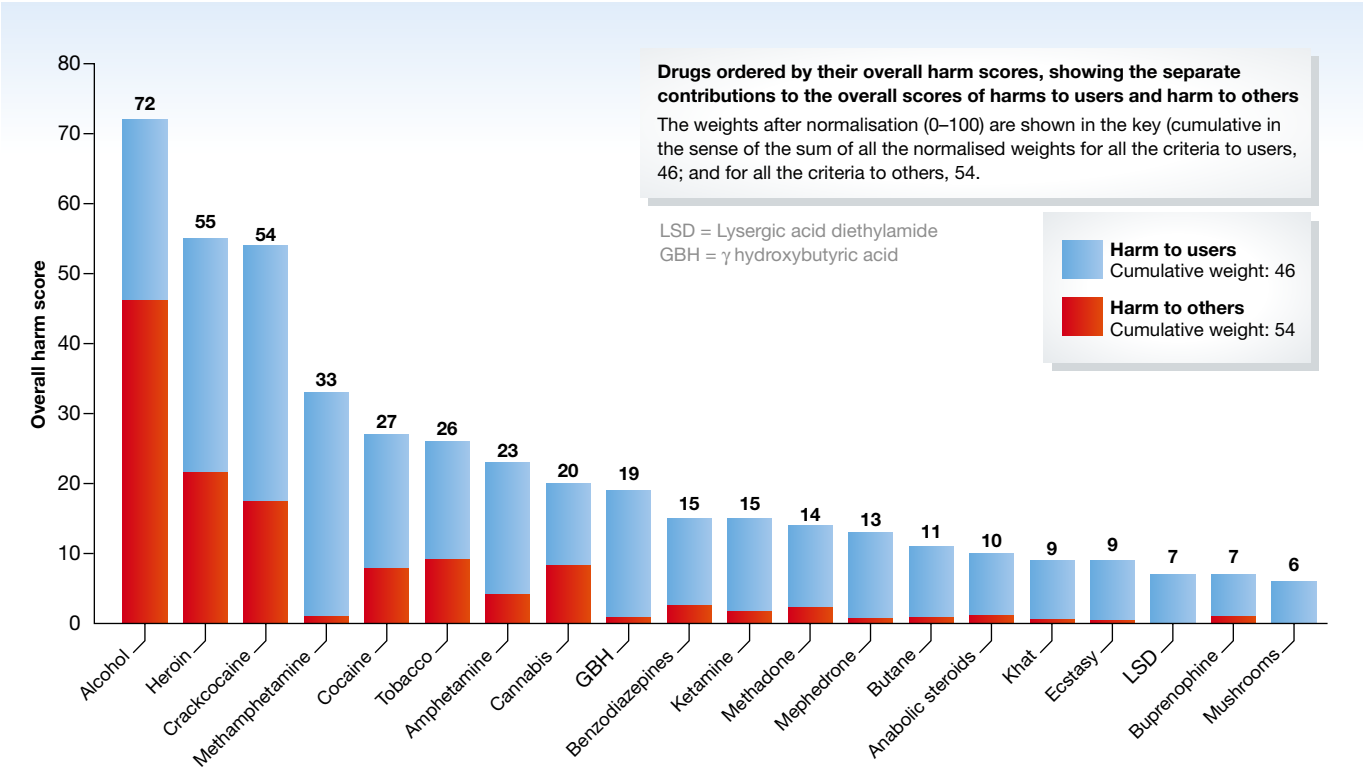

Figure 1. The relative harms of twenty different drugs from [12].

may be more perception than reality. Moreover, the harms that derive from the controls themselves may greatly exceed the harms of the drugs. For example, arrests and imprisonment for drug offences destroy lives and families, and there is no scientific evidence that the "softer" drugs, such as cannabis and ecstasy, exert possible deleterious effects that could justify such draconian penalties.

"Getting a Schedule 1 licence in the UK costs about £6,000 in fees and other costs and takes a year to issue"

The blind pursuance of these UN regulations has had equally disturbing impacts for research albeit this is less discussed. For example, about 1,000 studies involving some 40,000 subjects investigated the effects of LSD before it was banned in the 1960s. This impressive body of research was possible because the inventor of LSD, the pharmaceutical company Sandoz, made it widely available. The worldwide scientific community saw it as a hugely important scientific advance for the study of the brain and the development of new treatments. In the 50 years since its ban, there has been no new research despite the remarkable advances in neuroscience technologies such as PET and MRI that could allow a much greater understanding of its actions than were possible in the 1950s. A recent meta-analysis of the old clinical trials in which LSD was used to treat alcoholism [1] found that the effect size of LSD was as great as that of any other treatment of alcoholism developed since. As an effect of the ban, the therapeutic potential of LSD has been denied to patients.

Other Schedule 1 psychedelic drugs have similar potential for treatment uses. Psilocybin, which is obtained from "magic mushrooms", is a shorter-acting version of LSD that has been shown to be a possible treatment for obsessive-compulsive disorder [2] and cluster headaches [3]. Cannabis is arguably the oldest medicine in the world and was popular with Queen Victoria of England for period pains and childbirth. However, since cannabis was put into Schedule 1 in the 1961 UN convention, most countries have stopped its medical use, the notable exception being the Netherlands whose enlightened policies on recreational drug controls have been a beacon of sanity in a morass of prejudice and prohibition. It is important to note that the Dutch policy is still compliant with the UN convention, which the Netherlands signed.

The recent liberalisation of medicinal cannabis in many states in the USA reflects the public hostility to how the US government has interpreted the UN conventions, with hundred of thousands of people imprisoned, some for life, for cannabis offences. However, despite the fact that nearly half the US states allow its medicinal use, the US government mimics the prohibitionist stance and the US Drug Enforcement Agency (DEA) continues to pursue local cannabis providers. Hopefully, the decision by Colorado and Washington to make cannabis fully legal—which is in direct breech of the UN conventions—will provoke a change. Yet, current DEA regulations in the USA make it impossible for federally funded researchers

to study medicinal cannabis or even the effects of its liberalisation.

Governments have argued that the regulations do not prevent or hinder research as scientists could get licences to store and use these drugs. However, since there is almost no research, there has been a *de facto* ban. This censorship derives from the enforcement agencies misrepresenting the evidence about the harms of these drugs and denying their therapeutic potential by putting them into Schedule 1. In effect, the enforcers have assumed authority over the scientific and medical community without providing sufficient scientific evidence or other justification for their prohibitive policies. This is exemplified by this chilling exchange between US Senator Robert Kennedy and the USA Drug Enforcement Agency in the 1960s: "Why if [clinical LSD projects] were worthwhile six months ago, why aren't they worthwhile now? We keep going around and around. If I could get a flat answer about that I would be happy. Is there a misunderstanding about my question?" [4]. Despite being the most powerful person in US politics then, not even Kennedy could deny the censorship of research on LSD.

The extent of this censorship has been remarkable both in its depth and international reach, because most countries have signed up to the UN conventions. The only honourable exceptions have been the Dutch with their stance on cannabis and MDMA research and Switzerland where research with psilocybin has trickled along. I can think of no other comparable research censorship; the Bush administration ban on embryonic stem cell research had comparable impact but only for federally funded US scientists.

What stops the scientists from research? The most important hurdle is that complying with the regulations is very time-consuming and expensive. Getting a Schedule 1 licence in the UK costs about £6,000 in fees and other costs and takes a year to issue. This applies equally to the forensic chemist who needs a few milligrams as test standards and a large-scale pharmaceutical manufacturer and distributor. Even if the doses to be held are less than those that would produce a mind-altering effect in a single individual, the same licence is required. These rules have just made the most promising new PET tracer for the 5HT system illegal in the UK [5] without any recognition that the drug regulators even knew it had this scientific use. Obtaining the drugs is also difficult and expensive. We have been quoted more than £3,000 per 2-mg dose of psilocybin for an MRC-funded clinical trial on depression. Comparable compounds that are not controlled can be obtained for $1/100^{th}$ of that price. Some of the expense comes from the fact that there are almost no production facilities in the world that have the necessary licences for holding and dispensing Schedule 1 drugs.

> *"With so little work being done, there is little knowledge of the remarkable value that the study of these drugs might have for neuroscience or clinical treatment"*

With so little work being done, there is little knowledge of the remarkable value that the study of these drugs might have for neuroscience or clinical treatment [6]; thus, others do not even think about using them. I would argue that these drugs are central to certain areas of neuroscience research. How can one explore consciousness without perturbing it? Psychedelics offer a remarkable and safe way of doing this, and early results show unexpected and intriguing findings [7,8] and clinical implications [9]. I would contend that explaining the psychedelics state is one of the great challenges for human neuroscience research.

Similarly, the study of positive emotions such as trust and empathy requires tools to induce these states; MDMA is the most effective and powerful drug to achieve this. We have shown it to be perfectly safe in controlled conditions and to alter the impact of negative memories through changes in limbic blood flow [10], which may explain its potential for addressing treatment-resistant post-traumatic stress disorder [11]. There is a profound contrast with drugs such as heroin and metamphetamine, which are both widely used, mainly in animals, to understand the brain changes that underlie addiction and relapse. These substances are allowed in the laboratory both *because* they are addictive and *despite* them being addictive. Would it not make sense to encourage research on other psychoactive drugs that have less strong or even no addictive properties?

I suspect that this ongoing dearth of research is tacitly encouraged by governments as it might challenge the *status quo*. Lack of new evidence also perpetuates the justification for severe controls on the grounds of the precautionary principle. Politicians have tried to stop our work on psilocybin and MDMA on the grounds that it uses "illegal drugs"[13]. They have also attempted to disrupt our psilocybin depression trial by using Freedom of Information requests to our universities and the MRC.

The failure of the scientific community, particularly neuroscientists, to protest this effective censorship of research on these drugs that could offer so many insights into human brain function and such great opportunities for new treatments is one of the most disturbing failures of science in the past century and it must be rectified. How can we achieve this goal?

The best way is to overcome the UN conventions that put these drugs in Schedule 1. Surely, it is now time for the (neuro)scientific community to make the case to their governments for such changes? In the meantime, individual countries could exempt hospitals and research organisations from the need to apply for Schedule 1 licences. Preclinical research could be performed more easily if a licensing category was created for scientists who need only small amounts. Cellular work and work in animals, including transgenic animals, requires only a few milligrams of most substances, and even less with LSD. If the quantity needed for research is less than a single human dose, why is diversion control necessary at all?

> *"Preclinical research could be performed more easily if a licensing category was created for scientists who need only small amounts"*

I finish with an insight from one of the pioneers of using mind-altering drugs to explore the nature of consciousness—Aldous Huxley—whose words about the suppression of justice have considerable resonance with the current restraint of

neuroscience research. "Great is truth, but still greater, from a practical point of view, is silence about truth. Facts do not cease to exist because they are ignored. By simply not mentioning certain subjects… totalitarian propagandists have influenced opinion much more effectively than they could have by the most eloquent denunciations."

Conflict of interest

The author declares that he has no conflict of interest.

References

1. Krebs T, Johansen P-O (2012) LSD for alcoholism: a meta-analysis of controlled trials. *J Psychopharmacol* 26: 994 – 1002
2. Moreno FA, Wiegand CB, Taitano EK, Delgado PL (2006) Safety, tolerability and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *J Clin Psychiatry* 67: 1735 – 1740
3. Sewell RA, Halpern JH, Pope HG Jr (2006) Response of cluster headache to psilocybin and LSD. *Neurology* 66: 1920 – 1922
4. Lee MA, Shlain B (1985) *Acid Dreams: The Complete Social History of LSD, the CIA, the Sixties and Beyond*. New York, NY: Grove Weidenfeld, pp 93
5. Nutt DJ, King LA, Nichols DE (2013) New victims of current drug laws. *Nat Rev Neurosci* 14: 877
6. Nutt DJ, King LA, Nichols DE (2013) Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nat Rev Neurosci* 14: 577 – 585
7. Carhart-Harris RL, Erritzoe D, Williams TM, Stone JM, Reed LR, Colasanti A, Tyacke RJ, Leech R, Malizia AL, Murphy K *et al* (2012a) Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *PNAS* 109: 2138 – 2143
8. Muthukumaraswamy S, Carhart-Harris R, Moran R, Brookes M, Williams M, Erritzoe D, Sessa B, Papadopoulos A, Bolstridge M, Singh K *et al* (2013) Broadband cortical desynchronisation underlies the human psychedelic state. *J Neurosci* 33: 15171 – 15183
9. Carhart-Harris RL, Leech R, Williams TM, Erritzoe D, Abbasi N, Bargiotas T, Hobden P, Sharp DJ, Evans J, Feilding A *et al* (2012b) Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with psilocybin. *Br J Psychiatry* 200: 238 – 244
10. Carhart-Harris RL, Wall MB, Erritzoe D, Kaelen M, Ferguson B, De Meer I, Tanner M, Bloomfield M, Williams TM, Bolstridge M *et al* (2013) The effect of acutely administered MDMA on subjective and BOLD fMRI responses to favourite and worst autobiographical memories. *Int J Neuropsychopharmacol* DOI 10.1017/S1461145713001405
11. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Martin SF, Yazar-Klosinski B, Michel Y, Brewerton TD, Doblin R (2013) Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *J Psychopharmacol* 27: 28 – 39
12. Nutt DJ, King LA, Phillips LD (2010) Drug harms in the UK: a multicriteria decision analysis. *Lancet* 376: 1558 – 1565
13. United Kingdom House of Commons Hansard Debates (2012). Available at: http://www.publications.parliament.uk/