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The Acid Test: Evidence for using psychedelics to treat addiction

Abstract: Addictions are among the most important global health burdens, particularly in the industrialised world. Around 5% of annual global deaths can be attributed to harmful use of alcohol alone[1], and there are a huge and growing number of substances that can cause harmful addictive patterns in vulnerable people. One of the groups of substances showing some promise in aiding recovery from addiction, particularly in combination with therapy, are psychedelics. However, important research into these consciousness-altering substances is being hindered by stigma and legal barriers. This essay will focus on the emerging evidence of the potential benefits of psychedelics in addiction, some proposed explanations for these effects, and argue that reforms in drug law are needed to help drug users.

Introduction: What is Addiction?

Addiction is one of the most widespread and impactful psychiatric phenomena in society and holds a unique place in our collective consciousness as a hijacking of our control over our own choices, even an undermining of free will itself. It poses powerful, sometimes uncomfortable, questions about the human condition and exposes some of the flaws in the way evolution has sculpted the human brain to promote survival.

Addiction is a pattern of behaviour consisting of a) compulsive seeking and consumption b) loss of control over intake and c) emergence of a negative emotional state when deprived of the drug.[2]

Addiction is often linked to dependence, which has overlapping but non-identical pathways.[3] Dependence is characterised by the discontinuation of the drug leading to unpleasant withdrawal effects, leading to increased consumption to abate these negative effects. In contrast, addiction is seen as a compulsive seeking of a substance or behaviour that is independent of withdrawal. While the two tend to go hand in hand, there are circumstances where one can experience dependence without addiction or vice-versa.[4]

Humans, it seems, can become addicted to almost anything, from potent psychoactive substances such as opioids and alcohol to video games, gambling, sex and chocolate[5–8]. While some of these addictions (such as coffee addiction) are compatible with relatively normal functioning, others have profound impacts on the individual, their families and society. In fact, in modern Western civilisation, there are few people who can truly say they have not seen or experienced the impacts of serious addictions, whether through friends, family or people they pass on the street.

Recently, behavioural addictions are beginning to gain some recognition. The only behavioural addiction recognized by the DSM-5 and the ICD-10 is gambling addiction, but ICD-11 is introducing gaming addiction.[9] This represents an emerging consensus that behavioural addictions are real psychiatric disorders and rely on similar neurological mechanisms to substance misuse disorders.

Neurobiological Mechanisms of Addiction

Most research into the mechanisms of addiction to date have focused around one central theory, the dopamine hypothesis of addiction. This theory states that the mesolimbic pathway in the brain, which projects from the ventral tegmental area (VTA) to the nucleus accumbens, is responsible for reward learning and goal-directed behaviour, and encodes reward using the neurotransmitter dopamine. According to the dopamine hypothesis, this pathway is “hijacked” by addictive substances which causes behavioural reinforcement and consequently the psycho-social manifestations of addiction.

It has been shown to date that all known drugs of abuse act on the mesolimbic pathway.[2] For example, cocaine binds to and inhibits the dopamine transporter on the presynaptic membrane, causing dopamine accumulation in the synaptic cleft. Opioids such as heroin appear to exhibit most of their reinforcing effects through disinhibition of dopaminergic neurons in the VTA, along with some recently elucidated epigenetic mechanisms[10], and alcohol has been shown to exhibit a range of effects on the dopaminergic system directly, as well as the endogenous opioid system, GABAergic, and glutamatergic pathways[11]. Beyond being a simple signal of reward, mesolimbic dopamine release has been shown by Wolfram Schultz to specifically encode reward prediction error, which provides a further understanding of the features of tolerance and escalating goal-seeking behaviour to which the mesolimbic system is vulnerable[12].

However, to focus on this simple mechanistic explanation would be to ignore the wide variation in individual vulnerability to addiction. A recent review combines neurological as well as psychosocial data to propose their own interpretation of addiction, as a "socially engineered exploitation of natural biological vulnerability"[13]. In fact, as early as the late 70s, research by Bruce Alexander of Simon Fraser University demonstrated in rat models that a background of different life circumstances contributed significantly to an individual's vulnerability to addictive behaviour[14]. While some of the conclusions drawn from these "Rat Park" experiments remain controversial, with some critics claiming they cannot bridge the "translational gap", there is clearly huge variation in addictive potential between individuals, leaving ample space for modifiable social, environmental and genetic factors. The central theory of Alexander's work is that individuals who have other sources of meaning in life such as fulfilling relationships or a career path, tend not to become addicted to harmful substances, even when they are exposed to them. Proponents of this theory argue that "harm-reduction" strategies such as housing, employment, and access to addiction services without fear of legal repercussions are far more effective for tackling addiction than strict anti-drug laws, and the rapid change in the Portuguese government's approach to drugs since the 1990s and its effect on their national drug epidemic is often cited as real-world evidence of this.[15,16]

In summary, a "bio-psycho-social" approach to addiction is needed to promote high-quality research, treatment of addicts, and more effective public health policy and legislation.[3]

A Brief History of Psychedelics

Psychedelic substances (Greek: ψυχή *psychḗ* 'soul, mind' and δηλείν *dēleín* 'to manifest') are a group of substances that create non-ordinary states of consciousness. The term was coined by Humphrey Osmond in correspondence with Aldous Huxley[17]. Today, it is recognised that most of these mind-altering substances belong to one of 3 chemical groups: Tryptamines, Phenethylamines, and Lysergamides, and exert their psychedelic effects as agonists of 5-HT2a receptors (5-HT2ARs).

While in Western society the recreational use of these drugs is largely associated with the psychedelic revolution of the 1960s, spurred on by the availability of the semi-synthetic psychedelic lysergic acid diethylamide (LSD), naturally occurring psychedelic substances such as DMT (from ayahuasca, a psychoactive brew made from a variable recipe of Amazonian vines and shrubs), mescaline (from the San Pedro cactus) and psilocybin/psilocin (from *Psilocybe* mushrooms) have been used for thousands of years by a number of indigenous cultures around the world for their entheogenic effects, enhancing spiritual and religious rituals.

In the 1950s and 60s, spurred on by the discovery of LSD in 1943, psychedelics were explored as adjuncts to psychotherapy to treat a range of mood disorders, including depression and anxiety, with some promising results[18].

However, in 1971, many recognised psychedelic compounds were placed under Schedule I of the United Nations Convention on Psychotropic Substances, which is intended to apply to drugs with the greatest potential to cause harm and with no acceptable medical uses. In fact, in the United States, restrictions went one step further, and the Federal Analogue Act of 1986[19] automatically allows treatment of any compound "substantially similar" to an existing Schedule I drug to be treated as a Schedule I substance if intended for human consumption. It is worth noting that these decisions were not made in a political vacuum, nor were they encouraged or advised by reputable scientific bodies at the time of implementation. In fact, in 2016, a 22-year old interview surfaced with John Ehrlichman, former domestic policy chief under President Nixon, in which he revealed that "we knew we couldn't make it illegal to either be against the [Vietnam] war or black", implying that the decision to introduce heavy penalties for drug taking had the aim of disrupting and stigmatising communities that overwhelmingly opposed Nixon's government.[20]

However, in recent years this tide of restriction has begun to turn. In the United States, several cities have liberalised their laws around psilocybin, starting with Denver, Colorado[21] which decriminalised *Psilocybe* mushroom use in 2019, followed closely by Oakland, California[22]. In November 2020, Oregon became the first state to decriminalise psilocybin as well as legalise it for medical use[23].

These legal changes in the USA may spur on a recent shift in public and political opinion. Large studies with human participants have now been possible in a number of locations where they were not before, and they have begun to show significant and promising results which may be highly relevant for patients suffering from depression, anxiety or post-traumatic stress disorder (PTSD)[24]. However, one of the most exciting fields of research is their potential to be used to help those suffering from addictions, which will be the focus of the remainder of this essay.

How do psychedelics work?

As mentioned previously, psychedelics are understood to exert their classical effects through agonism of the 5-HT2AR, which is naturally a receptor for the endogenous neurotransmitter serotonin (5-hydroxytryptamine, 5-HT)[25]. At a network level, it has been shown that psychedelic-induced activation of 5-HT2AR causes profound changes in activity in resting state networks (RSNs).

RSNs are networks of the brain that are typically active in a resting state. The functional connectivity between areas of the brain is the statistical association between activity in one and activity in the other. In recent years, it has been possible to conduct resting-state functional connectivity (RSFC) studies using techniques such as BOLD-fMRI to characterize patterns of activity that are associated with different psychiatric and neurological conditions, including addiction, anxiety, depression and bipolar disorder[26]. One of the most important and well characterized RSNs is the Default Mode Network (DMN).

In studies using psilocybin, Carhart-Harris and colleagues have reported reduced connectivity – i.e. disintegration – of the DMN, particularly the posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC), and in studies with LSD, they have shown EEG changes in alpha and delta power, associated with the phenomenon of ego dissolution[27]. It has been proposed that the DMN is heavily involved in constructing a stable sense of self and it is hypothesized that the rumination theories of depression as well as overactivity of the mPFC may explain why psychedelics appear in trials to be beneficial for depressive patients.

More generally, in these human studies it has been shown that psychedelics break down well-established networks such as the DMN, and lead to increased activity of longer distance pathways which are rarely active in the normal resting state, that is to say, brain activity becomes more

entropic[28]. It has thus been hypothesised that this process of breaking down well-established and reinforced neural connections allows a process of re-establishing connections, and is consistent with the idea that psychedelics can make a patient more receptive to forming a new set of positive emotional associations when exposed to psychotherapy[29]. As well as explaining the potential positive results for depressed and anxious patients, this "rewiring" framework provides biological plausibility to the idea of psychedelics as powerful agents in treating substance misuse disorders.

5-HT2ARs are particularly dense on apical dendrites of Layer 5 cortical pyramidal cells. Agonism leads to an intracellular cascade resulting mobilization of intracellular calcium. This generally acts in glutamatergic neurons to make them more excitable.[26]

According to Carhart-Harris and others, the 5-HT2AR may have played an important role in human evolution. 5-HT2AR agonism has been shown to drive plasticity, through mechanisms such as increased brain-derived neurotrophic factor (BDNF) in cortical neurons, synaptogenesis, and learning and extinction learning, correlating with previously mentioned findings about increased potential for relearning associations and behaviours. Going further into the function of the receptor itself, it has been proposed that it allows adaptation in response to evolutionary pressures. Chronic stress has been shown to "prime" 5-HT2ARs, while acute stress increases release of serotonin.[28,30]

The fact that there is a particularly high density of 5-HT2a receptors in human brains has led to the hypothesis that these receptors helped drive adaptability to a wide range of environments through plasticity.[28,30,31] Recently, Brouwer and Carhart-Harris have proposed a unifying hypothesis for the role of the 5-HT2AR in adaptive stress responses, and have coined the term Pivotal Mental States[31] (PiMS) to allude to the unique cortical state of extreme hyperplasticity which allows psychological transformations to take place. According to this group, PiMS have 3 key identifying criteria: elevated cortical plasticity, enhanced rate of associative learning, and a unique potential for psychological transformation. While they may be triggered by a wide range of human experiences, they share a common pathway, with "priming" of the 5-HT2AR mediated by periods of chronic stress, and subsequent serotonin release mediated by acute stress. In fact, across a range of studies, acute stress is a reliable inducer of serotonin release[31,32], and a range of natural stressors, including hypoxia[33], inflammation[34], and maternal separation[35] upregulate 5-HT2AR expression, particularly in the cortex.

Brouwer and Carhart-Harris conceptualised these PiMS as a metaphorical "fork in the river", where entry into a hyperplastic state means that likelihood of major psychological change is enhanced, and the nature of that change is especially context dependent. That is to say, negative and positive outcomes are possible from the hyperplastic state, depending on whether the individual is immersed in a negative or positive environment at the time. To give an example, they apply the model to the pathogenesis of psychosis: Chronic and acute stress eventually leads to a PiMS. This PiMS is typically experienced contemporaneously with a set of highly negative environmental triggers and this leads to a net negative psychological outcome, including psychotic symptoms, or the negative symptoms associated with depression or schizophrenia.

Conversely, the PiMS explains the reported benefits of psychedelic-assisted therapy. In this context, the individual experiences a PiMS artificially generated by administration of a 5-HT2AR agonist, while being exposed to cognitive therapy, a safe environment, and an opportunity to re-learn a set of positive psychological associations, and thus, it is hypothesized, rather than a net maladaptive outcome such as a psychotic disorder, mental wellbeing can be improved rapidly and dramatically.

In this way, one can see the characteristics of positive and negative psychological transformation as two sides of the same coin, even having comparable characteristics and perceptual alterations such as ego-dissolution or self-fragmentation**.** In severe psychosis, this can be felt as invasive and unwelcome, while in psychedelic or natural spiritual contexts, it may be a profoundly positive experience.

So why does the 5-HT2AR PiMS system exist and what is the role of naturally produced endogenous serotonin? Previous attempts at a unifying model of the function of serotonin have focused on its role in moderating anxiety states[36], as well as impulsivity and aggression[37]. More recently, 5-HT, especially when acting on postsynaptic 5-HT1ARs, has been thought of as the main mediator of adaptive responses to adverse environments, i.e. in helping us to cope[38]. However, as all of us know, coping may not always be enough. Sometimes one must adapt quickly to overcome previously insurmountable hurdles in a new and changing environment. This is the proposed evolutionary role of the 5-HT2AR. When the adverse environment requires more than additional motivation and a positive determined outlook, the PiMS allows rapid learning and adaptability.

In fact, use of psychedelics is not the only way humans have hijacked this system: the Pivotal Mental States paradigm can help to explain a number of spiritual and religious phenomena, in which individuals achieve psychological transformation or "enlightenment" through natural stress-related triggers such as asceticism, fasting, meditation or celibacy.[31]

Now that we have elucidated some of the mechanisms by which psychedelics mediate psychological change, how are these relevant to the treatment of addiction? As discussed earlier, the mesolimbic dopaminergic reward learning system is seen as central to the development of addictions. In addition to the unifying PiMS hypothesis above, there is also a strong base of evidence that the 5-HT2AR directly modulates dopaminergic systems[39,40]. The REBUS (Relaxed Beliefs Under pSychedelics) model[41] offers an explanation of the relevance of the classic characteristics of a psychedelic "trip", such as ego dissolution and emotional lability, in assisting recovery from substance misuse disorders.

The REBUS Model combines previous theories (the entropic brain hypothesis and the free energy principle) to propose that a primary function of psychedelics is to increase entropy of neural activity and thus increase the richness of experience, which in turn relaxes beliefs or predictions about the world. Psychedelics act on 5-HT2ARs on deep pyramidal cells in the visual cortex and at other cortical areas. These deep-layer pyramidal neurons are thought to encode expectations, or priors. Through agonizing the 5-HT2ARs on these neurons, psychedelics relax the precision weighting of prior beliefs and sensitize the individual to external stimuli. The 5-HT2ARs are expressed most densely in high level cortical association areas, such as those associated with the DMN. There is evidence that the DMN constitutes a system for representation of the Freudian ego[41] and self-consciousness in humans. Under psychedelics, DMN alpha-wave activity is diminished, and this correlates well with the perceived experience of ego dissolution. Aberrant predictive processing has been demonstrated as one of the mechanisms of addiction[42] so the REBUS model provides another explanation of how psychedelics may help provide the plastic neurological state that is needed for recovery.

<u>Evidence for psychedelics as potential treatments for addiction</u>

Moving our attention more specifically to addiction, psychedelics have recently started to show promising results. Indeed, a number of studies have demonstrated an "afterglow" effect, where reduced cravings and substance-seeking behaviour persists for several weeks to months after

administration of a psychedelic.[43] The bulk of research into the therapeutic application of psychedelics for addiction focuses on LSD, peyote (*Lophophora williamsi*), ibogaine (from the root bark of the iboga tree (*Tabernanthe iboga*)) and ayahuasca, but psilocybin, ketamine and MDMA (the latter two of which are not classical psychedelics but have significant overlap in terms of pharmacological profile) have also shown potential benefits. The most widely investigated application in this field is the use of LSD to treat alcoholism, and a 2012 meta-analysis[44] showed that a single administration of LSD consistently provided a reduction in alcohol misuse for up to several months. While further studies are needed to establish optimum dosing regimens and potential accompanying therapy sessions, this meta-analysis constitutes robust evidence supporting the effectiveness of LSD in treating one of the most widespread and damaging addictions worldwide[1], and according to Winkelman, shows that psychedelics may be substantially more effective than existing pharmacological treatments for alcoholism.[43]

Psilocybin, the prodrug of the active psychedelic psilocin from *Psilocybe* (commonly known as "magic") mushrooms, is also showing evidence of beneficial therapeutic use, not only in depression[45,46] but also in addictions to tobacco and alcohol[47,48]

Moving on to evidence for other psychedelic substances, the majority of evidence concerning peyote in the treatment of alcoholism emanates from the experience of the Native American Church, which is in a unique position protected by federal US law to be able to use peyote in their cultural and religious practices[49]. There it has been found to be an effective treatment for alcoholism, a highly prevalent disorder in many Native American populations[50].

Ayahuasca is another substance with a long history of being used "entheogenically" i.e. in order to achieve a heightened sense of spirituality to enhance religious or cultural ceremonial practice. It has a continuous history of shamanic and ritual use by indigenous groups in several South American countries[51]. The primary active ingredient of the concoction is N,N-dimethyltryptamine (DMT), and the brew also contains the monoamine oxidase inhibitors (MAOIs) harmine and harmaline, without which the DMT would be inactivated by gastrointestinal and hepatic MAOs[43]. Gabor Maté has held multiple-day ayahuasca retreats as part of a small trial, and reported promising results such as reduced alcohol, tobacco and cocaine use from 6 month follow-up self reports[43]. While not an interventional study, regular users of ayahuasca score lower on measures of Alcohol Use than non-users[43]. Most of this evidence is from very small, mostly observational studies with a number of limitations, not least of which are the difficulties associated with running placebo-controlled studies on a complex botanical brew.

Ketamine is considered a dissociative anaesthetic drug, which acts primarily through antagonism of the n-methyl-d-aspartate (NMDA) glutamate receptor. However, sub-anaesthetic doses are known to produce psychedelic experiences including hallucinations, ego-dissolution and powerful feelings of spiritual connectedness, comparable to classical psychedelics.[52] Ketamine has been shown to have similar effects on glutamatergic corticolimbic circuitry, and crucially, similarly reduced connectivity in RSNs such as the DMN. These effects may represent a common pathway for both serotonergic psychedelics and ketamine in treatment of mental disorders, including addiction. Indeed, ketamine's rapid acting antidepressant effects have led to its approval for use in treatment-resistant depression in 2019[53] and in trials with recently detoxified alcoholics, ketamine increased one-year abstinence rates from 24% to 66%[54], and in another study it reduced cocaine use substantially more effectively than conventional treatments[55]. However, there is a significant lack of randomized controlled trials (RCTs) in this area, even though ketamine is only classified as a Schedule III drug.

<u>Summary and future challenges</u>

This essay has discussed some of the emerging evidence supporting further use of psychedelic drugs in research and therapy, with a focus on potential applications in the millions of people impacted by addictions. Clearly, progress is still slow. Political inertia in the UK and other countries lags significantly behind scientific advances, and the stigma associated with various drugs weighs heavily on public opinion.

Clinical studies such as the Phase II trial conducted by Carhart-Harris and colleagues at Imperial College London comparing psilocybin with escitalopram for patients with major depression[56] should be conducted for patients addicted to a wide range of substances and/or behaviours[57], so that their therapeutic potential can be fully exploited.

Psychiatrists can and should work as agents of political change and advocates for their patients. Non-profit organisations such as the MIND Foundation[58] are bringing together prominent psychiatrists, neuroscientists and other prominent researchers to promote research into psychedelics which is still scarce and small-scale.

I believe that the Royal College of Psychiatrists, and other organisations committed to improving public mental health, have a duty to lobby, educate on, and campaign for appropriate drug legislation which has a basis in science, allows crucial research to be undertaken, and promotes harm reduction for the huge number of people affected by addictions. The COVID-19 pandemic has presented a rare opportunity for change, with the public engaging more with scientists, and politicians having to take more advice on public policy from scientific circles than previously. Those of us in science should be bolder, and demand to be listened to not just on the immediate topic of infectious disease pandemics, but on the more insidious pandemic of mental health disorders.

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