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Tripping up addiction: the use of psychedelic drugs in the treatment of problematic drug and alcohol use

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Psychedelic drugs have been used as treatments in indigenous cultures for thousands of years. Yet, due to their legal status, there has been limited scientific research into the therapeutic potential of these compounds for psychiatric disorders. In the absence of other effective treatments however, researchers have begun again to systematically investigate such compounds and there is now evidence pointing to the use of psychedelic drugs in the treatment of addiction. In this review we focus on human evidence for the effectiveness of preparations used by indigenous cultures in the Amazon (ayahausca) and Africa (ibogaine) and worldwide (psilocybin), and more recently synthetised drugs such as the serotonergic hallucinogen LSD and the dissociative anaesthetic ketamine. Potential mechanisms explored are anti-depressant effects, changes in neuroplasticity and existential psychological effects of these drugs.

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''If, therefore, under LSD we can have a temporary reduction, so that we can better see what we are and where we are going — well, that might be of some help. The goal might become clearer. So I consider LSD to be of some value to some people, and practically no damage to anyone.'' Bill Wilson, founder of Alcoholics Anonymous [Francis Hartigan, Bill W., Chapter 25, pp. 190–197 and pp. 170–171, St. Martins Press, 2000].

The founder of alcoholics anonymous, Bill Wilson, is reported to have been treated with lysergic acid diethylamide (LSD) to help him stay abstinent from alcohol [1] and he credited it with helpful therapeutic properties. Yet the idea that illicit drugs can be used in the treatment of drug and alcohol addiction sits uncomfortably with many clinicians and researchers. It can appear paradoxical: illicit drugs are allegedly controlled due to their high abuse potential so it seems unethical to give them to people who already have a propensity for problematic alcohol and other drug use. Will they not then become addicted to the very substances that are being used to treat them? Centuries of practise and decades of research suggest that this is not the case. And now with emerging neurobiological understanding of their mechanisms, these compounds are poised to change the future of addiction treatment.

Lysergic acid diethylamide

LSD was first synthesised in 1938 from ergotamine, a chemical from the ergot fungus. LSD's psychological effects, usually last between 6 and 12 hours and can vary greatly in content across sets and settings [2]. Pharmacologically, LSD is a classic serotonergic hallucinogen, with its psychedelic effects attributed to its 5HT-2A receptor agonism [3].

In the 1950s and 1960s, there was substantial research into LSD being used as a treatment for alcohol dependence [4]. In recent years, this interest has been reignited. A number of review papers and one meta-analysis have reviewed studies from the height of LSD research [5,6••,7]. The meta-analysis [6••] combined the results of 6 randomised controlled trials, to assess efficacy of LSD as a treatment for alcoholism (536 participants in total). Across the studies included, 59% of active treatment participants versus 38% of controls showed reliable improvement during the first follow up (1–2 months) and these differences were still reliable at 6 months. Whilst most research has focused on alcohol, one study of patients addicted to opioids treated with LSD demonstrated some degree of effectiveness [8]. Importantly, the first study on the acute effects of LSD on brain mechanisms in healthy volunteers was recently published [9], which may herald a new era of medical use of the drug.

Psilocybin

Psilocybin is a compound that occurs naturally in over 200 species of mushrooms. Psilocybin mushrooms have been used as spiritual catalysts in indigenous cultures for millennia, where the mushrooms are revered as powerful spiritual sacraments that provide access to ancestors and other worlds. The effects of psilocybin last between 2 and

6 hours dependent on dose and individual metabolism. Psilocybin's psychedelic effects, like those of LSD, are attributable to its action as a 5HT-2A receptor agonist [10].

Psilocybin has been investigated as a tool to treat nicotine addiction [11•] and alcohol dependence [12•]. In one study, 15 nicotine dependent smokers were given moderate and high doses of psilocybin within a structured programme of cognitive behavioural therapy [11•]. At six-month follow up, 12 of the 15 participants were smoking free. At 12-month follow-up, 10 participants were still smoking abstinent. At long-term follow-up (>16 months), nine participants were still confirmed as smoking abstinent. In addition, when asked at 12-month follow-up 13 participants rated their psilocybin experiences among the five most personally meaningful and spiritually significant experiences of their lives [13]. Similarly, 10 volunteers with severe alcohol use disorder were given psilocybin alongside a psychosocial intervention. A significant reduction in drinking was observed relative to pre-psilocybin levels [12•]. Although promising, these studies suffer from the absence of control group; however, more rigorous studies are currently underway.

Ibogaine

Ibogaine is a psychoactive, indole alkaloid which is naturally found in the rootbark of a Central African plant called *Tabernanthe iboga*. Ibogaine produces a profound psychedelic state in which visual hallucinations, often focused on prior life events, occur and feelings of normality do not return for up to 72 hours [14]. Over the past three decades, ibogaine has received interest as a possible anti-craving and anti-withdrawal aid for drug addiction, primarily opiate and cocaine addictions [15]. In the mid-1990s, the National Institute on Drug Abuse (NIDA) began a programme of research into ibogaine's potentially therapeutic effects in drug addiction [16], although this was prematurely disbanded due to concerns over potential harms. Despite this, 'alternative' ibogaine treatment centres are used by people with addictions around the world [17•,18,19] and it is estimated that over 3000 people have taken ibogaine, chiefly as a treatment for drug addiction [18] and it is licensed as a treatment in New Zealand.

No double-blind, placebo-controlled clinical trials have investigated the efficacy of ibogaine to treat addiction. There are, however, a variety of observational reports which describe the moderate success of ibogaine treating opiate and cocaine addiction/withdrawal in informal treatment settings [14,20–23]. More recently, interest has been reignited with two new observational studies taking place in Mexico and New Zealand [24,25]. These results and ongoing studies are promising, but properly controlled experimental research is much needed. Importantly, there have been some well-reported fatalities associated with ibogaine use, specifically a woman from the Netherlands, whose death contributed to the closure of the NIDA-funded research in the 1990s [14,16]. This may be due to the tradition of using ibogaine during opioid withdrawal — where there is extreme physiological reactions that might exacerbate ibogaine toxicity. Trials using patients in abstinence might be better.

Ayahuasca

Ayahuasca is an Amazonian psychoactive brew made from the *Banisteriopsis caapi* vine and the *Psychotria viridis* bush, along with a variety of other Amazonian plants [26], which produces an altered state of consciousness involving perceptual and affective changes [27]. Ayahuasca is taken in religious and shamanistic settings, as well as in informal treatment centres [26]. The compounds thought to be critical in its psychedelic effects are dimethyltryptamine (DMT) and monoamine oxidase inhibitors such as harmine; the latter compounds allow DMT to be active via the oral route as they block its metabolism in gut and liver [28] and then bind strongly to 5HT-2A receptors [29].

There are a variety of reports that suggest ayahuasca consumption is associated with reduced alcohol and drug problems [30–32]. One recent observational study found reductions in alcohol, cocaine and tobacco use, and improvements in subjective wellbeing in a sample of 12 people who were treated with ayahuasca for drug problems [27].

Ketamine

Ketamine, an N-methyl-D-aspartate receptor (NMDAR) antagonist, when administered at sub-anaesthetic doses can lead to a psychedelic state. Researchers have attempted to incorporate this state into therapeutic interventions for addiction. Ketamine has a good safety profile with minimal impact on the respiratory system as well as a short half-life, so any psychedelic effects wear off quickly post infusion [33,34,35••]. Therefore, ketamine is an attractive drug to use in this treatment context.

One influential study demonstrated the remarkable potential for ketamine psychedelic therapy (KPT) to treat alcohol dependence [36]. An impressive 66% of detoxified alcoholics were found to maintain abstinence a year after KPT as compared to only 24% of those patients who engaged with conventional treatment. However, patients were not randomised to a condition, instead they chose whether to participate in KPT or conventional treatment. These preliminary findings have been supported by case studies using ketamine and transpersonal therapy; 70% abstinence rates at one year have been shown in 15 patients [37•]. As ever, randomised controlled trials (RCTs) are needed to fully understand efficacy and two RCTs investigating ketamine as a treatment for alcohol dependence are currently underway. One RCT has been conducted with heroin addicts, which reported substantially greater abstinence rates following a large,

'psychedelic' dose of ketamine compared to a low, 'non-psychedelic' dose of ketamine [38••]. No placebo control group was used in this study, however.

Impacts of ketamine administration on cocaine abuse have also been investigated. Ketamine administration, combined with relaxation, has been shown to increase motivation to quit, decrease craving and reduce cocaine self-administration in the laboratory 24 hours post-infusion [39,40]. Interestingly, the mystical element and intensity of the experience have been shown to mediate motivation to quit [41].

Mechanisms of action

These psychedelic drugs have plausibly different mechanistic actions, related to their specific effects on 5HT-2A or NMDA receptors. However, here, we strive for a more parsimonious explanation of the similar long-term changes in behaviour that are observed following administration of these compounds in people with problematic substance use.

Anti-depressant effects

Ketamine has emerged as a rapid acting and potent antidepressant [42]. Similarly, a small open-label trial with psilocybin has found preliminary evidence of efficacy following a single dose in treatment-resistant depressed patients [43]. In healthy humans, individuals have reported long-term increases in optimism following LSD [43] and increases in wellbeing and openness following psilocybin administration [44,45].

Depression occurs very frequently in addiction and large numbers of people with drug and alcohol problems have depressive symptoms upon entry into detoxification programmes [46,47]. Depressive symptoms also have been found to be a key factor in precipitating relapse in alcohol [48]. Effects of psychedelics on depressive symptoms may explain some of their treatment effects in addiction. Psychedelic drugs may also switch off or disrupt the brain circuits involved in the ruminative style of thinking observed both in depression and in problematic substance use [49].

Neuroplasticity

One promising candidate neurobiological mechanism for the lasting changes in behaviour seen following psychedelic and dissociative drugs is the stimulation of neuroplasticity, a mechanism common to both classic hallucinogens and synthetic compounds like ketamine. As ketamine is an NMDAR antagonist, it may seem paradoxical that the drug boosts plasticity. But recent work in animals also shows that ketamine-mediated blockade of NMDARs, triggers a sequence of intracellular signalling, the phosphorylation of eukaryotic elongation factor 2 (eEF2) that results in a *de-suppression* of brain derived neurotrophic factor (BDNF) translation [50–52].

Increased BDNF expression following NMDAR blockade by ketamine has been shown to potentiate synaptic responses in the CA1 and dentate gyrus fields of the rat and mouse hippocampus [52], areas crucial in learning and memory. Ketamine has been demonstrated to increase synaptic plasticity [53] and synaptogenesis [54] at 24 hours post-infusion in rats. Ketamine also persistently enhances induction of long-term potentiation 24 hours after injection and increases the NMDAR-NR2B concentration on cell surface at rat hippocampus and medial prefrontal cortex synapses *in vitro* [53]. Animal studies show increased plasticity and learning at 24 hours post infusion.

A limited number of studies have investigated these processes in classical hallucinogens. Single dose administration of LSD in rats induces gene transcription in the prefrontal cortex associated with increased plasticity [55]. Additionally, existing studies in rats suggest that administration of DOI, a synthetic 5HT-2A agonist, enhances BDNF in the parietal cortex [56] and produces a remodelling of pyramidal cells that transiently increases the dendritic spine size in cortical neurons [57]. Furthermore, ibogaine treatment reduces alcohol self-administration rats and its effects are mediated by an increase in glial cell line-neurotrophic factor [GDNF] expression [58].

Experiential changes

Across all these compounds, emerging data suggest that the intensity of the subjective effects correlate with reductions in substance use [12•,40,59]. These mystical experiences have been described by various authors as an experience of a reality surpassing normal human understanding or experience, especially a reality perceived as essential to the nature of reality, feelings of unity and interconnectedness, sacredness, peace and joy, distortion of time and space perception [45,60,61]. Recent pilot work giving psilocybin in nicotine addiction found that mystical experiences were associated with a greater reduction in smoking [59] and in alcohol dependence, both the intensity of subjective effects and mystical experience, were associated with greater improvements [12•]. The mystical element of the ketamine experience and the intensity of this experience have been shown to mediate motivation to quit using cocaine [41]. Importantly, there seems relative specificity for the mystical experiences as predictors, therefore this is likely not just a non-specific effect reflecting an individual's sensitivity to the drug. Psychologically, it has been suggested that the psychedelic 'spiritual awakening', can give the individual a different perspective on life and a sense of meaning [62]. Long-term changes in a person's outlook [44,45] could be critical in helping to maintain abstinence.

Conclusions

Following years of hiatus, research into psychedelic drug treatment has been reinvigorated and there is emerging

evidence for the effectiveness of drugs like ketamine, LSD and psilocybin in addiction, with full trials underway. In the next 5 years clearer evidence for the use of the compounds should become available. Ayahuasca and iboagine show promise from lower quality studies but RCTs are needed and concerns about safety, in the case of ibogaine, should be addressed.

Abuse potential of all of these compounds particularly when used therapeutically appears to be low: the serotonergic hallucinogens have not been associated with subsequent addiction [12•] whereas ketamine and dissociated anaesthetics have some potential for abuse, although this has not been observed when it has been used in therapeutic settings [34]. The therapeutic mechanisms of these drugs in addiction treatment remain unclear but anti-depressant effects, and the consequent stimulation of neuroplasticity, as well as positive psychological effects stemming from mystical experiences with these drugs are candidates, and of course are not mutually exclusive. This is an exciting time for research into psychedelic drugs, the evidence reviewed here suggests a potential place in modern medicine for these compounds, if we are able to overcome the historical stigma associated with this class of drugs and the immense regulatory burden that their illegal schedule 1 status imposes.

Conflict of interest

The authors declare no competing interests.

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