

Ketamine for the treatment of addiction: evidence and potential mechanisms

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Abstract

Ketamine is a dissociative anaesthetic drug which acts on the central nervous system chiefly through antagonism of the n-methyl-d-aspartate (NMDA) receptor. Recently, ketamine has attracted attention as a rapid-acting anti-depressant but other studies have also reported its efficacy in reducing problematic alcohol and drug use. This review explores the preclinical and clinical research into ketamine's ability to treat addiction. Despite methodological limitations and the relative infancy of the field, results thus far are promising. Ketamine has been shown to effectively prolong abstinence from alcohol and heroin in detoxified alcoholics and heroin dependent individuals, respectively. Moreover, ketamine reduced craving for and self-administration of cocaine in non-treatment seeking cocaine users. However, further randomised controlled trials are urgently needed to confirm ketamine's efficacy. Possible mechanisms by which ketamine may work within addiction include: enhancement of neuroplasticity and neurogenesis, disruption of relevant functional neural networks, treating depressive symptoms, blocking reconsolidation of drug-related memories, provoking mystical experiences and enhancing psychological therapy efficacy. Identifying the mechanisms by which ketamine exerts its therapeutic effects in addiction, from the many possible candidates, is crucial for advancing this treatment and may have broader implications understanding other psychedelic therapies. In conclusion, ketamine shows great promise as a treatment for various addictions, but well-controlled research is urgently needed.

Key words: ketamine; addiction treatment; alcohol use disorder; neurogenesis; psychedelic therapy

Introduction

Addiction is considered to be a chronic relapsing disorder that is characterised by cravings, habitual drug seeking and an unpleasant subjective experience during abstinence (American Psychiatric Association, 2013; Koob and Volkow, 2010). Despite decades of research into the causes of and treatment for addiction, it continues to be a global problem. Drug addiction is a huge economic burden due to its impact on productivity, health-care costs, and crime (Wittchen et al., 2011). Around 5% of the world's adult population experience alcohol use disorder (Gowing et al., 2015). In the U.K., over 9% of men and 4% of women meet criteria for alcohol dependence (NHS, 2011). In the U.S., 2.9% of people are dependent on an illicit substance. Furthermore, the leading cause of accidental deaths in the US is drug overdose, with opioids (heroin and prescription opioids) as the most prevalent (Rudd et al., 2016)

Relapse rates for current therapies range between 40%-80% at one year post-treatment initiation (McLellan et al., 2000). Additionally, dependency to stimulants or cannabis have no convincing pharmacological treatments to date (Lingford-Hughes et al., 2012). Existing pharmacological treatments for drug addiction can act as a substitute for the drug of abuse (e.g. methadone for heroin dependence) or can enhance abstinence via other means (e.g. acamprosate for alcohol dependence). However, novel pharmacological treatments are urgently needed to improve abstinence, treat unresponsive patients and deal with substance use disorders with no effective pharmacological treatments. In this review, we explore the potential of ketamine to be used as a treatment for addiction and its possible mechanism.

Ketamine: from anaesthesia to addiction

Ketamine belongs to the chemical class of drugs known as arylcyclohexylamines, which were developed by Parke-Davies in its endeavour to find a safe and reliable anaesthetic. The first drug of this kind was phencyclidine (PCP) (Domino, 2010; Kolp et al., 2014). Ketamine was first synthesised in 1962 by the chemist Calvin L. Stevens as he produced a series of PCP derivatives (ketamine was first called CI-581).

One of its first clinical applications was during the Vietnam War where it was used as an anaesthetic for soldiers in the battlefield. Ketamine has a good safety profile and lacks the major drawback that many other anaesthetics have: respiratory

suppression. Therefore, it has been determined by World Health Organisation as an essential medicine, since it is possible to administer it without the oxygen and electricity supply necessary for the administration of many other anaesthetics (Morgan and Curran, 2012; WHO, 2015). Consequently, it is the only anaesthetic available in many developing countries (WHO, 2015). Today it is also the most extensively used anaesthetic in veterinary settings, especially in equine medicine (Spadavecchia et al., 2002; Enderle et al., 2008; Peterbauer et al., 2008; WSAVA, 2016).

In clinical settings, it is normally administered intravenously, where it rapidly induces dissociation, sedation and analgesia. At sub-anaesthetic doses, it can also produce psychedelic experiences (Constantinou et al., 2010; Domino et al., 1965; Jansen and Sferios, 2001; Kolp et al., 2014; Morgan and Curran, 2012; Sleight et al., 2014). Well-reported psychological effects of ketamine are: hallucinations, delirium, delusions, confusion, mystical experiences, and at higher doses 'near-death' and 'out-of-body' experiences. These effects are usually considered adverse, being a limiting factor in its worldwide medical use (Morgan and Curran, 2012). However, recreational users find some of these effects appealing. The most tempting effects reported by users are 'giggleness', 'visual hallucinations', 'out-of body experiences' and 'melting into the surroundings' (Morgan and Curran, 2012).

The characteristic psychosis-like effects induced by ketamine have resulted in its use as pharmacological model of schizophrenia. The first ever ketamine-induced psychedelic experiences were described as 'vivid dreamlike experiences or frank hallucinations' (Domino et al., 1965). Since then, several researchers have investigated the quality and the nature of the experience induced by ketamine. In 1972, Collier documented that at sub-anaesthetic doses ketamine induces psychedelic experiences with perceptions of floating, feeling disembodied as a soul or a mind, a disconnection from surroundings, journeys to different worlds, and even dying (Collier, 1972). The effects of ketamine have been utilised as a model of schizophrenia in rats (Keilhoff et al., 2004) and in healthy humans, for neuroimaging research (Driesen et al., 2013), and pharmacological research (Krystal et al., 2000, 1999, 1998, 1994).

Researchers have defined four specific stages of ketamine-induced non-ordinary states of consciousness as a function of drug dose (Jansen and Sferios, 2001; Kolp et al., 2014). An empathogenic experience occurs with low sub-psychedelic doses (25 – 50 mg i.m. shots). The experience is characterised by happiness and an increased awareness of the body and empathy. At medium psychedelic doses (75 mg – 125 mg i.m. shots), people experience out-of-body experiences, meaning that subjects feel a

complete separation from one's body (Kolp et al., 2014). Finally, subjects undergo an ego-dissolving transcendental experience at high doses (150 – 200 mg i.m. shots). In this state, individuals feel a dissolution of boundaries between the external reality and self and can experience a 'near death' experience (Jansen and Sferios, 2001).

While its application in clinical settings as an anaesthetic and its study in the scientific community increased, so did its recreational use. In Europe, recreational use was rare until the 1990s when it appeared during the 'rave culture' (Morgan and Curran, 2012). Its abuse liability as a recreational drug has led many countries to make ketamine a controlled substance. There is an on-going international debate regarding the optimal legislation for this drug, with China requesting that ketamine be internationally controlled and the WHO recommending against this, due to its importance in medicine, especially in developing countries (Domino, 2010; Morgan and Curran, 2012; WHO, 2015).

Pharmacology and applications

Although ketamine is classically considered a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, it is actually a wide ranging pleiotropic molecule that affects a variety of receptors and cellular processes (Sleigh et al., 2014). Ketamine blocks nicotinic acetylcholine ion channels (Lydic and Baghdoyan, 2002; Scheller et al., 1996), increases dopaminergic and noradrenergic neuromodulation and it also acts as a weak agonist of delta and mu-opioid receptors (Cai et al., 1997; Kubota et al., 1999; Wang et al., 2012). Since ketamine is a lipid-soluble drug, it rapidly crosses the blood-brain barrier, exerting its effects on the CNS within 5 minutes after injection. Ketamine has a relatively short half-life of 1-3 hours, so its subjective effects cease quickly after administration stops (Clements et al., 1982).

Importantly, the molecule has an asymmetric carbon atom; thus, ketamine is a racemate of the two enantiomers: S-ketamine and R-ketamine. S-ketamine has greater affinity for NMDA receptor (Ebert et al., 1997), but R-ketamine shows more potency and longer-lasting anti-depressant effects in animal models (Yang et al., 2015; Zhang et al., 2014; Zanos et al., 2016). However, S-ketamine produces greater analgesic effects, stronger alterations in hearing and body image, and a more profound reduction in visual acuity (Oye et al., 1992). Moreover, ketamine is metabolised by the liver into four distinct metabolites: hydroxynorketamine (HNK), dehydronorketamine, hydroxyketamine and norketamine (Zanos et al. 2016).

Ketamine is a very effective analgesic which impedes 'wind-up'; a type of neuroplasticity where neurons in the dorsal horn of the spinal cord become hypersensitive (Sunder et al., 2008). It has been used to treat chronic pain syndromes such as fibromyalgia, burns, neuropathic pain, post-herpetic neuralgia and migraine (Domino, 2010; Garg et al., 2012; Huge et al., 2010; O'Hara et al., 2014). For this reason, it is used in human and veterinary medicine for pain management. For instance, post-operative pain relief is reduced with low doses of ketamine before, during and after surgery (Berti et al., 2009; Canbay et al., 2008; Clarke et al., 2011) and it is used as a co-analgesic to potentiate the analgesic effect of opioids (Carstensen and Møller, 2010; Kurdi et al., 2014).

More recently, ketamine has been explored as a treatment for depression. In 2000, a double-blind, placebo-controlled study reported that a single infusion of ketamine resulted in rapid antidepressant effects (Berman et al., 2000). This was a breakthrough in psychiatry and more research replicated these results in the following years (DiazGranados et al., 2010; Sos et al., 2013; Singh et al., 2016; Zarate et al., 2006). These findings stimulated a great deal of psychiatric research into ketamine. Both before and after this major finding in psychiatry, research had been conducted into ketamine as a useful medicine in helping to treat various drug addictions with generally positive results. Our review article will focus on this addiction research.

Preclinical evidence in addiction

Preclinical research on the anti-addictive properties of ketamine is somewhat sparse, however one study compared the effects of memantine and ketamine on ethanol and saccharin drinking (Sabino et al., 2013). Alcohol-preferring rats could self-administer 0.08% weight/volume saccharin, 10% weight/volume ethanol or water. After intraperitoneal administration of either ketamine or memantine, operant responding and motor activity were assessed. A dose of 20 mg/kg of ketamine reduced ethanol administration significantly (33.3% less than vehicle-treated rats) without affecting motor activity and water consumption. Importantly, co-administration of rapamycin blocked ketamine-mediated reduction of alcohol intake, but not that of memantine (Sabino et al., 2013). Similarly, ketamine's antidepressant effects are suppressed by rapamycin (Li et al., 2010).

Addiction is characterised by disruptions in learning and memory. Addicts develop cue-specific responses to drug-related cues. Research has explored the effects of ketamine on the expression of drug related memories. One preclinical study

examined the effects of ketamine administration on reconsolidation – where memories are rendered more labile following reactivation - of morphine-induced conditioned place preference (CPP) in rats. After morphine CPP was induced, rats were intraperitoneally administered 60 mg/kg of ketamine after being reexposed to the conditioned context or while they were in their home cages. After ketamine administration, preference for morphine decreased significantly in the first retest. Interestingly, after a priming injection of morphine, the suppression of place preference was maintained as measured in a second retest. A control group that did not receive ketamine showed morphine CPP, but preference scores remained high in both retests (Zhai et al., 2008). This has been interpreted as evidence that ketamine successfully disrupted reconsolidation of the environment-drug memory.

Clinical studies of ketamine in the treatment of addiction

The earliest recorded work using ketamine in the treatment of addiction was that of Salvador Roquet, the controversial psychotherapist, who used the drug, alongside other compounds like LSD in a form of psychotherapy in Mexico between 1964-1974 (Barney, 1977), which ultimately resulted in his incarceration. However the capacity of ketamine to treat addiction was not investigated scientifically until decades later when Krupitsky and Grinenko (1997), published work that reported the use of ketamine to reduce relapse in recently detoxified alcoholics. These published results were a review of 10 years of previous research. The procedure that was investigated was referred to as Ketamine Psychedelic Therapy (KPT) and had been applied since the mid-80s in the former Soviet Union, until ketamine was banned in Russia 1998.

KPT consisted of three stages. The first step was the preparation, during which patients underwent a preliminary psychotherapy session where a psychotherapist discusses with them the content of the psychedelic experience. They were told that under the influence of ketamine, they would view the world in symbolically, realise the negative aspects of alcohol dependence and see the positive sides of sobriety. They were also told that they would become aware of unconscious mental concepts about the negative aspects of their addiction, such as their personal problems and their self-identity. These insights would help them to accept new life values, purposes and meaning of life and in turn – to overcome their alcoholism. The second stage was the ketamine session in which ketamine was intramuscularly injected and the psychotherapist interacted with the patient. The psychotherapist verbally guided the patient, with the aim of creating new meaning and purpose in life. At moments of highly intense psychedelic experience, the smell of alcohol was introduced to the

individuals. The idea was to enhance the negative emotional valence of the thoughts related to alcohol during the session. Finally, group psychotherapy was performed after the session. Patients shared their experiences with others the day after the ketamine session, with the assistance of a therapist. The aim of this session was to help patients integrate insights of psychedelic experience into their lives (Krupitsky & Grinenko 1997). It is reported that this procedure was used in over 1,000 alcoholics with no reported complications (Krupitsky, 1992).

In Krupitsky & Grinenko's 1997 report, relapse rates in a group of recently detoxified alcohol dependent patients undergoing KPT (n=111) were compared with a another group of alcohol dependent patients who were treated with treatment as usual (n=100). Both groups underwent alcohol detoxification before treatment.. After these sessions, the KPT group received an intramuscular injection of ketamine (2.5 mg/kg) along with the corresponding preparation. The control group received 'conventional, standard methods of treatment' in the same hospital. Only 24% of the control group remained abstinent after a year, whereas 66% of the KPT group did not relapse during the same period ($p < 0.01$) (Krupitsky and Grinenko, 1997). Thus, there was a profound difference between the groups, which is suggestive of ketamine's powerful and positive effects in helping to maintain abstinence in alcohol dependent people. However, this study lacked two critical features of modern-day, gold-standard clinical trials: randomization and blinding. Indeed, patients volunteered themselves for the KPT condition and so differences in motivation and willingness to experiment with a novel treatment could have contributed to the results. Furthermore, a placebo drug was not administered to the control group, and the therapies delivered to the groups differed in content. Therefore, simply receiving a drug (i.e. the placebo effect) and the difference in therapy content, could have contributed to the group difference.

In a further study, 70 detoxified heroin-dependent patients were randomized into two KPT groups, who were injected different doses of ketamine, in a double-blind manner (Krupitsky et al., 2002). One group (n=35) received 0.2 mg/kg i.m. of ketamine, which was considered an active placebo, whereas the experimental group (n=35) received 2.0 mg/kg i.m. After two years, the higher dose of ketamine resulted in a greater rate of abstinence (17% vs 2% abstinent subjects, $p < 0.05$). Additionally, the experimental group had a larger positive change in nonverbal unconscious emotional attitudes and a greater and longer-lasting reduction in craving for heroin. The authors therefore concluded that effectiveness of ketamine was dose dependent (Krupitsky et al., 2002). This evidence in favor of this conclusion is stronger than the previous study (Krupitsky & Grinenko, 1997) due to the randomized design of the current experiment.

Therefore, it provides good evidence for ketamine's ability to treat heroin dependence. The lack of inactive placebo is one concern because it is feasible that both doses of ketamine might be less effective than an inactive placebo, although this is unlikely given previous positive findings.

In 2007, Krupitsky's lab compared the impact of a single vs three KPT sessions (dose: 2.0 mg/kg, i.m.) (Krupitsky et al., 2007). Fifty-nine detoxified heroin dependent patients first received a KPT session. After this, 6 participants relapsed and abandoned the treatment. The remaining participants were randomized into two groups: one received a further two KPT sessions (n=26) in monthly intervals, whereas the other underwent two counseling sessions (n=27) also in monthly intervals. After a year, 50% in the 3-session KPT group remained abstinent compared to 22% in the single KPT ($p<0.05$) (Krupitsky et al., 2007). This clearly demonstrates the superior efficacy of three KPT sessions in comparison to one KPT session, which indicates that the KPT sessions are beneficial. It also suggests that repeated doses of ketamine have a greater impact. Although this study controlled for the psychological effect of therapy by providing two counseling sessions in the control group, it did not include a pharmacological placebo in the control arm. However, it still adds to the evidence that ketamine has a helpful effect in prolonging abstinence in heroin dependent individuals.

In a private psychiatric practice in the US, another psychiatrist has successfully conducted KPT since 1994. He has not only treated patients with drug addiction, but also individuals with other types of addictions (e.g. food addiction) and other psychological disorders. His reported anecdotal, clinical findings are positive, having adhered strictly to the original protocol (Kolp et al., 2006, 2009).

In 2014, 8 cocaine dependent males disinterested in treatment received 3 infusions in a double-blind, cross-over design: 0.41 mg/kg ketamine, 0.71 mg/kg ketamine, and 2mg lorazepam (an active benzodiazepine control, which induces mild subjective and anxiolytic effects) (Dakwar et al., 2014b). Infusions lasted 52 minutes and were separated by 48 hours. Before and after each infusion, motivation to quit cocaine and cue-induced craving were assessed. Relative to the lorazepam, motivation to quit cocaine was enhanced and cue-induced craving for cocaine was reduced by the 0.4mg/kg ketamine (both $ps=0.012$), and this latter effect was augmented by the 0.71mg/kg ketamine dose. During the psychedelic experience, dissociation and mystical-type effects were assessed. As predicted, the higher dose of ketamine led to greater mystical experiences. Strikingly, these mystical-type experiences, but not the dissociative effects, were found to mediate motivation to quit. However, the small non-

treatment-seeking sample, the absence of an inactive placebo and the cross-over design, limit the study's implications (Dakwar et al., 2014b). Having said that, the participants showed a significant reduction in the frequency and amount of cocaine consumed in normal life in the 4 weeks following the experiment, compared to baseline.

The same research group assessed effects of a single infusion of ketamine on cocaine self-administration in the laboratory in 20 non-depressed, cocaine-dependent participants who were unwilling to seek treatment (Dakwar et al., 2016). In this instance, it was a randomised and crossover design (sessions were separated by 2 weeks). Patients were administered midazolam (0.025 mg/kg) or ketamine intravenously (0.71 mg/kg) over 52 minutes. The study was designed to evaluate cocaine self-administration, cocaine craving, and cue-induced reactivity. Cocaine self-administration was examined using a cocaine vs. money choice paradigm. The ketamine administration produced a 67% reduction in cocaine choice compared to baseline and substantially fewer cocaine choices were made in the ketamine condition relative to the midazolam condition ($p < 0.0001$). Furthermore, ketamine significantly reduced craving ($p < 0.01$) and reactivity ($p < 0.05$), which are both key contributors in relapse, up to 48 hours post infusion. Cocaine use in their normal life was also significantly reduced within the first 3 days following ketamine administration compared to midazolam ($p < 0.05$) and some participants remained abstinent for the entire 2-week follow-up (Dakwar et al., 2016).

Ketamine's potential mechanisms of action in addiction

Plasticity, neurogenesis and synaptogenesis

Neural plasticity is defined as the cellular and structural reorganisation of the brain. Synaptogenesis is a crucial mechanism for plasticity, since for change to happen within brain circuitry new synapses between neurons must be formed. Surface expression of AMPARs and upregulation of other synaptic proteins are involved in the process of synaptogenesis. Diminished glutamatergic synaptic transmission and reduced plasticity are thought to be associated with addiction (Kalivas, 2009; Kalivas and Volkow, 2005).

Existing models suggest that ketamine's blockade of NMDA receptors increases synaptogenesis by stimulating protein synthesis and the insertion of AMPA receptors

(Li et al., 2010). Hence, ketamine's effects help to reverse the glutamatergic changes associated with depression and addiction. The fact that administration of rapamycin (an mTOR antagonist) blocks both the ketamine-induced reduction in alcohol intake (Sabino et al., 2013) and the antidepressant effects (Li et al., 2010) suggests that the underlying mechanism of both effects might be the same: synaptogenesis. Moreover, a previous study showed that ketamine's metabolites, (R,S)-norketamine and (2S,6S)-HNK, contribute to ketamine-mediated increase of mTOR signalling both *in vivo* in rats and *in vitro* (Paul et al., 2014). Therefore, this represents a mechanism by which ketamine could redress an imbalance in addiction.

However, subsequent work casts doubt upon this possible mechanism. Zanos et al. (2016) assessed the behavioural effects of (2R,6R)-HNK, a metabolite of ketamine, on mice in the forced-swim and learned helplessness tests – animal models of depression. They also assessed this metabolite's effects on NMDA and AMPA currents in slices of the rats' hippocampi as well as the expression of mTOR, BDNF and GluA1-2 (2 subunits of AMPAR) in hippocampal and PFC slices of mice (Zanos et al. 2016). They found that HNK is not active at NMDR but still produces antidepressant effects independent of differences in mTOR levels. Further research is needed to assess the relationship between changes in synaptogenesis and any effects of ketamine on addiction.

Neurogenesis refers to the birth of new neurons in the brain. In the adult brain, the newly formed neurons differentiate from adult neural stem cells in the lateral ventricles, the olfactory bulb and in the hippocampus (Zhao et al., 2008; Ernst et al., 2014). Animal models of addiction, depression and other psychiatric disorders have been linked to a reduction in adult neurogenesis (Chambers, 2013; Duman et al., 2016). It has been suggested that in addiction the loss of neurogenesis, especially in cortical and hippocampal regions, may contribute to levels of self-administration and the vulnerability of relapsing (Mandyam & Koob, 2012; Noonan et al., 2010).

The reduction of neurogenesis in addiction is supported in humans by the reduction in BDNF serum levels. In a study, 37 subjects with diagnosis of alcohol dependence showed significantly reduced BDNF serum levels compared to healthy individuals (Zanardini et al., 2011). Similarly, cocaine- and heroin-dependent patients have significantly lower serum BDNF levels and these seem to recover during withdrawal (Sönmez et al. 2016; Corominas-Roso et al. 2013; Angelucci et al. 2007). Therefore, increasing or stabilising BDNF could help to treat addiction.

Rapid and transient up-regulation of the neuroplasticity marker BDNF is implicated as a critical component of the antidepressant mechanism of ketamine (Autry et al., 2011; Ota and Duman, 2013). BDNF knock-out mice do not show antidepressant response to ketamine in animal models of depression (Kavalali and Monteggia, 2015) and injection of BDNF antibodies into the mPFC block the antidepressant effect (Lepack et al., 2015). Recent research has demonstrated that ketamine increases peripheral plasma BDNF in depressed people who respond to treatment but not in treatment non-responders or patients receiving an active placebo (Haile et al., 2014). These BDNF increases in depressed people given ketamine are robustly correlated with the drug's antidepressant effects (Haile et al., 2014). In a further study, changes in peripheral BDNF were directly proportional to slow wave sleep (SWA: a surrogate marker of synaptic plasticity) and change in SWA in turn predicted antidepressant response to ketamine (Duncan et al., 2013). Given the reduction in BDNF levels in people with various addictions this seems a plausible mechanism for ketamine to have an anti-addictive effect. However, one study in human patients with depression failed to show an increase in BDNF plasma levels 4 hours after ketamine infusion (Machado-Vieira et al., 2009) and further research suggests that ketamine's action on BDNF levels might be age-dependent (Keilhoff et al. 2004; Huang et al. 2016) suggesting the picture may be more complex.

Disruption of functional networks

Research into serotonergic psychedelics (e.g. LSD and psilocybin) has experienced a renaissance over the last decade (Sessa, 2012). Ketamine, despite acting in a pharmacologically different way to classic serotonergic psychedelics, shares the modulation of glutamatergic neurotransmission in the corticolimbic circuitry and similar psychological effects with these psychedelics (Vollenweider and Komater, 2010). Therefore, by considering serotonergic psychedelics and why they might be helpful in treating addiction, we may learn how ketamine exerts its anti-addictive effects.

Two landmark studies examined psychedelic experiences using fMRI (LSD and psilocybin) (Carhart-Harris et al., 2016, 2012). They found a dispersion in normal brain connectivity and the disruption of the usual pattern of communication (Carhart-Harris et al., 2016, 2012). The integrity of functional networks decreased, being the change maximal in functional hubs such as the thalamus, putamen and high-level association cortices. In particular, connectivity within the Default Mode Network was reduced

between the posterior cingulate cortex and the mPFC (Carhart-Harris et al., 2012). The connectivity between the parahippocampal and the retrosplenial cortex also decreased as well as the segregation between other major functional networks such as the salience, attention and different visual networks (Carhart-Harris et al., 2016, 2012). The experience on LSD elicited increased blood flow in visual cortical areas (Carhart-Harris et al., 2016), whereas psilocybin only produced decreases in cerebral blood flow (Carhart-Harris et al., 2012).

Similarly, infusions of ketamine have shown to decrease connectivity between and within resting-state consciousness networks. Connectivity between the mPFC and the rest of the Default Mode Network (via the posterior cingulate cortex) has been found to be reduced, along with the integrity and activity of the salience and visual networks are also affected (Bonhomme et al., 2016; Niesters et al., 2012; Scheidegger et al., 2012). Since it is known that connectivity with the mPFC is elevated in depression (Sheline et al., 2010), the reduction of connectivity in the Default Mode Network observed during the psychedelic experience might be a mechanism that helps treat depressive states, which are very common in addicts and predictive of relapse.

On the other hand, PET studies by Vollenweider and colleagues have shown that both ketamine and psilocybin acutely increase neuronal activity, especially in prefrontal cortical areas, anterior cingulate cortex and insula (Vollenweider et al., 1997a, 1997b, 1997c). Vollenweider has recently proposed that a common mechanism of psychedelics in treating depression is the increase in activity in these areas. This may help to normalise the corticolimbic system connectivity- which is disrupted in addiction - via the elevation of extracellular glutamate levels (Vollenweider and Komater, 2010).

Importantly, psychedelics have shown promising results in treating various addictions (Bogenschutz et al., 2015; Johnson et al., 2014; Krebs and Johansen, 2012). However, more randomised controlled trials with larger sample sizes are needed before strong conclusions can be made (Morgan et al., 2017). Nevertheless, the ways in which these psychedelics modulate the activity of functional networks and produce subjective effects may well have an important role in ketamine's therapeutic value for both addiction and depression.

Rapid antidepressant effects

Given addiction is highly co-morbid with depression (Hasin et al., 2005) and ketamine's role within psychiatry changed dramatically when it was discovered to be

an anti-depressant, we now briefly describe the research concerning ketamine and depression. In 2000, the first clinical trial hinted at the potential of ketamine as a treatment for depression. Four subjects diagnosed with depression were intravenously administered 0.5 mg/kg of ketamine in a randomised, double-blind design. The results were compared to the injection of saline solutions in 3 subjects with an equivalent diagnosis. Comparison on the Hamilton Rating Scale for Depression (HAM-D) showed moderate evidence for a greater reduction in scores after ketamine infusion compared to saline (Berman et al., 2000). The reduction was rapid and outlasted the subjective effects of ketamine, lasting for 3 days after infusion. Despite the small sample size and the limited follow-up, this result and anti-depressant effects observed in animal models of depression (Moghaddam et al., 1997; Li et al., 2010; Autry et al., 2011) encouraged researchers in the field to perform more studies in humans (Krystal et al. 2013). Since then, over 30 studies have examined the antidepressant effects of ketamine in patients with treatment-resistant major depressive and bipolar disorders (Lener et al., 2017).

A recent systematic review and meta-analysis assessed the results of seven randomised, double-blind, placebo-controlled trials that evaluated the efficacy of ketamine in the treatment of major depressive disorder (MDD) (McGirr et al., 2015). One of the trials administered ketamine intranasally, whereas the rest provided intravenous infusions of the drug. Ketamine was associated with higher rates of clinical remission and clinical response at 24 h, 3 and 7 days compared to saline or midazolam (used as an active placebo, in order to produce transient subjective effects). Ketamine produced short-lived psychotomimetic effects, but there were no serious complications, persistent psychosis or affective switches. After 24h, depression scores were significantly reduced for patients treated with ketamine compared to placebo treated patients (see McGirr et al., 2015).

Ketamine has shown a 65-70% response rate in treating depression within 24 hours, which contrasts with the ~47% response rate of conventional monoaminergic antidepressants after weeks or months (Lener et al., 2017; Trivedi et al., 2006). Furthermore, ketamine's antidepressant actions are almost immediate and last for approximately a week (Lener et al., 2017; McGirr et al., 2015), whereas conventional antidepressive medications take weeks to have an effect, are given daily and most of them fail to exert long-lasting effects (Lingford-Hughes et al., 2012). Furthermore, studies have consistently shown that after a ketamine infusion there is a significant reduction in suicidal ideation which also lasts for several days (Rebecca et al. 2017; DiazGranados et al. 2010; Larkin & Beautrais 2011; Ballard et al. 2014).

Depression and addiction's co-expression is almost ubiquitous (Hasin et al. 2005). People with alcohol, opioids, cannabis and cocaine use disorders show notably higher rates of depression than the average of the general population (Curran et al., 2016; Markou et al., 1998). Furthermore, high levels of depression and anxiety may predispose relapse to: heroin, alcohol, cannabis and cocaine (White et al. 2004; Willinger et al. 2002; Markou et al. 1998; Greenfield et al. 1998). Hence, a drug, which can rapidly and reliably alleviate depression symptoms (i.e. ketamine), in those experiencing addiction, should be effective in enhancing abstinence. Importantly, conventional anti-depressants do not reduce drinking, and depressive symptoms remain a main trigger of relapse (Mason et al., 1996; Pettinati, 2004). It may be that conventional anti-depressants fail to reduce relapse because they take some time to reduce depressive symptoms.

The novel benefits of ketamine as a pharmacological treatment for depression is its high response rate and its rapid onset of antidepressant action. Given the important role depression plays in addiction (Hasin et al. 2005; Kessler et al. 2003; Grant et al. 2004; Quello et al. 2005), the robust evidence that ketamine produces rapid antidepressant effects provides substantial support for its potential use to treat addiction.

It is thought that many individuals take drugs and drink alcohol to escape negative affective states (i.e. the self-medication hypothesis). This may initially alleviate the unwanted mood state, but chronic use and withdrawal symptoms could synergistically lead to drug addiction (Markou et al., 1998; Quello et al., 2005). Furthermore, stress plays an important role in the development and maintenance of both addiction and depression. Depression is often considered to be a stress-related disorder associated with changes in the hypothalamic-pituitary-adrenal axis (Raison & Miller 2003; Duman et al. 2016). Similarly, addiction is linked with a dysregulation of the stress response and chronic stress is a well-established risk factor for drug addiction (Sinha, 2008). In fact, stress exposure is known to increase drug use, which at the same time further imbalances the stress response system. This results in a dangerous cycle that feeds compulsive behavior. Hence, reducing negative affective states might help addicts to reduce their drug intake. Indeed, research has shown that in some samples treating depressive symptoms decreases drug consumption and craving (Hobbs et al., 2011; Lingford-Hughes et al., 2012). Therefore, ketamine's reliability to reduce depression may be one anti-addictive mechanism.

Depression predisposes and can predict future relapse to different drugs (Greenfield et al., 1998; Markou et al., 1998; White et al., 2004; Willinger et al., 2002). For instance, almost all alcoholics have depressive symptoms when they enter detoxification programmes (Hasin et al. 2005). Additionally, withdrawal syndromes make individuals more vulnerable to depression, which as discussed above increases the chances of drug intake (Brower et al., 1988; Covey et al., 1997; Kosten and O'Connor, 2003). Therefore, the fast-acting relief of early depressive symptoms of ketamine may be crucial to prevent relapse in the vulnerable period post-detoxification in alcohol dependence, and other drug addictions.

Reconsolidation

Once consolidated, memories are thought to be stored in a stabilised state after initial acquisition. Shortly after reactivation (i.e. remembered) of consolidated memories, these are rendered transiently unstable and labile, before they then re-stabilise. This process has been named reconsolidation (Alberini and Ledoux, 2013; Giese, 2012; Lee, 2009; Lewis, 1979). After reconsolidation, the memories are stored again, but they may have been slightly altered or updated. Each time memories are reactivated the latest version is retrieved and they are again susceptible to change (Alberini and Ledoux, 2013; Lee, 2009).

During reconsolidation memories may be vulnerable to manipulation and disruption. This was first demonstrated in animals using fear conditioning. Rodents were trained to associate a neutral stimulus with a shock such that the neutral stimulus elicited a fear response. Researchers eliminated this fear response by pharmacologically disrupting the reconsolidation process (Nader et al. 2000). Reward memories can also be disrupted such that a neutral stimulus that once elicited appetitive behaviour no longer does so. Therefore, non-pharmacological and drug therapies that aim at weakening drug-cue memories via manipulation of reconsolidation are of interest (Lee et al., 2005; Miller and Marshall, 2005; Lee et al. 2006; Tronson and Taylor, 2007; Xue et al., 2012).

Preclinical studies have shown that ketamine affects reconsolidation of drug memories. A recent review has suggested that ketamine (along with other psychedelics) may be able to disrupt maladaptive appetitive memories (REF). Furthermore, a meta-analysis of pre-clinical studies found evidence suggesting that NMDAR antagonists can be used to target reward memory reconsolidation, and more successfully than adrenergic antagonists such as propranolol (Das et al., 2013). On the

other hand, a human study that explored the possibility of memantine (another NMDAR antagonist) as an enhancer of reconsolidation found no significant difference between placebo and this drug in quitting cigarette smoking (Das et al., 2015). However, memantine produces none of the psychological effects that ketamine produces. Research investigating whether ketamine can disrupt appetitive drug-related memories via reconsolidation is urgently needed in human samples.

Mystical experiences and psychedelic effects

Mystical experiences and psychedelic effects provoked by classic psychedelic drugs have been shown to be psychologically beneficial in long-term studies (Grof, 1985; Hoffer, 1967; Jansen and Sferios, 2001; Strassman, 1995). They have not only been linked with positive outcomes in various treatments, but also to 'life-changing', 'spiritually meaningful' and 'eye opening' events. In the ketamine studies described above, anecdotal and qualitative reports suggest that the subjective psychedelic experience seemed to help patients. For example, to help them: undergo a cathartic process, improve relationships with the world and other people, maintain positive psychological changes and enhance self-awareness and personal growth (Kolp et al. 2007; Kolp et al. 2014; Krupitsky et al. 2002; Krupitsky & Grinenko 1997; Dakwar et al., 2014a)

During KPT, patients reported a feeling of 'resolution' and 'catharsis' of some psychological problems, mainly those related to alcohol. Furthermore, the degree of mystical experience was also linked to the insight and impact of KPT reported by patients (Krupitsky & Grinenko 1997; Krupitsky et al. 2002). Interestingly, the intensity of the negative experiences (experiences associated with negative emotions, fear and horror) during the ketamine session was associated with longer remission. This was blindly and quantitatively assessed by analysing patient's self-reports. Moreover, spirituality, self-concept, emotional attitudes to other people and positive changes in life values and purposes were improved after the ketamine experience (Krupitsky & Grinenko 1997; Krupitsky et al. 2002). These changes were considered as favorable to promote abstinence. They also helped patients to feel less depressed and anxious, more self-confident and more emotionally open.

Notably, ketamine's mystical experiences, but not dissociative effects, were found to mediate ketamine's increase motivation to quit 24 h after the infusion in cocaine addicts (Dakwar et al., 2014a). Moreover, consistent with previous studies, it

was also observed that mystical experiences were positively dose-dependent. This study therefore provides evidence that the mystical experience induced by ketamine is important in its therapeutic mechanism (Dakwar et al., 2014a). Speculatively, mystical experiences may help to rapidly shift patients' mindsets towards the integration and acceptance of a sober lifestyle (Dakwar et al., 2016, 2014a; Krupitsky et al. 2002; Krupitsky & Grinenko, 1997).

The acute disruptions of the functional networks, especially the alterations to the default mode network, are related to the psychedelic experience. In fact, the degree of network dissolution in LSD and psilocybin is correlated with the intensity of the psychedelic experience (Carhart-Harris et al., 2016, 2014, 2012). The disruption to the default mode network may engender a reduction in rumination and maladaptive repetitive thoughts. Psychological therapies for addiction often aim to help the patient consider different ways of life, especially those without the drug, and a pharmacological agent such as ketamine which expedites that process may be useful in treating addiction.

Mystical and psychedelic experiences have been considered as adverse side-effects in the majority of the literature, and have limited the worldwide medical use of the drug. This has fed the debate about whether ketamine's psychedelic effects are necessary for its antidepressant, and its putatively antiaddictive, effects. The fact that in animal models ketamine's metabolites exert antidepressant effects without the psychotomimetic effects is an argument against the requirement of this experience (Zanos et al. 2016). However, it is limited by translation to humans and the studies presented in this review suggest that these subjective effects have an important impact in the treatment of addicts and their psychological healing. Therefore, re-framing these experiences as therapeutic should be encouraged to destigmatise and facilitate their research.

Enhancing psychological therapy

Whilst the neurobiological and subjective psychological effects of ketamine may important in its effects in addictive disorders, ketamine's ability to enhance the efficacy of psychological therapies is likely to play an additional role. Speculatively, ketamine can provide a unique mental state during and after acute drug effects that facilitates and enriches therapeutic experiences, which in turn may improve efficacy and lengthen treatment effects (Grof, 1985; Hansen et al., 1988; Kolp et al., 2014). Furthermore, synaptogenesis and neurogenesis are putatively critical in learning new

information (Giese, 2012). The uptake of psychological therapy may therefore be facilitated after ketamine infusions due increases in synaptogenesis and neurogenesis, and thus improved learning of relapse-reducing strategies, such as those used in relapse-prevention based cognitive behavioural therapy (CBT). In fact, the idea that neurogenesis and synaptogenesis work synergistically with psychological therapies is becoming recognised as a new approach in the treatment of mental disorders (Harmer and Cowen, 2013). Theoretically, the administration of ketamine (which can produce a 'psychedelic' experience) may open people's minds so they are more able to embrace what is presented during therapy as well as enhancing the uptake of new therapeutic content. In order to determine whether enhancement of therapy is a mechanism for ketamine-induced change, researchers have designed experiments with and without active therapy conditions. One current study includes two factors (Drug: ketamine/placebo and Therapy: CBT/placebo therapy) to explore this mechanism, with the aim of helping alcohol dependent people who are sober remain abstinent (McAndrew et al., 2017).

Evaluating ketamine as a treatment for addiction

The promise of ketamine in the treatment of addiction is supported by research with large treatment effect sizes, especially in comparison to existing treatments. In recently detoxified alcoholics, ketamine treatment increased one-year abstinence rates in alcoholics from 24% in the control to 66% in the ketamine group (Krupitsky & Grinenko, 1997) and reduced cocaine self-administration by 67% relative to baseline in non-treatment seeking cocaine users (Dakwar et al., 2016). These results clearly demonstrate profound effects of ketamine administration (with and without therapy) on drug and alcohol use, of an order of magnitude which is 2 or 3 times more effective than existing pharmacotherapies.

However, there are also clear limitations of much of this research. Firstly, there is a surprising lack of preclinical research investigating whether ketamine can disrupt addictive drug use in animals. A standard approach for exploring whether compounds might be useful in treating addiction is to allow animals to acquire compulsive drug use and then investigate how another compound affects self-administration of this drug (O'Brien and Gardner, 2005). Experiments like this would be able to compare the consequences of ketamine across a variety of drug addictions and also examine neural mechanisms underlying the beneficial effects.

Furthermore there is a dearth of randomised controlled trials which meet modern-day clinical trial standards and specifically test the efficacy of ketamine vs. placebo on reducing relapse in treatment-seeking addicted individuals. The field must prioritise conducting these trials so that experimental data and less controlled data can be confirmed in high quality clinical trials. Current findings are limited by their lack of randomisation, blinding and adequate control group (Krupitsky et al., 1997) and non-treatment seeking samples (Dakwar et al., 2016, 2014b). Two trials with heroin dependent individuals did use randomisation and blinding to some extent (Krupitsky et al., 2002; Krupitsky et al., 2007). However one (Krupitsky et al., 2002) compared a low ketamine dose with a high ketamine dose, and so the effectiveness of ketamine relative to placebo cannot be calculated. The other (Krupitsky et al., 2007) compared the efficacy of one session of KPT to three KPT sessions, but no placebo drug administration took place for those in the single session group. Hence, there is much room for improvement.

Ketamine's use as a recreational drug may have hampered its seemingly counterintuitive clinical application in addiction. However, no complications were observed in any of the studies on addiction discussed above. Furthermore, evidence from longitudinal studies suggests that ketamine has to be taken daily and heavily to develop addiction and other complications such as ulcerative cystitis (Morgan and Curran, 2012). In healthy volunteers, the cognitive effects of ketamine have been shown to completely dissipate 3 days after a single exposure (Morgan et al., 2004). Therefore, the dangers of using ketamine as a treatment for addiction, in properly selected patients is low (Singh et al., 2017).

A clear advantage of using ketamine over competing treatments for addiction is that daily administration of the drug is not needed. Ketamine doses are isolated and given for a limited time period only. This is likely to be less stigmatizing than the requirement to take daily medication for patients struggling with addiction and would hopefully increase medication adherence. However, most studies to date have administered ketamine via injections. If ketamine was to be applicable in non-specialised units and as prescription drug, a simple and cost-effective method of administration would be needed. Intranasal administration seems the optimal method of administration. In fact, in 2014, a small sample size (n=20) showed significantly greater improvement of depressive symptoms after 24 hours of intranasal ketamine administration compared to placebo (Lapidus et al., 2014). There are currently further trials studying intranasal administration of (S)-ketamine for the treatment of depression.

Conclusions

Ketamine is a promising drug for treating addiction. Research studies have shown that ketamine can promote abstinence in alcohol dependence (Krupitsky and Grinenko, 1997) and heroin dependence (Krupitsky et al., 2007, 2002), and reduce craving and self-administration of cocaine (Dakwar et al., 2016, 2014b). However, these studies have limitations and more high quality clinical research in humans is urgently needed to confirm that ketamine can help reduce relapse in people who have recently stopped using drugs. Furthermore, preclinical and experimental research must clarify which mechanisms underpin its potentially efficacious effects, and different combinations of ketamine and therapy should be examined. Ketamine is both a fascinating psychedelic and a medically accepted drug; if previous studies are replicated,, ketamine is destined to become one of the most exciting directions in the treatment of addiction.

Conflict of Interest

CJAM has consulted for Janssen pharmaceuticals, the other authors declare no conflict of interest

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