Neuropharmacology 142 (2018) 72–82

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Ketamine for the treatment of addiction: Evidence and potential mechanisms

I. Ivan Ezquerra-Romano [a], W. Lawn [b], E. Krupitsky [c], C.J.A. Morgan [b, d, *]

[a] Department of Neuroscience, Physiology and Pharmacology, University College London, Gower Street, London, UK
[b] Clinical Psychopharmacology Unit, University College London, Gower Street, London, UK
[c] St.-Petersburg Pavlov State Medical University and Bekhterev Research Psychoneurological Institute, St. Petersburg, Russia
[d] Psychopharmacology and Addiction Research Centre, University of Exeter, Exeter, UK

ARTICLE INFO

Article history:
Received 28 October 2017
Received in revised form
8 January 2018
Accepted 11 January 2018
Available online 12 January 2018

Keywords:
Ketamine
Addiction treatment
Alcohol use disorder
Neurogenesis
Psychedelic therapy

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.

This article is part of the Special Issue entitled 'Psychedelics: New Doors, Altered Perceptions'.

Contents

* Corresponding author. Psychopharmacology and Addiction Research Centre, University of Exeter, Exeter, UK.
E-mail address: celia.morgan@exeter.ac.uk (C.J.A. Morgan).

https://doi.org/10.1016/j.neuropharm.2018.01.017
0028-3908/

1. Introduction

Addiction is a chronic relapsing disorder that is characterised by cravings, habitual drug seeking and unpleasant subjective experiences 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 and 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.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% and 80% at one year post-treatment initiation (Mclellan et al., 2000). Additionally, both stimulant and cannabis use disorder 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 mechanisms.

1.1. 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) and ketamine was later synthesised in 1962 by the chemist Calvin L. Stevens as he produced a series of PCP derivatives (ketamine was first called CI-581).

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 (Enderle et al., 2008; Peterbauer et al., 2008; Spadavecchia et al., 2002; WSAVA, 2016).

In clinical settings, ketamine 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; Sleigh 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 effects reported that are considered most positiveby users are 'giggliness', '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).

1.2. 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 it effects on the CNS within 5 min after injection. Ketamine has a relatively short half-life of 1–3 h, 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.

1.3. 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.

1.4. 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 and 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 discussed with them the content of the psychedelic experience. They were told that under the influence of ketamine, they would view the world symbolically, realise about 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 and Grinenko, 1997). It is reported that this procedure was used in over 1000 alcoholics with no reported complications (Krupitsky, 1992).

In Krupitsky and Grinenko, 1997 report, relapse rates in a group of recently detoxified alcohol dependent patients undergoing KPT ($n = 111$) were compared with 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 ($p < .01$) (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: randomisation 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 randomised 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, $p < .05$). 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 and Grinenko, 1997) due to the randomised 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 randomised 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 ($p < .05$) (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., 2009, 2006).

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 2 mg lorazepam (an active benzodiazepine control, which induces mild subjective and anxiolytic effects) (Dakwar et al., 2014b). Infusions lasted 52 min and were separated by 48 h. 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 0.4 mg/kg ketamine (both $ps = 0.012$), and this latter effect was augmented by the 0.71 mg/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 min. 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 ($p < .0001$). Furthermore, ketamine significantly reduced craving ($p < .01$) and reactivity ($p < .05$), which are both key contributors in relapse, up to 48 h post infusion. Cocaine use in their normal life was also significantly reduced within the first 3 days following ketamine administration compared to midazolam ($p < .05$) and some participants remained abstinent for the entire 2-week follow-up (Dakwar et al., 2016).

2. Ketamine's potential mechanisms of action in addiction

2.1. 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 (Ernst et al., 2014; Zhao et al., 2008). 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 and 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 (Angelucci et al., 2007; Corominas-Roso et al., 2013; Sönmez et al., 2016). 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 anti-depressant 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 anti-depressant 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 h after ketamine infusion (Machado-Vieira et al., 2009) and further research suggests that ketamine's action on BDNF levels might be age-dependent (Huang et al., 2016; Keilhoff et al., 2004) suggesting the picture may be more complex.

2.2. 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 Kometer, 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 Kometer, 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.

2.3. 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 (Autry et al., 2011; Li et al., 2010; Moghaddam et al., 1997) encouraged researchers in the field to perform more studies in

humans (Krystal et al., 2013). Since then, over 30 studies have examined the antidepressants 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 24 h, 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 h, 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 (Ballard et al., 2014; DiazGranados et al., 2010; Larkin and Beautrais, 2011; Rebecca et al., 2009).

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 (Markou et al., 1998; Greenfield et al., 1998; White et al., 2004; Willinger et al., 2002). 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 antidepressants 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.

2.4. 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., 2006, 2005; Miller and Marshall, 2005; Tronson and Taylor, 2007; Xue et al., 2012).

Preclinical studies have shown that ketamine affects reconsolidation of drug memories (Corlett et al., 2013; Goulart et al., 2010; Parwani et al., 2005; Wang et al., 2006; Zhai et al., 2008). A recent review has suggested that ketamine (along with other psychedelics) may be able to disrupt maladaptive appetitive memories (Fattore et al., 2017). 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 (a competitive 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 and despite being an NMDAR antagonist its competitive mechanism means that it differs pharmacologically. Research investigating whether ketamine can disrupt appetitive drug-related memories via reconsolidation is urgently needed in human samples.

2.5. 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 (Griffiths et al., 2008, 2006; Grof, 1985; Hoffer, 1967; Jansen and Sferios, 2001; MacLean et al., 2011; 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 (Garcia-Romeu et al., 2014; Griffiths et al., 2008, 2006; Johnson et al., 2017; Krupitsky and Grinenko, 1997). 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 (Dakwar et al., 2014a; Kolp et al., 2014, 2007; Krupitsky et al., 2002; Krupitsky and Grinenko, 1997)

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 et al., 2002; Krupitsky and Grinenko, 1997). 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 et al., 2002; Krupitsky and Grinenko, 1997). 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 and 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.

2.6. 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).

3. 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 and 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 repeated 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 and Grinenko, 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, 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 h 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.

4. 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.

Conflicts of interest

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

Acknowledgement

This work was funded by an MRC grant (MR/L023032/1) to CJAM and HVC.

References

Alberini, C.M., Ledoux, J.E., 2013. Memory reconsolidation. Curr. Biol. 23, R746–R750. https://doi.org/10.1016/j.cub.2013.06.046.
American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed. fifth ed.. Washington, DC: Author.
Angelucci, F., Ricci, V., Pomponi, M., Conte, G., Mathé, A.A., Attilio Tonali, P., Bria, P., 2007. Chronic heroin and cocaine abuse is associated with decreased serum concentrations of the nerve growth factor and brain-derived neurotrophic factor. J. Psychopharmacol. 21. https://doi.org/10.1177/0269881107078491.
Autry, A.E., Adachi, M., Nosyreva, E., Na, E.S., Los, M.F., Cheng, P.F., Kavalali, E.T., Monteggia, L.M., 2011. NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. Nature 475, 91–95. https://doi.org/10.1038/nature10130.
Ballard, E.D., Ionescu, D.F., Voort, J.L., Vande, Niciu, M.J., Ameli, R., Richards, E.M., Luckenbaugh, D.A., Brutsch, N.E., Furey, M.L., Zarate, C.A.J., 2014. Improvement in suicidal ideation after ketamine infusion: relationship to reductions in depression and anxiety, 58, 161–166. https://doi.org/10.1016/j.jpsychires.2014.07.027.
Barney, W., 1977. Mexican Therapy: “Like the End of the world.”. San Fr. Exam. 24.
Berman, R.M., Cappiello, A., Anand, A., Oren, D.A., Heninger, G.R., Charney, D.S., Krystal, J.H., 2000. Antidepressant effects of ketamine in depressed patients. Soc. Biol. Psychiatry 47, 351–354. https://doi.org/10.1016/S0006-3223(99)00230-9.
Berti, M., Baciarello, M., Troglio, R., Fanelli, G., 2009. Clinical uses of low-dose ketamine in patients undergoing surgery. Curr. Drug Targets 10, 707–715. https://doi.org/10.2174/138945009788982496.
Bogenschutz, M.P., Forcehimes, A.A., Pommy, J.A., Wilcox, C.E., Barbosa, P.C.R., Strassman, R.J., 2015. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J. Psychopharmacol. 29, 289–299. https://doi.org/10.1177/0269881114565144.
Bonhomme, V., Vanhaudenhuyse, A., Demertzi, A., Bruno, M.-A., Jaquet, O., Bahri, M.A., Plenevaux, A., Boly, M., Boveroux, P., Soddu, A., Brichant, J.F., Maquet, P., Laureys, S., 2016. Resting-state network-specific breakdown of functional connectivity during ketamine alteration of consciousness in volunteers. Anesthesiology 873–888. https://doi.org/10.1097/ALN.0000000000001275.
Cai, Y.C., Ma, L., Fan, G.H., Zhao, J., Jiang, L.Z., Pei, G., 1997. Activation of N-methyl-D-aspartate receptor attenuates acute responsiveness of delta-opioid receptors. Mol. Pharmacol. 51, 583–587. https://doi.org/10.1124/mol.51.4.583.
Canbay, O., Celebi, N., Sahin, A., Celiker, V., Ozgen, S., Aypar, U., 2008. Ketamine gargle for attenuating postoperative sore throat. Br. J. Anaesth. 100, 490–493. https://doi.org/10.1093/bja/aen023.
Carhart-Harris, R., Leech, R., Hellyer, P., Shanahan, M., Feilding, A., Tagliazucchi, E., Chialvo, D., Nutt, D., 2014. The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. Front. Hum. Neurosci. 8 (20). https://doi.org/10.3389/fnhum.2014.00020.
Carhart-Harris, R.L., Erritzoe, D., Williams, T., Stone, J.M., Reed, L.J., Colasanti, A., Tyacke, R.J., Leech, R., Malizia, A.L., Murphy, K., Hobden, P., Evans, J., Feilding, A., Wise, R.G., Nutt, D.J., 2012. Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. Proc. Natl. Acad. Sci. U. S. A 109, 2138–2143. https://doi.org/10.1073/pnas.1119598109.
Carhart-Harris, R.L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., Tagliazucchi, E., Schenberg, E.E., Nest, T., Orban, C., Leech, R., Williams, L.T., Williams, T.M., Bolstridge, M., Sessa, B., McGonigle, J., Sereno, M.I., Nichols, D., Hellyer, P.J., Hobden, P., Evans, J., Singh, K.D., Wise, R.G., Curran, H.V., Feilding, A., Nutt, D.J., 2016. Neural correlates of the LSD experience revealed by multimodal neuroimaging. Proc. Natl. Acad. Sci. 113 (201518377). https://doi.org/10.1073/pnas.1518377113.
Carstensen, M., Møller, A.M., 2010. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. Br. J. Anaesth. 104, 401–406. https://doi.org/10.1093/bja/aeq041.
Chambers, R., 2013. Adult hippocampal neurogenesis in the pathogenesis of addiction and dual diagnosis disorders. Drug Alcohol Depend. 130. https://doi.org/10.1016/j.drugalcdep.2012.12.005.
Clarke, H., Woodhouse, L.J., Kennedy, D., Stratford, P., Katz, J., 2011. Strategies aimed at preventing chronic post-surgical pain: comprehensive perioperative pain management after total joint replacement surgery. Physiother. Can. 63, 289–304. https://doi.org/10.3138/ptc.2009-49P.
Clements, J.A., Nimmo, W.S., Grant, I.S., 1982. Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. J. Pharm. Sci. 71, 539–542. https://doi.org/10.1002/jps.2600710516.
Collier, B.B., 1972. Ketamine and the conscious mind. Anaesthesia 27, 120–134. https://doi.org/10.1111/j.1365-2044.1972.tb08186.x.
Constantinou, N., Morgan, C.J.A., Battistella, S., O'Ryan, D., Davis, P., Curran, H.V., 2010. Attentional bias, inhibitory control and acute stress in current and former opiate addicts. Drug Alcohol Depend. 109, 220–225. https://doi.org/10.1016/j.drugalcdep.2010.01.012.
Corlett, P.R., Cambridge, V., Gardner, J.M., Piggot, J.S., Turner, D.C., Everitt, J.C., Arana, F.S., Morgan, H.L., Milton, A.L., Lee, J.L., Aitken, M.R.F., Dickinson, A., Everitt, B.J., Absalom, A.R., Adapa, R., Subramanian, N., Taylor, J.R., Krystal, J.H., Fletcher, P.C., 2013. Ketamine effects on memory reconsolidation favor a learning model of delusions. PLoS One 8, e65088. https://doi.org/10.1371/journal.pone.0065088.
Corominas-Roso, M., Roncero, C., Eiroa-Orosa, F.J., Gonzalvo, B., Grau-Lopez, L., Ribases, M., Rodriguez-Cintas, L., Sánchez-Mora, C., Ramos-Quiroga, J.A., Casas, M., 2013. Brain-derived neurotrophic factor serum levels in cocaine-dependent patients during early abstinence. Eur. Neuropsychopharmacol 23, 1078–1084. https://doi.org/10.1016/j.euroneuro.2012.08.016.
Curran, H.V., Freeman, T.P., Mokrysz, C., Lewis, D.A., Morgan, C.J.A., Parsons, L.H., 2016. Keep off the grass? Cannabis, cognition and addiction. Nat. Rev. Neurosci. 17, 293–306. https://doi.org/10.1038/nrn.2016.28.
Dakwar, E., Anerella, C., Hart, C.L., Levin, F.R., Mathew, S.J., Nunes, E.V., 2014a. Therapeutic infusions of ketamine: do the psychoactive effects matter? Drug Alcohol Depend. 136, 153–157. https://doi.org/10.1016/j.drugalcdep.2013.12.019.
Dakwar, E., Hart, C.L., Levin, F.R., Nunes, E.V., Foltin, R.W., 2016. Cocaine self-administration disrupted by the N-methyl-D-aspartate receptor antagonist ketamine: a randomized, crossover trial. Mol. Psychiatry 1–6. https://doi.org/10.1038/mp.2016.39.
Dakwar, E., Levin, F., Foltin, R.W., Nunes, E.V., Hart, C.L., 2014b. The effects of sub-anesthetic ketamine infusions on motivation to quit and cue-induced craving in cocaine-dependent research volunteers. Biol. Psychiatry 76, 40–46. https://doi.org/10.1016/j.biopsych.2013.08.009.
Das, R.K., Freeman, T.P., Kamboj, S.K., 2013. The effects of N-methyl d-aspartate and B-adrenergic receptor antagonists on the reconsolidation of reward memory: a meta-analysis. Neurosci. Biobehav. Rev. 37, 240–255. https://doi.org/10.1016/j.neubiorev.2012.11.018.
Das, R.K., Hindocha, C., Freeman, T.P., Lazzarino, A.I., Curran, H.V., Kamboj, S.K., 2015. Assessing the translational feasibility of pharmacological drug memory reconsolidation blockade with memantine in quitting smokers. Psychopharmacology (Berl) 232, 3363–3374. https://doi.org/10.1007/s00213-015-3990-2.
DiazGranados, N., Ibrahim, L.A., Brutsche, N.E., Ameli, R., Henter, I.D., Luckenbaugh, D.A., Machado-Vieira, R., Zarate, C.A.J., 2010. Rapid resolution of suicidal ideation after a single infusion of an NMDA antagonist in patients with treatment-resistant major depressive disorder. J. Clin. Psychiatr. 71, 1605–1611. https://doi.org/10.4088/JCP.09m05327blu.Rapid.
Domino, E.F., 2010. Taming the ketamine tiger. Anesthesiology 113, 678–686.

https://doi.org/10.1097/ALN.0b013e3181ed09a2.
Domino, E.F., Chodoff, P., Corssen, G., 1965. Pharmacologic effects of Cl-581, a new dissociative anesthetic, in man. Clin. Pharmacol. Ther. 6, 279–291. https://doi.org/10.1002/cpt196563279.
Driesen, N.R., McCarthy, G., Bhagwagar, Z., Bloch, M., Calhoun, V., D'Souza, D.C., Gueorguieva, R., He, G., Ramachandran, R., Suckow, R.F., Anticevic, A., Morgan, P.T., Krystal, J.H., 2013. Relationship of resting brain hyperconnectivity and schizophrenia-like symptoms produced by the NMDA receptor antagonist ketamine in humans. Mol. Psychiatry 18, 1199–1204. https://doi.org/10.1038/mp.2012.194.
Duman, R.S., Aghajanian, G.K., Sanacora, G., Krystal, J.H., 2016. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat. Med. 22, 238–249. https://doi.org/10.1038/nm.4050.
Duncan, W.C., Sarasso, S., Ferrarelli, F., Selter, J., Riedner, B.A., Hejazi, N.S., Yuan, P., Brutsche, N., Manji, H.K., Tononi, G., Zarate, C.A.J., 2013. Concomitant BDNF and sleep slow wave changes indicate ketamine-induced plasticity in major depressive disorder. Int. J. Neuropsychopharmacol. 16, 301–311. https://doi.org/10.1017/S1461145712000545.
Ebert, B., Mikkelsen, S., Thorkildsen, C., Borgbjerg, F.M., 1997. Norketamine, the main metabolite of ketamine, is a non-competitive NMDA receptor antagonist in the rat cortex and spinal cord. Eur. J. Pharmacol. 333, 99–104. https://doi.org/10.1016/S0014-2999(97)01116-3.
Enderle, A.K., Levionnois, O.L., Kuhn, M., Schatzmann, U., 2008. Clinical evaluation of ketamine and lidocaine intravenous infusions to reduce isoflurane requirements in horses under general anaesthesia. Vet. Anaesth. Analg. 35, 297–305. https://doi.org/10.1111/j.1467-2995.2007.00391.x.
Ernst, A., Alkass, K., Bernard, S., Salehpour, M., Perl, S., Tisdale, J., Possnert, G., Druid, H., Frisén, J., 2014. Neurogenesis in the striatum of the adult human brain. Cell 156, 1072–1083. https://doi.org/10.1016/j.cell.2014.01.044.
Fattore, L., Piva, A., Zanda, M.T., Fumagalli, G., Chiamulera, C., 2017. Psychedelics and reconsolidation of traumatic and appetitive maladaptive memories: focus on cannabinoids and ketamine. Psychopharmacology (Berl) 1–13. https://doi.org/10.1007/s00213-017-4793-4.
Garcia-Romeu, A., Griffiths, R.R., Johnson, M.W., 2014. Psilocybin-Occasioned mystical experiences in the treatment of tobacco addiction. Curr. Drug Abuse Rev. 7, 157–164.
Garg, R., Joshi, S., Mishra, S., Bhatnagar, S., Joshi, S., Mishra, S., 2012. Evidence based practice of chronic pain. Indian J. Palliat. Care 18, 155–161. https://doi.org/10.4103/0973-1075.105684.
Giese, K.P., 2012. Memory Mechanisms in Health and Disease: Mechanistic Basis of Memory. World Scientific.
Goulart, B.K., de Lima, M.N.M., de Farias, C.B., Reolon, G.K., Almeida, V.R., Quevedo, J., Kapczinski, F., Schröder, N., Roesler, R., 2010. Ketamine impairs recognition memory consolidation and prevents learning-induced increase in hippocampal brain-derived neurotrophic factor levels. Neuroscience 167, 969–973. https://doi.org/10.1016/J.NEUROSCIENCE.2010.03.032.
Gowing, L.R., Ali, R.L., Allsop, S., Marsden, J., Turf, E.E., West, R., Witton, J., 2015. Global statistics on addictive behaviours: 2014 status report. Addiction 110, 904–919. https://doi.org/10.1111/add.12899.
Grant, B.F., Stinson, F.S., Dawson, D.A., Chou, S.P., Dufour, M.C., Compton, W., Pickering, R.P., Kaplan, K., 2004. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the national epidemiologic survey on alcohol and related conditions. Arch. Gen. Psychiatr. 61, 807–816. https://doi.org/10.1001/archpsyc.61.8.807.
Greenfield, S.F., Weiss, R.D., Muenz, L.R., Vagge, L.M., Kelly, J.F., Bello, L.R., Michael, J., 1998. The effect of depression on return to drinking: a prospective study. Arch. Gen. Psychiatr. 55, 259–265. https://doi.org/10.1001/archpsyc.55.3.259.
Griffiths, R., Richards, W., Johnson, M., McCann, U., Jesse, R., 2008. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. J. Psychopharmacol. 22, 621–632. https://doi.org/10.1177/0269881108094300.
Griffiths, R., Richards, W., Mccann, U., Jesse, R., 2006. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacol 187, 268–283. https://doi.org/10.1007/s00213-006-0457-5.
Grof, S., 1985. Beyond the Brain: Birth, Death, and Transcendence in Psychotherapy. Suny Press.
Haile, C.N., Murrough, J.W., Iosifescu, D.V., Chang, L.C., Al Jurdi, R.K., Foulkes, A., Iqbal, S., Mahoney, J.J., De La Garza, R., Charney, D.S., Newton, T.F., Mathew, S.J., 2014. Plasma brain derived neurotrophic factor (BDNF) and response to ketamine in treatment-resistant depression. Int. J. Neuropsychopharmacol. 17, 331–336. https://doi.org/10.1017/S1461145713001119.
Hansen, G., Jensen, S.B., Chandresh, L., Hilden, T., 1988. The psychotropic effect of ketamine. J. Psychoact. Drugs 20, 419–425. https://doi.org/10.1080/02791072.1988.10472511.
Harmer, C.J., Cowen, P.J., 2013. "It's the way that you look at it'–a cognitive neuropsychological account of SSRI action in depression. Philos. Trans. R. Soc. Lond. B Biol. Sci. 368 (20120407). https://doi.org/10.1098/rstb.2012.0407.
Hasin, D.S., Goodwin, R.D., Stinson, F.S., Grant, B.F., 2005. Epidemiology of major depressive disorder: results from the national epidemiologic survey on alcoholism and related conditions. Arch. Gen. Psychiatr. 62, 1097–1106. https://doi.org/10.1001/archpsyc.62.10.1097.
Hoffer, A., 1967. A Program for the Treatment of Alcoholism: LSD, Malvaria and Nicotinic Acid, in the Use of LSD in Psychotherapy and Alcoholism. Bobbs-Merrill, Indianapolis.
Huang, H., Liu, C.M., Sun, J., Hao, T., Xu, C.M., Wang, D., Wu, Y.Q., 2016. Ketamine affects the neurogenesis of the hippocampal dentate gyrus in 7-day-old rats. Neurotox. Res. 30, 185–198. https://doi.org/10.1007/s12640-016-9615-7.
Huge, V., Lauchart, M., Magerl, W., Schelling, G., Beyer, A., Thieme, D., Azad, S.C., 2010. Effects of low-dose intranasal (S)-ketamine in patients with neuropathic pain. Eur. J. Pain 14, 387–394. https://doi.org/10.1016/j.ejpain.2009.08.002.
Jansen, K.L.R., Sferios, E., 2001. Ketamine: Dreams and Realities. Multidisciplinary Association for Psychedelic Studies.
Johnson, M.W., Garcia-Romeu, A., Cosimano, M.P., Griffiths, R.R., 2014. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J. Psychopharmacol. 28, 983–992. https://doi.org/10.1177/0269881114548296.
Johnson, M.W., Garcia-Romeu, A., Griffiths, R.R., 2017. Long-term follow-up of psilocybin-facilitated smoking cessation. Am. J. Drug Alcohol Abuse 43, 55–60. https://doi.org/10.3109/00952990.2016.1170135.
Kalivas, P.W., 2009. The glutamate homeostasis hypothesis of addiction. Nat. Rev. Neurosci. 10, 561–572. https://doi.org/10.1038/nrn2515.
Kalivas, P.W., Volkow, N.D., 2005. The neural basis of addiciton: a pathology of motivation and choice. Am. J. Psychiatr. 162, 1403–1413. https://doi.org/10.1176/appi.ajp.162.8.1403.
Kavalali, E.T., Monteggia, L.M., 2015. How does ketamine elicit a rapid antidepressant response? Curr. Opin. Pharmacol. 20, 35–39. https://doi.org/10.1016/j.coph.2014.11.005.
Keilhoff, G., Bernstein, H.G., Becker, A., Grecksch, G., Wolf, G., 2004. Increased neurogenesis in a rat ketamine model of schizophrenia. Biol. Psychiatry 56, 317–322. https://doi.org/10.1016/j.biopsych.2004.06.010.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). Jama 289, 3095–3105.
Kolp, E., Friedman, H.L., Krupitsky, E., Jansen, K., Sylvester, M., Young, M.S., Kolp, A., 2014. Ketamine psychedelic psychotherapy: focus on its pharmacology, phenomenology, and clinical applications. Int. J. Transpers. Stud 33, 84–140.
Kolp, E., Friedman, H.L., Young, M.S., Krupitsky, E., 2006. Ketamine enhanced psychotherapy: preliminary clinical observations on its effectiveness in treating alcoholism. Humanist. Psychol. 34, 399. https://doi.org/10.1207/s15473333thp3404_7.
Kolp, E., Krupitsky, E., Friedman, H., Young, M.S., 2009. Entheogen-enhanced transpersonal psychotherapy of addictions: focus on clinical applications of ketamine for treating alcoholism. Praeger Int. Collect. Addict 3, 403–417.
Kolp, E., Krupitsky, E., Young, M.S., Jansen, K., Friedman, H., O'Connor, L.A., 2007. Ketamine-enhanced psychotherapy: preliminary clinical observations on its effects in treating death anxiety. Int J Transpers. Stud 26.
Koob, G.F., Volkow, N.D., 2010. Neurocircuitry of addiction. Neuropsychopharmacology 35, 217–238. https://doi.org/10.1038/npp.2009.110.
Krebs, T.S., Johansen, P.-Ø., 2012. Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J. Psychopharmacol. 26, 994–1002. https://doi.org/10.1177/0269881112439253.
Krupitsky, E.M., 1992. Ketamine psychedelic therapy (KPT) of alcoholism and neurosis. Multidiscip. Assoc. Psychedelic Stud. Newsl. 3, 24–28.
Krupitsky, E.M., Burakov, A., Romanova, T., Dunaevsky, I., Strassman, R., Grinenko, A., 2002. Ketamine psychotherapy for heroin addiction: immediate effects and two-year follow-up. J. Subst. Abuse Treat. 23, 273–283. https://doi.org/10.1016/S0740-5472(02)00275-1.
Krupitsky, E.M., Burakov, A.M., Dunaevsky, I.V., Romanova, T.N., Slavina, T.Y., Grinenko, A.Y., 2007. Single versus repeated sessions of ketamine-assisted psychotherapy for people with heroin dependence. J. Psychoact. Drugs 39, 13–19. https://doi.org/10.1080/02791072.2007.10399860.
Krupitsky, E.M., Grinenko, A.Y., 1997. Ketamine psychedelic therapy (KPT): a review of the results of ten years of research. J. Psychoact. Drugs 29, 165–183. https://doi.org/10.1080/02791072.1997.10400185.
Krystal, J.H., Bennett, A., Abi-Saab, D., Belger, A., Karper, L.P., D'Souza, D.C., Lipschitz, D., Abi-Dargham, A., Charney, D.S., 2000. Dissociation of ketamine effects on rule acquisition and rule implementation: possible relevance to NMDA receptor contributions to executive cognitive functions. Biol. Psychiatry 47, 137–143. https://doi.org/10.1016/S0006-3223(99)00097-9.
Krystal, J.H., D'Souza, D.C., Karper, L.P., Bennett, A., Abi-Dargham, A., Abi-Saab, D., Cassello, K., Bowers Jr., M.B., Vegso, S., Heninger, G.R., 1999. Interactive effects of subanesthetic ketamine and haloperidol in healthy humans. Psychopharmacology (Berl) 145, 193–204. https://doi.org/10.1007/s002130051049.
Krystal, J.H., Karper, L.P., Bennett, A., D'Souza, D.C., Abi-Dargham, A., Morrissey, K., Abi-Saab, D., Bremner, J.D., Bowers Jr., M.B., Suckow, R.F., 1998. Interactive effects of subanesthetic ketamine and subhypnotic lorazepam in humans. Psychopharmacology (Berl) 135, 213–229.
Krystal, J.H., Karper, L.P., Seibyl, J.P., Freeman, G.K., Delaney, R., Bremner, J.D., Heninger, G.R., Bowers, M.B., Charney, D.S., 1994. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch. Gen. Psychiatr. 51, 199–214. https://doi.org/10.1001/archpsyc.1994.03950030035004.
Krystal, J.H., Sanacora, G., Duman, R.S., 2013. Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. Biol. Psychiatry 73, 1133–1141. https://doi.org/10.1016/j.virol.2008.08.028.Macropinocytosis.
Kubota, T., Hirota, K., Yoshida, H., Takahashi, S., Anzawa, N., Ohkawa, H., Kushikata, T., Matsuki, A., 1999. Effects of sedatives on noradrenaline release from the medial prefrontal cortex in rats. Psychopharmacol 146, 335–338. https://doi.org/91460335.213.

Kurdi, M.S., Theerth, K.A., Deva, R.S., 2014. Ketamine: current applications in anesthesia, pain, and critical care. Anesth. Essays Res. 8, 283–290. https://doi.org/10.4103/0259-1162.143110.
Lapidus, K.A.B., Levitch, C.F., Perez, A.M., Brallier, J.W., Michael, K., Soleimani, L., Feder, A., Iosifescu, D.V., Charney, D.S., Murrough, J.W., 2014. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol. Psychiatry 76, 970–976. https://doi.org/10.1016/j.biopsych.2014.03.026.A.
Larkin, G.L., Beautrais, A.L., 2011. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department, 1127–1131. https://doi.org/10.1017/S1461145711000629.
Lee, J.L.C., 2009. Reconsolidation: maintaining memory relevance. Trends Neurosci. 32, 413–420. https://doi.org/10.1016/j.tins.2009.05.002.
Lee, J.L.C., Di Ciano, P., Thomas, K.L., Everitt, B.J., 2005. Disrupting reconsolidation of drug memories reduces cocaine-seeking behavior. Neuron 47, 795–801. https://doi.org/10.1016/j.neuron.2005.08.007.
Lee, J.L.C., Milton, A.L., Everitt, B.J., 2006. Cue-induced cocaine seeking and relapse are reduced by disruption of drug memory reconsolidation. J. Neurosci. 26, 5881–5887. https://doi.org/10.1523/JNEUROSCI.0323-06.2006.
Lener, M.S., Kadriu, B., Zarate, C.A., 2017. Ketamine and beyond: investigations into the potential of glutamatergic agents to treat depression. Drugs 77, 381–401. https://doi.org/10.1007/s40265-017-0702-8.
Lepack, A.E., Fuchikami, M., Dwyer, J.M., Banasr, M., Duman, R.S., 2015. BDNF release is required for the behavioral actions of ketamine. Int. J. Neuropsychopharmacol. 18 pyu033-pyu033. https://doi.org/10.1093/ijnp/pyu033.
Lewis, D.J., 1979. Psychobiology of active and inactive memory. Psychol. Bull. 86, 1054.
Li, N., Lee, B., Liu, R.J., Banasr, M., Dwyer, J.M., Iwata, M., Li, X.Y., Aghajanian, G., Duman, R.S., 2010. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists (80-.). Science 329, 959–964. https://doi.org/10.1126/science.1190287.
Lingford-Hughes, A., Welch, S., Peters, L., Nutt, D., 2012. BAP updated guidelines: evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity: recommendations from BAP. J. Psychopharmacol. 26, 899–952. https://doi.org/10.1177/0269881112444324.
Lydic, R., Baghdoyan, H.A., 2002. Ketamine and MK-801 decrease acetylcholine release in the pontine reticular formation, slow breathing, and disrupt sleep. Sleep 25, 617–622.
Machado-Vieira, R., Salvadore, G., Diazgranados, N., Zarate, C.A.J., 2009. Ketamine and the next generation of antidepressants with a rapid onset of action. Pharmacol. Ther. 123, 143–150. https://doi.org/10.1016/j.pharmthera.2009.02.010.
MacLean, K.A., Johnson, M.W., Griffiths, R.R., 2011. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. J. Psychopharmacol. 25, 1453–1461. https://doi.org/10.1177/0269881111420188.
Mandyam, C.D., Koob, G.F., 2012. The addicted brain craves new neurons: putative role for adult-born progenitors in promoting recovery. Trends Neurosci. 35, 250–260. https://doi.org/10.1016/j.tins.2011.12.005.
Markou, A., Kosten, T.R., Koob, G.F., 1998. Neurobiological similarities in depression and drug dependence: a self- medication hypothesis. Neuropsychopharmacology 18, 135–174. https://doi.org/10.1016/S0893-133X(97)00113-9.
Mason, B.J., Kocsis, J.H., Ritvo, E.C., Cutler, R.B., 1996. A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. JAMA1 275, 761–767. https://doi.org/10.1001/jama.1996.03530340025025.
McAndrew, A., Lawn, W., Stevens, T., Porffy, L., Brandner, B., Morgan, C.J.A., 2017. A proof-of-concept investigation into ketamine as a pharmacological treatment for alcohol dependence: study protocol for a randomised controlled trial. Trials 18 (159). https://doi.org/10.1186/s13063-017-1895-6.
McGirr, A., Berlim, M.T., Bond, D.J., Fleck, M.P., Yatham, L.N., Lam, R.W., 2015. A systematic review and meta-analysis of randomized, double-blind, placebo-controlled trials of ketamine in the rapid treatment of major depressive episodes. Psychol. Med. 45, 693–704. https://doi.org/10.1017/S0033291714001603.
Mclellan, A., Lewis, D., O'Brien, C., Kleber, H., 2000. Drug dependence, a chronic medical illness. JAMA, J. Am. Med. Assoc. 284, 1689. https://doi.org/10.1001/jama.284.13.1689.
Miller, C.A., Marshall, J.F., 2005. Molecular substrates for retrieval and reconsolidation of cocaine-associated contextual memory. Neuron 47, 873–884. https://doi.org/10.1016/J.NEURON.2005.08.006.
Moghaddam, B., Adams, B., Verma, A., Daly, D., 1997. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J. Neurosci. 17, 2921–2927. https://doi.org/10.1016/0091-3057(93)90217-H.
Morgan, C.J.A., Curran, H.V., 2012. Ketamine use: a review. Addiction 107, 27–38. https://doi.org/10.1111/j.1360-0443.2011.03576.x.
Morgan, C.J.A., McAndrew, A., Stevens, T., Nutt, D., Lawn, W., 2017. Tripping up addiction: the use of psychedelic drugs in the treatment of problematic drug and alcohol use. Curr. Opin. Behav. Sci. 13, 71–76. https://doi.org/10.1016/j.cobeha.2016.10.009.
Morgan, C.J.A., Mofeez, A., Brandner, B., Bromley, L., Curran, H.V., 2004. Ketamine impairs response inhibition and is positively reinforcing in healthy volunteers: a dose-response study. Psychopharmacology (Berl) 172, 298–308. https://doi.org/10.1007/s00213-003-1656-y.
Nader, K., Schafe, G.E., Le Doux, J.E., 2000. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. Nature 406, 722. https://doi.org/10.1038/35021052.
Niesters, M., Khalili-Mahani, N., Martini, C., Aarts, L., van Gerven, J., van Buchem, M.a., Dahan, A., Rombouts, S., 2012. Effect of subanesthetic ketamine on intrinsic functional brain connectivity. Anesthesiology 117, 868–877. https://doi.org/10.1097/ALN.0b013e31826a0db3.
Noonan, M.A., Bulin, S.E., Fuller, D.C., Eisch, A.J., 2010. Reduction of adult hippocampal neurogenesis confers vulnerability in an animal model of cocaine addiction. J. Neurosci. 30, 304–315. https://doi.org/10.1523/JNEUROSCI.4256-09.2010.
O'Brien, C.P., Gardner, E.L., 2005. Critical assessment of how to study addiction and its treatment: human and non-human animal models. Pharmacol. Ther. 108, 18–58. https://doi.org/10.1016/j.pharmthera.2005.06.018.
O'Hara, D., Ganeshalingam, K., Gerrish, H., Richardson, P., 2014. A 2 year experience of nurse led conscious sedation in paediatric burns. Burns 40, 48–53. https://doi.org/10.1016/J.BURNS.2013.08.021.
Ota, K.T., Duman, R.S., 2013. Environmental and pharmacological modulations of cellular plasticity: role in the pathophysiology and treatment of depression. Neurobiol. Dis. 57, 28–37. https://doi.org/10.1016/j.nbd.2012.05.022.
Oye, I., Paulsen, O., Maurset, A., 1992. Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. J. Pharmacol. Exp. Therapeut. 260, 1209.
Parwani, A., Weiler, M.A., Blaxton, T.A., Warfel, D., Hardin, M., Frey, K., Lahti, A.C., 2005. The effects of a subanesthetic dose of ketamine on verbal memory in normal volunteers. Psychopharmacology (Berl) 183, 265–274. https://doi.org/10.1007/s00213-005-0177-2.
Paul, R.K., Singh, N.S., Khadeer, M., Moaddel, R., Sanghvi, M., Green, C.E., O'Loughlin, K., Torjman, M.C., Bernier, M., Wainer, I.W., 2014. (R,S)-Ketamine metabolites (R,S)-norketamine and (2S,6S)-hydroxynorketamine increase the mammalian target of rapamycin function. Anesthesiology 121, 149–159. https://doi.org/10.1097/ALN.0000000000000285.
Peterbauer, C., Larenza, P.M., Knobloch, M., Theurillat, R., Thormann, W., Mevissen, M., Spadavecchia, C., 2008. Effects of a low dose infusion of racemic and S-ketamine on the nociceptive withdrawal reflex in standing ponies. Vet. Anaesth. Analg. 35, 414–423. https://doi.org/10.1111/j.1467-2995.2008.00402.x.
Pettinati, H.M., 2004. Antidepressant treatment of co-occurring depression and alcohol dependence. Biol. Psychiatry 56, 785–792. https://doi.org/10.1016/j.biopsych.2004.07.016.
Quello, S.B., Brady, K.T., Sonne, S.C., 2005. Mood disorders and substance use disorder: a complex comorbidity. Sci. Pract. Perspect 3, 13.
Rebecca, B., Nock, M.K., Charney, D.S., Link, C., 2009. Effects of intravenous ketamine on explicit and implicit measures of suicidality in treatment-resistant depression. Biol. Psychiatry 66, 522–526. https://doi.org/10.1016/j.biopsych.2009.04.029.
Rudd, R., Seth, P., Felicita, D., Scholl, L., 2016. Increases in drug and opioid-involved overdose deaths — United States, 2010–2015. MMWR Morb. Mortal. Wkly. Rep. 65, 1445–1452. https://doi.org/10.15585/mmwr.mm655051e1.
Sabino, V., Narayan, A.R., Zeric, T., Steardo, L., Cottone, P., 2013. mTOR activation is required for the anti-alcohol effect of ketamine, but not memantine, in alcohol-preferring rats. Behav. Brain Res. 9–16. https://doi.org/10.1016/j.bbr.2013.02.030.mTOR.
Scheidegger, M., Walter, M., Lehmann, M., Metzger, C., Grimm, S., Boeker, H., Boesiger, P., Henning, A., Seifritz, E., 2012. Ketamine decreases resting state functional network connectivity in healthy subjects: implications for antidepressant drug action. PLoS One 7, 1–9. https://doi.org/10.1371/journal.pone.0044799.
Scheller, M., Bufler, J., Hertle, I., Schneck, H.J., Franke, C., Kochs, E., 1996. Ketamine blocks currents through mammalian nicotinic acetylcholine receptor channels by interaction with both the open and the closed state. Anesth. Analg. 83, 830–836. https://doi.org/10.1097/00000539-199610000-00031.
Sessa, B., 2012. The Psychedelic Renaissance: Reassessing the Role of Psychedelic Drugs in 21st Century Psychiatry and Society, First. ed. Muswell Hill Press.
Sheline, Y.I., Price, J.L., Yan, Z., Mintun, M.A., 2010. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc. Natl. Acad. Sci. 107, 11020–11025. https://doi.org/10.1073/pnas.1000446107.
Singh, I., Morgan, C., Curran, V., Nutt, D., Schlag, A., McShane, R., 2017. Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight. The Lancet Psychiatry 4, 419–426. https://doi.org/10.1016/S2215-0366(17)30102-5.
Singh, J.B., Fedgchin, M., Daly, E.J., De Boer, P., Cooper, K., Lim, P., Pinter, C., Murrough, J.W., Sanacora, G., Shelton, R.C., Kurian, B., Winokur, A., Fava, M., Manji, H., Drevets, W.C., Van Nueten, L., 2016. A double-blind, randomized, placebo-controlled, dose-frequency study of intravenous ketamine in patients with treatment-resistant depression. Am. J. Psychiatry 173, 816–826. https://doi.org/10.1176/appi.ajp.2016.16010037.
Sleigh, J., Harvey, M., Voss, L., Denny, B., 2014. Ketamine - more mechanisms of action than just NMDA blockade. Trends Anaesth. Crit. Care 4, 76–81. https://doi.org/10.1016/j.tacc.2014.03.002.
Sönmez, M.B., Görgülü, Y., Köse Çınar, R., Kahyacı Kılıç, E., Ünal, A., Vardar, M., 2016. Alterations of BDNF and GDNF serum levels in alcohol-addicted patients during alcohol withdrawal. Eur. J. Psychiatr. 30, 109–118.
Sos, P., Klirova, M., Novak, T., Kohutova, B., Horacek, J., Palenicek, T., 2013. Relationship of ketamine's antidepressant and psychotomimetic effects in unipolar depression, 55, 57–63.

Spadavecchia, C., Stucki, F., Moens, Y., Schatzmann, U., 2002. Anaesthesia in horses using halothane and intravenous ketamine-guaiphenesin: a clinical study. Vet. Anaesth. Analg. 29, 20–28. https://doi.org/10.1046/j.1467-2987.2001.00060.x.

Strassman, R.J., 1995. Hallucinogenic drugs in psychiatric research and treatment: perspectives and prospects. J. Nerv. Ment. Dis. 183, 127–138. https://doi.org/10.1097/00005053-199503000-00002.

Sunder, R.a, Toshniwal, G., Dureja, G.P., 2008. Ketamine as an adjuvant in sympathetic blocks for management of central sensitization following peripheral nerve injury. J. Brachial Plexus Peripher. Nerve Inj. 3, 22. https://doi.org/10.1186/1749-7221-3-22.

Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M., 2006. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am. J. Psychiatry 163, 28–40. https://doi.org/10.1176/appi.ajp.163.1.28.

Tronson, N.C., Taylor, J.R., 2007. Molecular mechanisms of memory reconsolidation. Nat. Rev. Neurosci. 8, 262. https://doi.org/10.1038/nrn2090.

Vollenweider, F.X., Kometer, M., 2010. The neurobiology of psychedelic drugs: implications for the treatment of mood disorders. Nat. Rev. Neurosci. 11. https://doi.org/10.1038/nrn2884.

Vollenweider, F.X., Leenders, K.L., Oye, I., Hell, D., Angst, J., 1997a. Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). Eur. Neuropsychopharmacol 7, 25–38. https://doi.org/0924-977X.

Vollenweider, F.X., Leenders, K.L., Scharfetter, C., Antonini, A., Maguire, P., Missimer, J., Angst, J., 1997b. Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [18F]-fluorodeoxyglucose (FDG). Eur. Neuropsychopharmacol 7, 9–24. https://doi.org/10.1016/S0924-977X(96)00039-9.

Vollenweider, F.X., Leenders, K.L., Scharfetter, C., Maguire, P., Stadelmann, O., Angst, J., 1997c. Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. Neuropsychopharmacology 16, 357–372. https://doi.org/10.1016/S0893-133X(96)00246-1.

Wang, J.H., Fu, Y., Wilson, F.A.W., Ma, Y.Y., 2006. Ketamine affects memory consolidation: differential effects in T-maze and passive avoidance paradigms in mice. Neuroscience 140, 993–1002. https://doi.org/10.1016/J.NEUROSCIENCE.2006.02.062.

Wang, M., Wong, A.H., Liu, F., 2012. Interactions between NMDA and dopamine receptors: a potential therapeutic target. Brain Res. 1476, 154–163. https://doi.org/10.1016/j.brainres.2012.03.029.

White, A.M., Jordan, J.D., Schroeder, K.M., Acheson, S.K., Georgi, B.D., Sauls, G., Ellington, R.R., Swartzwelder, H.S., 2004. Predictors of relapse during treatment and treatment completion among marijuana- dependent adolescents in an intensive outpatient substance abuse program. Subst. Abuse 25 (1), 53–59. https://doi.org/10.1300/J465v25n01.

WHO, 2015. WHO Recommends against International Control of Ketamine [WWW Document]. URL. http://www.who.int/medicines/access/controlled-substances/recommends_against_ick/en/ (accessed 12.2.17).

Willinger, U., Lenzinger, E., Hornik, K., Fischer, G., Schönbeck, G., Aschauer, H.N., Meszaros, K., 2002. Anxiety as a predictor of relapse in detoxified alcohol-dependent patients. Alcohol Alcohol 37, 609–612. https://doi.org/10.1093/alcalc/37.6.609.

Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., van Os, J., Preisig, M., Salvador-Carulla, L., Simon, R., Steinhausen, H.C., 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol 21, 655–679. https://doi.org/10.1016/j.euroneuro.2011.07.018.

WSAVA, 2016. The WSAVA Global Pain Council (GPC)'s Statement on Ketamine [WWW document]. URL. https://www.wsava.org/sites/default/files/TheWSAVAGlobalPainCouncilStatementonKetamine.pdf (accessed 12.2.17).

Xue, Y.X., Luo, Y.X., Wu, P., Shi, H.S., Xue, L.F., Chen, C., Zhu, W.L., Ding, Z.B., Bao, Y.P., Shi, J., Epstein, D.H., 2012. A memory retrieval-extinction procedure to prevent drug craving and relapse (80-.). Science 336, 241–245. https://doi.org/10.1126/science.1215070.A.

Yang, C., Shirayama, Y., Zhang, J., Ren, Q., Yao, W., Ma, M., Dong, C., Hashimoto, K., 2015. R -ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. Transl. Psychiatry 5, 1–8. https://doi.org/10.1038/tp.2015.136.

Zanardini, R., Fontana, A., Pagano, R., Mazzaro, E., Bergamasco, F., Romagnosi, G., Gennarelli, M., Bocchio-Chiavetto, L., 2011. Alterations of brain-derived neurotrophic factor serum levels in patients with alcohol dependence. Alcohol Clin. Exp. Res. 35, 1529–1533. https://doi.org/10.1111/j.1530-0277.2011.01489.x.

Zanos, P., Moaddel, R., Morris, P.J., Georgiou, P., Fischell, J., Elmer, G.I., Alkondon, M., Yuan, P., Pribut, H.J., Singh, N.S., Dossou, K.S.S., Fang, Y., Huang, X.-P., Mayo, C.L., Wainer, I.W., Albuquerque, E.X., Thompson, S.M., Thomas, C.J., Zarate, C.A.J., Gould, T.D., 2016. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 533, 1–18. https://doi.org/10.1038/nature17998.

Zarate, C.A.J., Singh, J.B., Carlson, P.J., Brutsche, N.E., Ameli, R., Luckenbaugh, D.A., Charney, D.S., Manji, H.K., 2006. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch. Gen. Psychiatr. 638. https://doi.org/10.1001/archpsyc.63.8.856.

Zhai, H., Wu, P., Chen, S., Li, F., Liu, Y., Lu, L., 2008. Effects of scopolamine and ketamine on reconsolidation of morphine conditioned place preference in rats. Behav. Pharmacol. 19, 211–216. https://doi.org/10.1097/fbp.0b013e3282fe88a0.

Zhang, J.-C., Li, S.-X., Hashimoto, K., 2014. R(−)-ketamine shows greater potency and longer lasting antidepressant effects than S(+)-ketamine. Pharmacol., Biochem. Behav. 116, 137–141. https://doi.org/10.1016/j.pbb.2013.11.033.

Zhao, C., Deng, W., Gage, F.H., 2008. Mechanisms and functional implications of adult neurogenesis. Cell 132, 645–660. https://doi.org/10.1016/J.CELL.2008.01.033.