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OVERVIEW

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Ketamine use: a review

Celia J. A. Morgan & H. Valerie Curran
on behalf of the Independent Scientific Committee on Drugs (ISCD)

Clinical Psychopharmacology Unit, Clinical Health Psychology, University College London, London, UK

ABSTRACT

Aims Ketamine remains an important medicine in both specialist anaesthesia and aspects of pain management. At the same time, its use as a recreational drug has spread in many parts of the world during the past few years. There are now increasing concerns about the harmful physical and psychological consequences of repeated misuse of this drug. The aim of this review was to survey and integrate the research literature on physical, psychological and social harms of both acute and chronic ketamine use. **Method** The literature on ketamine was systematically searched and findings were classified into the matrix of Nutt *et al.*'s (2007) rational scale for assessing the harms of psychoactive substances. **Results** A major physical harm is ketamine induced ulcerative cystitis which, although its aetiology is unclear, seems particularly associated with chronic, frequent use of the drug. Frequent, daily use is also associated with neurocognitive impairment and, most robustly, deficits in working and episodic memory. Recent studies suggest certain neurological abnormalities which may underpin these cognitive effects. Many frequent users are concerned about addiction and report trying but failing to stop using ketamine. **Conclusions** The implications of these findings are drawn out for treatment of ketamine-induced ulcerative cystitis in which interventions from urologists and from addiction specialists should be coordinated. Neurocognitive impairment in frequent users can impact negatively upon achievement in education and at work, and also compound addiction problems. Prevention and harm minimization campaigns are needed to alert young people to these harmful and potentially chronic effects of ketamine.

Keywords Addiction, chronic, cognitive, dependence, harms, ketamine, neurological, physical harms, social harms, ulcerative cystitis.

Correspondence to: H. Valerie Curran, Clinical Psychopharmacology Unit, Clinical Health Psychology, University College London, Gower Street, London WC1E 6BT, UK. E-mail: v.curran@ucl.ac.uk
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INTRODUCTION

Since it was first introduced as an anaesthetic in 1964, ketamine has had a fascinating history. Its safety profile made it the key anaesthetic for American soldiers injured during the Vietnam War. Today it remains the most widely used anaesthetic in veterinary medicine. Ketamine's psychosis-like effects have led to it being used as a pharmacological 'model' of schizophrenia. These same effects have also contributed to it becoming used as a recreational drug. Famously, the physician John Lilly took ketamine repeatedly in the late 1970s, describing his experience as like being 'a peeping Tom at the keyhole of eternity'. Recreational use of ketamine ('K', 'ket', 'Special K') has increased over recent years in many parts of the world and new problems have emerged—especially for those using heavily—including physical harms and addiction. At the same time, ketamine now plays a medical role in pain management and is being explored for its possible anti-depressant effects.

Pharmacologically, ketamine's main action is on glutamate, the major excitatory neurotransmitter in the brain. It is a non-competitive antagonist at one of the three glutamate receptors: the N-methyl D-aspartate (NMDA) receptor. Because of its role in synaptic plasticity, the NMDA-receptor is central to learning and memory. Ketamine also has less prominent actions at other receptor sites. It blocks muscarinic acetylcholine receptors and may potentiate the effects of gamma-aminobutyric acid (GABA) synaptic inhibition. Ketamine also induces activation of dopamine release [1] and acts as a weak agonist at mμ opioid receptors [2]. Ketamine exists as two optimal isomers—(S)-(+) and (R)-(-)-2-(2-chlorophenyl)-2-(methylamino) cyclohexanone with differing affinities

at the NMDA-receptor. Both the more potent S-(+) and the less potent R(-) enantiomers have similar pharmacokinetic profiles.

Medical uses of ketamine

Ketamine's important medical uses should be clearly distinguished from its non-medical use. Ketamine was first synthesized as a replacement for phencyclidine (PCP, 'angel dust'), which had a range of adverse effects. Like phencyclidine, ketamine was shown to be a potent 'dissociative anaesthetic' that produced profound analgesia and amnesia without any slowing of heart rate or breathing. However, patients often reported a variety of unusual symptoms when recovering from ketamine anaesthesia. These 'emergence phenomena' included delusions, hallucinations, delirium and confusion, and sometimes 'out-of-body' and 'near-death' experiences. In turn, these phenomena led to ketamine being withdrawn from mainstream anaesthetic use with humans.

Ketamine is still used today in specialist anaesthesia, particularly paediatrics, veterinary anaesthesia and field medicine. Its good safety profile (relative preservation of airway reflexes and haemodynamic stability; spontaneous ventilation) has also led to it being the anaesthetic drug of choice in parts of the world that have limited availability of resuscitation equipment. In veterinary medicine, ketamine is the most widely used anaesthetic agent in all animal species. Its popularity in equine medicine is reflected in a common street name: 'the horse tranquillizer'.

Ketamine also has a role in pain management in both human and veterinary medicine. It is a potent analgesic which prevents 'wind-up', where neurones in the spinal cord become sensitized to painful stimuli [3]. In this way, low doses of ketamine given before, during and after surgery improves post-operative pain relief. In humans, low doses (0.1–0.5 mg/kg/hour) of ketamine can be used as local anaesthetics and co-analgesics, and are particularly effective for neuropathic pain [4] which is notoriously difficult to treat. Low-dose ketamine is also effective in treating complex regional pain syndrome [5]. It can also be used to relieve acute pain, although its psychosis-like side effects may make co-administration of a benzodiazepine necessary. Ketamine has also been used in intensive care management of cases of prolonged epileptic seizures [6].

Other potential medical uses of ketamine are currently being researched (see [7]), particularly in treatment-resistant depression (e.g. [8]) and in heroin and alcohol addiction [9]. There are also experimental studies using single doses to explore the 'ketamine model' of psychosis (e.g. [10,11]).

Non-medical use of ketamine

Precisely those effects that limited the clinical use of ketamine made the drug appealing to recreational drug users. The first reports of non-medical ketamine use appeared in the 1960s [12], but use remained rare in Europe until the 1990s, when it appeared on the 'rave' scene as an adulterant to ecstasy tablets [13]. At low doses ketamine induces distortion of time and space, hallucinations and mild dissociative effects. According to users, the most appealing aspects of ketamine use are 'melting into the surroundings', 'visual hallucinations', 'out-of-body experiences' and 'giggliness' [30]. At large doses, ketamine induces a more severe dissociation commonly referred to as a 'K-hole', wherein the user experiences intense detachment to the point that their perceptions appear completely divorced from their previous reality. Some users—astronauts of the psyche or 'psychonauts'—value these profoundly altered states of consciousness, whereas others see the resulting decreased sociability as a less appealing aspect of ketamine use.

Ketamine is primarily obtained in a powder form and administered through snorting or inhaling. Other forms of ingestion include liquid injected intramuscularly or occasionally intravenously. Ketamine is rarely taken orally, as by this route ketamine is metabolized to norketamine quickly and produces a more sedative and less psychedelic experience.

Although a controlled drug in many countries, ketamine is not currently under international control and figures on its use world-wide are unavailable. The United Nations *World Drug Report* [14] describes the spread of the drug across East Asia, Australia, North America and Europe and stressed: 'the dramatically increasing use and availability of ketamine in parts of South-East Asia linked to the absence of international restrictions on the drug' (p. 114). In Hong Kong, ketamine was deemed to be the single most abused drug. Diversion from the legitimate trade remains the primary source of ketamine but industrial-scale manufacture of illicit ketamine is now emerging. For example, in 2009, China reported the seizure from two illicit laboratories of 8.5 million tons of the immediate precursor chemical for ketamine [14].

In the United Kingdom, ketamine was classified as a Class C substance in 2006. According to the annual DrugScope [15] survey, the average price of a gram of ketamine in the United Kingdom fell from £30 to £20 between 2005 and 2008 and has since become cheaper still. Ketamine has been included in the British Crime Survey (BCS) since 2006 and estimates suggest an increase in numbers of ketamine users from around 85 000 in 2006/07 to 113 000 in 2008/09 [16]. Use in the previous year among young people aged 16–24 doubled between 2007/08 and 2008/09 (from 0.9% to

1.9%) but was steady in 2009/10 (1.7%) [17]. This compares with 2009/10 use of cannabis (16.1%), cocaine (5.5%), ecstasy (4.3%), amyl nitrate (3.2%), amphetamines (2.4%) and magic mushrooms (1.2%). Numbers in this age group having ever used ketamine have unsurprisingly increased (2.2% 2007/8; 3.6% 2008/9; 4% 2009/10). In the United States, ketamine is a schedule III drug which has been 'ever used' by an estimated 1–2% of 10th- and 12th-graders [18].

While the use of ketamine was initially confined to certain subcultures [13], it has recently become more mainstream. For example, a survey of clubbers in 2001 found that 25% of respondents had taken ketamine [19], while a similar survey in 2009 showed that this had increased to 68% [20]. These latest data show a third of respondents reported using ketamine in the previous month, suggesting that ketamine is now the fourth most popular drug among UK clubbers after cannabis, ecstasy and cocaine.

Since ketamine was classified in the United Kingdom and its use has become more widespread, further data have emerged suggesting a range of risks associated with ketamine use that were not known at the time of the original review by the Advisory Council on the Misuse of Drugs (ACMD) [21]. Therefore the Independent Scientific Committee on Drugs (ISCD) decided to review ketamine again in the light of this new information.

Methodology

The 'rational scale' developed by Nutt and colleagues [22] was used as a framework for assessing the harms associated with ketamine use. This divides the harms associated with psychoactive substances into a matrix of nine under three broad categories, each with three subcategories: 'physical harms' (acute physical risks, chronic risks, propensity for intravenous use); 'dependence-related harms' (acute pleasure, risk of physical dependence, propensity for psychological dependence) and 'social harms' (acute social harms of intoxication, harms to the individual within society, costs to the health service).

A comprehensive search syntax was developed using indexed keywords (e.g. MeSH). The following databases were searched: MEDLINE, PsycINFO, Web of Knowledge and Google Scholar. The outputs of searches were considered against pre-specified inclusion and exclusion criteria. Initially all evidence was reviewed to September 2010. Conclusions were drawn from studies on the basis of a pre-defined hierarchy of research design:

- Level 1: Pre-existing systematic research syntheses of clinical data (systematic reviews, meta-analyses, syntheses of qualitative data)
- Level 2: Controlled observational studies (cohort studies, case–control studies, etc.)
- Level 3: Uncontrolled observational evidence (case reports and case series)
- Level 4: Pre-clinical data

Preferred evidence was levels 1 and 2, but due to the limited research on ketamine, levels 3 and 4 data were also included. Authors were also contacted where necessary for clarification and any new data. Additionally, sweeps of drug user forum sites, using the same search criteria, were made to monitor any mentions of ketamine harms not noted in the scientific literature.

A note on terminology: frequency of ketamine use

There is a very marked variation in how often individuals use ketamine. Much published research has used the term 'ketamine addict', 'heavy user' or 'frequent user' without fully defining what is meant in terms of frequency, dose or duration of use. In this review, the terms given within the particular published articles have been used. The terms 'recreational ketamine user' and 'infrequent user' generally refer to non-dependent ketamine users whose use is confined predominantly to weekends.

PHYSICAL AND PSYCHOLOGICAL HARMS

Acute physical risks

Safety ratio

One of the ways in which the acute physical risk associated with a drug is assessed is the 'safety ratio'. For drugs of abuse, this is the ratio of a usual recreational dose to a fatal or lethal dose (LD). Gable [23] gave ketamine a safety ratio of 25 based on reports that the rodent oral ketamine median lethal dose (LD_{50}: the dose of a drug that produces death in 50% of experimental animals tested) averaged around 600 mg/kg [24] or approximately 4.2 g for a 70 kg human (although other papers with mice suggest it may be much lower at 42.9mg/kg [25]. Rodent data were reduced by a factor of 10 to take into account interspecies differences. This also assumed a greater human oral LD_{50} of 4.2 g, with an oral recreational dose of 175 mg [26]. It is important to emphasize that all these estimates are extrapolated from rodent data and based on oral doses.

Risk of death from an acute dose

In humans, ketamine has a wide margin of safety, with no adverse outcomes reported even in medical settings of marked overdose [27]. Green *et al.* [28] reported no adverse outcomes in nine cases in which children in emergency departments were injected inadvertently with five to 100 times the intended dose. This may reflect special properties of ketamine anaesthesia whereby

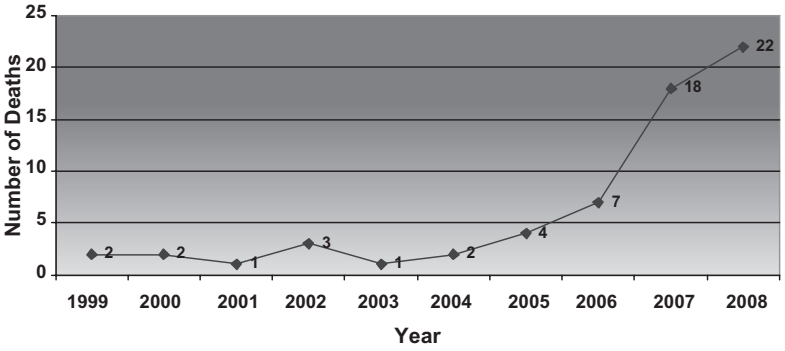

Figure 1 UK post-mortem toxicology mentions of ketamine in the United Kingdom 1999–2008 [105; additional data courtesy of Dr J. Corkery]

patients are able to maintain their own airway, and so it can be used safely in special populations and circumstances such as in the 'field'. These respiratory properties reduce the potential risks for the recreational user. Coughing and swallowing reflexes are also maintained, again protecting recreational users from harm because there is no suppression of the gag reflex even when extremely intoxicated.

Other data, shown in Fig. 1, reported the number of unexplained deaths in the United Kingdom between 1999 and 2008 in which ketamine was mentioned. Although the levels are low, they increased 10-fold over this period. In the majority of cases, ketamine was mentioned alongside a range of other psychotropics. Further, these data should also be evaluated cautiously, because toxicology screens are only performed in two-thirds of cases and among these, ketamine is not tested routinely.

Acute physical risk of death from accidents

Both Jansen [29] and Stewart [30] concluded that accidental death when intoxicated was the highest mortality risk. Two frequent ketamine users from a sample of 30 in a longitudinal study by Morgan *et al.* [31] died between baseline testing and 12-month follow-up as a result of their acute ketamine use—one through drowning in a bath and one of hypothermia.

Despite anecdotal reports of a high risk of accidental injury while acutely intoxicated with ketamine, due largely to the dissociation and analgesia (e.g. [32,33]), there are sparse scientific data on this risk. Because ketamine is a powerful analgesic, the intoxicated user is more vulnerable to being damaged. One case study reported a hospital worker who had injected ketamine collapsing with their face on an electric fire and suffering third-degree burns (cf. [34]). Muetzelfeldt *et al.* [35] found that of 90 ketamine users, 13% reported personally being involved in an accident as a direct result of taking ketamine, whereas 83% knew someone who had. An important harm reduction message is therefore that those acutely intoxicated with ketamine should not be left alone in case of accidents as well as being accompanied by someone who has not taken the drug.

Acute ketamine poisoning and ER admissions

The UK National Poisons Unit provides information for doctors on poisons in their TOXBASE website. Of 570 000 TOXBASE hits in 2008/2009, 0.3% were ketamine-related (1710 cases), a sixfold increase from 2000 (0.05%; 285 cases).

There are currently few data on the number of emergency room (ER) presentations of patients with ketamine toxicity. In a London teaching hospital, Wood *et al.* [36] recorded 116 ER presentations involving recreational ketamine use, only 11% of which involved ketamine alone [co-ingested drugs included ethanol (39%), gamma hydroxy-butyrate/gamma-butyrolactone (GHB/GBL) (47%), cocaine (19%) and 3,4-methylenedioxymethamphetamine (MDMA) (53%)]. Most cases (72%) were discharged directly from the ED, and no case where ketamine alone had been ingested required admission to critical care.

Ng *et al.* [37] reviewed 233 cases of ER presentations of ketamine users in Hong Kong. Users had an average age of 22 years, two-thirds were male and the most common presenting symptoms were: impaired consciousness (45%); abdominal pain (21%); lower urinary tract symptoms (12%); and dizziness (12%), suggesting a lack of severe acute physical health consequences. The most common physical 'symptoms' reported as helping to identify acute ketamine intoxication were high blood pressure (40%), tachycardia (39%), abdominal tenderness (18%) and white powder in the nostrils (17%).

Acute cardiac risks from ketamine use

Ketamine stimulates the cardiovascular system leading to increased heart rate, cardiac output and blood pressure. Therefore, taking ketamine may present an acute risk for people with hypertension and severe cardiac disease, those at risk of a stroke or with raised intracranial

pressure. Acute cardiac risk is increased when ketamine is taken in conjunction with stimulant drugs.

Chronic physical and psychological effects of ketamine

Ketamine-induced ulcerative cystitis

Ketamine-induced ulcerative cystitis is a recently identified condition which can have a severe and potentially long-lasting impact on the individual. Shahani *et al*. [38] first documented cases in nine dependent ketamine users, describing symptoms such as frequency and urgency of urination, dysuria, urge incontinence and occasionally painful haematuria (blood in urine). Computerized tomography (CT) scans of these individuals revealed a marked thickening of the bladder wall, a small bladder capacity and perivesicular stranding consistent with severe inflammation. At cystoscopy all patients had severe ulcerative cystitis. Biopsies in four of these cases found denuded urothelial mucosa with thin layers of reactive and regenerating epithelial cells and ulcerations with vascular granulation tissue and scattered inflammatory cells. Cessation of ketamine use provided some relief of symptoms.

Since then a number of case reports of ketamine-induced ulcerative cystitis have been published (e.g. [39,40]), all describing 'ketamine addicts' or 'near-daily' users. Oxley *et al*. [41] conducted a histopathology study of 17 'addicts' and suggested that ketamine mimics carcinoma *in-situ* and could increase the risk of bladder cancer. It is clearly important that young people presenting with urinary tract symptoms are asked about their drug use when no other causes are found.

A larger study of 59 'ketamine bladder' patients [42] found 42 (71%) had a cystoscopy that showed various degrees of epithelial inflammation similar to that seen in chronic interstitial cystitis. Urodynamically, either detrusor overactivity or decreased bladder compliance with or without vesico-ureteric reflux was detected to some degree in 47 patients and eight also had raised serum creatinine. Prevalence data are difficult to obtain. Of 90 UK ketamine users, 30% reported urinary tract symptoms while they used ketamine [35]. Among frequent users, nearly half had sought medical attention for ketamine-induced cystitis. Cottrell & Gillatt [43] suggest that the course of disease varies, with approximately one-third of cases resolving after stopping ketamine use, one-third remaining static and one-third worsening.

The aetiology of ketamine-induced ulcerative cystitis is unclear. It appears to be most common in those misusing the drug frequently, mainly daily, over an extended period. Ketamine is commonly administered as a few repeated doses in veterinary and medical anaesthesia and analgesia. We found only one case study reporting ketamine-induced ulcerative cystitis during its medical use—a 16-year-old treated for chronic pain [40]. Her urinary tract symptoms remitted completely following reduction of her of ketamine dose.

Kidney dysfunction

Another emergent physical health problem associated with frequent, high-dose ketamine use appears to be hydronephrosis (water on the kidney) secondary to urinary tract problems. In their study of ketamine-induced ulcerative cystitis, Chu *et al*. [42] reported that 30 (51%) patients presented with either unilateral (7%) or bilateral (44%) hydronephrosis (water on the kidney). On the initial assessment four patients also showed papillary necrosis (destruction of kidney cells), and this led to renal failure in one, who had complete obstruction of the urethra.

'K-cramps'

A third of 90 ketamine users in one study spontaneously reported 'K-cramps'—intense abdominal pain—as a result of prolonged, heavy ketamine use [35]. Frequent ketamine users often report taking more ketamine to alleviate this pain and this can make attempts to quit using fail. The aetiology of K-cramps remains unclear, but three small case studies (one, three and two patients, respectively) have reported the existence of 'colicky' upper gastric pain in young ketamine users [44–46], all of whom also presented with abnormal liver function. CT scans of these patients found dilation of the common bile duct with a smooth tapered end, mimicking choledochal cysts (congenital conditions associated with benign cystic dilatation of bile ducts). These symptoms abated when the patients stopped using ketamine.

A larger study of ER presentations [46] also reported that 21% of ketamine patients presented with abdominal pains and 15% with abnormal liver function, which concur with these reports of biliary problems.

Among ketamine users there is a belief that 'K-cramps' or 'K-belly' arises from swallowing the drips when ketamine is snorted intranasally. Some harm reduction advice given on user forums (partvibe.org; drugforum.net; squatjuice.org) is not to swallow the drips. However, this advice would seem to be incorrect based on evidence reviewed above.

Depression

Increased depression (assessed with the Beck Depression Inventory) in both daily users and ex-ketamine users was found over the course of 1 year in our longitudinal study [31] but not in current infrequent (>1 per month, <3 times per week) users. However, this elevated depression

was not at clinical levels and the increase was not correlated with changes in ketamine use.

In contrast, a preliminary study of seven patients suggested that one dose of ketamine can have rapid and relatively prolonged antidepressant effects in depressed patients who did not respond to usual treatments [47]. Enthusiasm for this approach was rekindled by a larger study of 18 treatment-resistant patients administered 0.5 mg/kg ketamine over 40 minutes [48]. Twelve of the patients showed an immediate 50% reduction in measures of depression compared with none of 14 patients given placebo. The antidepressant effects of one dose lasted 1–2 weeks in eight patients, but they all relapsed thereafter, leading to calls for repeated ketamine treatment of depression (e.g. [8]). In the first clinical trial, Aan het Rot *et al.* [49] gave depressed patients six infusions of ketamine (on days 0, 3, 5, 8, 10 and 12). Of the nine patients who received repeated infusions (dependent upon their response to the first infusion), eight relapsed within an estimated mean 30 days after the first infusion or 19 days after the sixth infusion. The rapid response to ketamine contrasts with the 3–4-week lag in response to mainstream antidepressants. However, the chronic effects of the drug should be monitored if repeated dosing is to be a strategy in the treatment of depression.

Psychosis

In healthy volunteers, one dose of ketamine induces transient positive and negative symptoms of schizophrenia (e.g. [50]). In schizophrenic patients who have been stabilized on antipsychotic medication, ketamine causes a resurgence of psychotic symptoms [51] which are remarkably similar to those each individual exhibited in the acute phase of their illness [52].

Pre-clinical studies giving small numbers (~5) of repeated doses of ketamine to rats have also found 'schizophrenia-like' changes such as abnormal hippocampal neurogenesis, particularly reductions in hippocampal parvalbumin containing GABAergic interneurons [53], as well as increased dopamine binding in the hippocampus and decreased glutamate binding in the prefrontal cortex [54]. Studies with infrequent (>1 per month <3 times per week) and daily ketamine users assessing subclinical psychotic symptomatology have found that scores on measures of delusions, dissociation and schizotypy are higher in daily ketamine users compared to infrequent users and in infrequent users compared to polydrug controls who do not use ketamine [31,55]. Morgan *et al.* [31] found that daily ketamine users showed a similar pattern of 'basic symptoms' to individuals prodromal for schizophrenia. However, there is no evidence of clinical psychotic symptoms in infrequent ketamine users [56]. Despite anecdotes (e.g. [32,34]), there is little evidence of any link between chronic, heavy use of ketamine and diagnosis of a psychotic disorder.

Cognitive impairment

The NMDA receptor is thought to underpin the form of synaptic plasticity known as long-term potentiation, which is central for learning and memory. Given that the principle action of ketamine is at this NMDA receptor, the consequences of ketamine use on cognition have been fairly widely investigated. In humans, a single dose of ketamine induces marked, dose-dependent impairments in working and episodic memory which would impact profoundly on users' ability to function [57]. In mice, impaired fear memory (decreasing fear in a fear conditioning paradigm) has been found after 4 but not 2 weeks of daily injection of 5 mg/kg [58].

Several studies have examined cognitive function in infrequent and frequent ketamine users (e.g. [11,55,56,59–61]). Overall, infrequent or recreational ketamine use does not appear to be associated with long-term cognitive impairment (e.g. [56]). The most robust findings are that frequent ketamine users exhibit profound impairments in both short- and long-term memory (for review see [57]). Many studies have been cross-sectional and cannot address causation. However, in a longitudinal study, frequent ketamine use caused impairments in visual recognition and spatial working memory that correlated with changes in level of ketamine use over 12 months [30]. Other impairments in planning and frontal functions have been observed, but appear so far to be unrelated to measures of ketamine use [11]. Memory impairments may be reversible when individuals stop using the drug, as they were not found in a group of 30 ex-ketamine users who had been abstinent for at least a year. The cognitive consequences of repeated ketamine use in paediatric anaesthesia would also merit further investigation [62].

Neurological changes

Increased D1 receptor binding in the right dorsolateral prefrontal cortex of ketamine users has been reported, indicating upregulation of dopaminergic receptors [56]. White matter abnormalities have been observed in ketamine addicts compared to controls [63]. Reduced fractional anisotropy correlated with the degree of ketamine use in the bilateral frontal and left temporoparietal regions. However, similar changes have been observed in other drug-dependent populations [64], so these may not be specific effects of ketamine. There were also small changes in the temporal region that may relate to the drug's impairment of episodic memory.

DEPENDENCE-RELATED HARMS

Acute pleasure associated with taking the drug

Neurochemical actions

Dopaminergic modulation may underpin the reinforcing properties of many recreational drugs (e.g. [65]). Acutely, ketamine increases extracellular dopamine (DA) concentrations in the rat striatum and prefrontal cortex [66] and some positron emission tomography (PET) studies in humans have shown that it elicits striatal DA release [67–69].

Ketamine also interacts with μ-opioid receptors and non-opioid σ receptor sites, which may also relate to its rewarding properties, although affinity of the drug for these receptors is relatively low. There has been a suggestion that different isoforms of ketamine may have different neurochemical and possibly reinforcing properties [33]. S+ ketamine has a much greater affinity for the NMDA-receptor, and R- ketamine has a greater opioid action.

Pharmacokinetic parameters and route of administration

The most common way in which ketamine is taken recreationally is 'snorted' intranasally, like cocaine. In the United States intravenous use of ketamine is rare even among injecting users of other drugs [70]. Insufflation of ketamine leads to a relatively rapid (~5 minutes) onset of effects on the brain. A rapid 'high' is thought to increase the abuse potential of a substance. In addition, the short half-life of ketamine (1–2 hours) may both promote bingeing and increase its appeal over longer-lasting hallucinogens such as lysergic acid diethylamide (LSD) or 'magic' mushrooms [71].

Acute reinforcing effects in animals and humans

Pre-clinical findings suggest clear similarities between ketamine and other addictive drugs in a wide range of behavioural paradigms. Rats will self-administer ketamine [72,73], show conditioned place preference [74] and locomotor sensitization following repeated doses has been observed [75–77]. Furthermore, ketamine substitutes for ethanol in drug discrimination paradigms in rats [78,79]. Humans dependent on alcohol show enhanced NMDA receptor function [80], and in recently detoxified alcoholics ketamine produces ethanol-like subjective effects, including a 'high' [81].

Studies with healthy volunteers have found that ketamine increases subjective ratings of 'high' [82] and this relates to its abuse potential. In one study, subanaesthetic doses (0.4 mg/kg and 0.8 mg/kg) or placebo were infused intravenously to healthy, ketamine-naive volunteers [83]. They rated how much they 'liked' the drug and 'wanted more' of it. An inverted U-shaped dose–response curve was found. Shortly after the infusion started, they both liked and wanted more of both doses. Towards the end of the 80-minute infusion, these ratings had markedly reduced in the high-dose group, whereas the low-dose group still liked and wanted more of the drug.

Psychological and physical dependence

Incidence of ketamine dependence

There are some case reports of ketamine dependence in the literature (e.g. [84–87]) but no large-scale studies, and so the incidence of ketamine dependence is unknown. An interview study of 90 ketamine users found that 57% of frequent users, 43% of infrequent users and 60% of ex-users expressed concerns about ketamine addiction [35]. The majority of frequent users in that study reported using the drug without stopping until supplies ran out, so compulsive patterns of behaviour are also a concern.

Withdrawal symptoms following abstinence

There is conflicting evidence of the existence of a 'withdrawal syndrome' following cessation of ketamine use. Cravings seem to be a key problem in frequent users: 28 of the 30 daily users in a study by Morgan *et al*. [88] reported having tried to stop taking the drug but failed; all reported ketamine cravings as the reason for failure. The same study found 12 of the 30 daily users reported withdrawal symptoms characterized by anxiety, shaking, sweating and palpitations when they stopped using. A few published case studies also show craving and somatic and psychological aspects of anxiety as withdrawal symptoms [89–91]. However, a specific ketamine withdrawal syndrome has not yet been described.

Tolerance

The need for increasing doses is one index of a substance's addictive potential. Studies with rats [92] and monkeys [93] as well as children undergoing anaesthesia (e.g. [94]) have convincingly demonstrated a rapid development of tolerance—'tachyphylaxis'—with repeated ketamine dosing. This may be due to induction of liver enzymes [95]. It is also possible that it reflects neuronal adaptations in receptor numbers or receptor sensitivity.

Frequent ketamine users report escalating doses over time, with one study finding a 600% increase from first use to current use [88]. Objective data from hair analyses showed a doubling of ketamine concentrations in hair over a year in infrequent ketamine users [31]. Frequent users' hair ketamine did not change, but they were probably already using maximal amounts.

SOCIAL HARMS OF KETAMINE

Social harms of intoxication

Risk of accidental injury

As a dissociative anaesthetic, ketamine can render an individual oblivious to their environment. This puts the user not only at risk of accidental injury to themselves, as already discussed, but also more vulnerable to assault by others. Ketamine also impairs psychomotor performance dose-dependently, such as hand–eye movement coordination and balance [96]. This increases the risks of causing accidents in complex motor tasks such as driving. Over a 4-year period, 21% of fatal vehicle crashes in Hong Kong involved alcohol or drugs and 9% of those involved ketamine [97]. Recreational users often seek out safe 'chill-out' areas to consume the drug and reduce risks [71], whereas more dependent users report using the drug in most situations, including while driving [35].

Risk-taking behaviour

Ketamine use has been found to be associated with an increased incidence of unsafe sex among gay men in the United States (e.g. [98]). Ketamine is not associated with violent behaviour, so the risk of social violence is not increased [21].

Harms to the ketamine user within society

There is little information about the degree to which ketamine use affects users' place within society. For frequent users, most social risks are similar to those of any addictive illegal drug such as disruptions to education and employment.

Educational and professional achievement

Dependent ketamine users in the United Kingdom are often part of subcultures, such as the 'traveller' and 'free party' scenes, that may have limited interest in participating in mainstream society [99,100]. Irrespective of their ketamine use, many of their educational and professional achievements may have differed from the norm. At present there are no data on how ketamine dependence impacts on achievement. An interview study of 100 recreational users found that 20% perceived employment related problems to result from their ketamine use [101]. Morgan *et al.* [31] found that frequent/daily users had spent significantly fewer years in education than infrequent or non-users.

Engagement in criminal activities

The degree to which ketamine may lead users towards criminal activities to fund their use is unknown, partly as there are no drug treatment orders for ketamine use. Since its classification, ketamine smuggling has become an organized crime and the drug's street price has decreased [15]. There were 1266 ketamine seizures in 2008/09 in the UK and arrests for ketamine appear to be increasing [102].

Ketamine use in pregnancy

No data on human use of ketamine in pregnancy were available. Research with rats has shown that cocaine and a combination of cocaine and ketamine reduced fetal birth weight but not ketamine alone [103].

Cost to the health service

The majority of costs will stem from chronic physical health problems. In particular, ketamine-induced ulcerative cystitis is associated with a variety of costly procedures, as symptoms may be difficult to manage. A number of cystoscopies may be required, as well as catheterization of the bladder for symptomatic relief, and in severe cases, bladder reconstruction or ultimately cystectomy (bladder removal; [43]). In such cases the patient will need to be followed-up for life, at a very high cost to the health service. Treatment of ketamine dependence may be another emerging cost.

DISCUSSION

After nearly 50 years of medical use, ketamine still occupies a unique place in the pharmacological tool boxes of anaesthetists, pain clinicians and veterinarians [104]. More recent research suggests that it may potentially have other clinical applications, including treatment of resistant depression [7]. It is also an important experimental compound used in medical research.

At the same time, this review has highlighted a number of harms stemming from the chronic, recreational use of ketamine. Of most concern is ketamine-induced ulcerative cystitis which appears more common in, but is not restricted to, those using the drug on a frequent, often daily basis. It is important that young people presenting with urinary tract symptoms are asked about drug use when no other causes are found. Key questions which research needs to address are what mechanisms lead to this condition and why do some users develop it while others do not?

There is also concern that some individuals develop dependence, although the incidence of this is currently hard to gauge. Although a specific withdrawal syndrome has not yet been identified, tolerance to the drug develops rapidly. Many daily users report having tried but failed to stop using ketamine. Anecdotally, we have encountered many frequent users who have difficulties stopping the

drug and yet cannot gain access to drug treatment services in the United Kingdom.

There is a need for joined-up treatment of those who have developed ketamine-induced ulcerative cystitis. Urological interventions should be coordinated with psychosocial interventions that promote future abstinence from the drug.

Young people should be made aware of the long-term physical risks of using ketamine. Ulcerative cystitis and loss of bladder control do not mesh well with desirable images of being young and attractive, and so a strong harm-reduction message could be constructed. Similarly, users should minimize the risk of accidental injury or death by ensuring that intoxicated friends are always accompanied by others who are not intoxicated. In a similar vein, the potential of neurological and cognitive changes following frequent use of the drug should be communicated and implications stressed for poor performance at school, college or work. The long-term neurological, neurocognitive and psychiatric effects must be investigated further in longitudinal designs which also follow-up on those who subsequently stop using ketamine. Such studies could ideally be interdisciplinary and allow further investigation of ketamine's physical effects, including K-cramps and effects on kidney function.

There is variation across the world in the legal status of ketamine. The current classification of ketamine in the United Kingdom under the Misuse of Drugs Act (Class C) suggests that its harms are less severe than some other drugs such as cannabis (class B) or ecstasy (class A). Our review of the scientific evidence suggests that this classification of ketamine does not reflect accurately its known and potentially severe harms. At the same time, there is currently little evidence that changing a drug's legal classification impacts on drug users' behaviours; in fact, since classification the prevalence of ketamine has increased and cost decreased, and a more stringent classification would present many practical hurdles for the legitimate, medical use of ketamine.

Declaration of interest

None.

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