REVIEW ARTICLE

COACTION PUBLISHING

The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use

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Ketamine was originally synthesised for use as a dissociative anaesthetic, and it remains widely used legitimately for this indication. However, there is increasing evidence of non-medical recreational use of ketamine, particularly in individuals who frequent the night-time economy. The population-level and sub-population (clubbers) prevalence of recreational use of ketamine is not known but is likely to be similar, or slightly lower than, that of other recreational drugs such as cocaine, MDMA, and amphetamine.

The predominant features of acute toxicity associated with the recreational use of ketamine are neuro-behavioural abnormalities such as agitation, hallucinations, anxiety, and psychosis. Secondary to these, individuals put themselves at greater risk of physical harm/trauma. Cardiovascular features (hypertension and tachycardia) occur less frequently and the risk of death from recreational use is low and is predominately due to the physical harm/trauma.

Long-term recreational use of ketamine can be associated with the development of psychological dependence and tolerance. There are reports of gastro-intestinal toxicity, particularly abdominal pain and abnormal liver function tests, and of neuropsychiatric disorders, typically a schizophrenia-like syndrome, in long-term users. Finally, there are increasing reports of urological disorders, particularly haemorrhagic cystitis, associated with long-term use. The management of these problems associated with the long-term use of ketamine is largely supportive and abstinence from ongoing exposure to ketamine.

In this review we will collate the available information on the epidemiology of recreational use of ketamine and describe the patterns of acute and chronic toxicity associated with its recreational use and the management of this toxicity.

Keywords: *ketamine*; *2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone*; *recreational drugs*; *epidemiology*; *acute toxicity*; *chronic toxicity*; *dependence*; *haemorrhagic cystitis*

Received: 26 November 2010; Revised: 13 January 2011; Accepted: 3 February 2011; Published: 15 April 2011

Ketamine, 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone is a dissociative anaesthetic that was first synthesised in the United States in 1962 (1). It is listed by the World Health Organisation as an essential medicine (2) and is widely used as a general anaesthetic, both in veterinary and human practice. It is characterised by its ability to cause unconsciousness, amnesia, and analgesia whilst sparing airway reflexes and maintaining haemodynamic stability (3). Ketamine is also gaining favour as an alternative analgesia, particularly in chronic non-cancer pain (4).

Its clinical use has always been limited by a hallucinogenic effect, the so-called emergence delirium described during its first human volunteer trial (1). This effect has however led to recreational, non-medical misuse and there has been evidence of this since 1967 (5). Common street names for ketamine include 'K', 'Special K', 'Kit-Kat', and 'Cat Valium'. It should be noted that colloquial names of recreational drugs change with time and differ between countries and communities, so it is not possible to give a contemporaneous and complete list of common street names for ketamine.

Ketamine is subject to control under recreational drug legislation in many countries; it was added to Schedule III in the United States in 1999 and in the United Kingdom it was controlled as a Class C agent under the Misuse of Drugs Act, 1971 in 2006. The prevalence and geographic spread of ketamine misuse has increased greatly over the past 20 years, and a pattern of adverse effects that differs from that expected from occasional

Citation: Emerging Health Threats Journal 2011, **4**: 7107 - DOI: 10.3402/ehtj.v4i0.7107

legitimate general anaesthetic use has become apparent. In addition, there is an accumulating literature on ketamine-related chronic toxicity, in particular neuropsychological and urological effects. This review will collate the available information on the epidemiology of recreational use of ketamine and describe the patterns of acute and chronic toxicity associated with its recreational use.

Pharmacology

Ketamine produces dissociative anaesthesia by causing electrophysiological dissociation between the limbic and thalamoneocortical systems, resulting in a trance-like cataleptic state characterised by unconsciousness, amnesia, deep analgesia but with intact ocular, laryngeal, and pharyngeal reflexes (1). There are also sympathomimetic, anti-cholinergic and analgesic effects: these start at sub-anaesthetic doses, but persist throughout the period of unconsciousness (1). Of note, ketamine is a chiral molecule with two stereoisomers, and the S(+)-isomer is more potent for inducing general anaesthesia by a ratio of 4:1 (6).

Ketamine is both water- and lipid-soluble, which allows administration by many routes. Intravenous, intramuscular, subcutaneous, oral, nasal, and rectal administration are described both therapeutically (3) and for recreational, non-medical ketamine misuse (7). Extensive first-pass hepatic metabolism of ketamine to its main metabolite norketamine substantially reduces its bioavailability following either oral or rectal administration (see Table 1) (3, 8–10). Ketamine has a short α half-life (2–4 min) and longer β half-life (8–16 min), and its effects vary according to plasma concentration. Analgesia begins at 100 ng/ml, drowsiness and perceptual distortions occur between 50–200 ng/ml, and general anaesthesia requires 2,000–3,000 ng/ml, with awakening occurring when levels fall to 500–1,000 ng/ml (3).

Ketamine has two major metabolites: norketamine, which has one-third the potency of ketamine (11) and dehydronorketamine. Norketamine is produced by cytochrome P450-mediated N-demethylation, mainly by CYP3A4 but with minor contributions from CYP2C9 and CYP2B6 (12). Norketamine is then dehydrogenated to dehydronorketamine and both these metabolites undergo hepatic conjugation. Ketamine and its metabolites are all renally excreted, mostly as conjugates (80%) and dehydronorketamine (16.2%), with very small proportions as ketamine (2.3%) or norketamine (1.6%) (13). They can be detected in the urine for many days: ketamine, 5–11 days; norketamine, 6–14 days; dehydronorketamine, 10 days (14, 15).

Ketamine has activity at several receptors. Primarily, it is an antagonist of the glutaminergic N-methyl-D-aspartate receptor (NMDA-R), both centrally and in the spinal cord (16). Ketamine binds non-competitively to the so-called phencyclidine-binding site of the NMDA-R and prevents neuronal Ca^{2+} influx, with the S(+)-isomer showing 3–4 times greater affinity (17). This disrupts cortical-cortical and cortical-subcortical signalling (18), producing dissociative anaesthesia, interference with neuronal plasticity, learning and memory, analgesia at central and spinal cord level, as well as interruption of the central sensitization core to chronic pain syndromes (3). Norketamine is also an NMDA-R antagonist, contributing to the effects of ketamine (19).

Ketamine is also reported to be a weak agonist of μ-opioid receptors (20), though the NMDA-R antagonism is believed to be more important for its analgesic activity. Its sympathomimetic activity is reportedly due to agonist activity at α_1- and β_2-adrenoceptors (21), as well as catecholamine re-uptake blockade (22). Ketamine also has a profound anticholinergic effect, produced by antagonism of the central nervous system muscarinic acetylcholine receptors (23) and inhibition of acetylcholinesterase (24), although one of the resultant effects—bronchodilatation—may also be caused by a direct antagonism of endothelin-1-induced bronchial smooth muscle constriction (25). In a rat model, acute ketamine administration resulted in increased dopamine and 5-hydroxyindoleacetic levels in the medial prefrontal cortex (26); however, repeated daily ketamine administration for 7 days attenuated dopamine but enhanced 5-hydroxyindoleacetic acid release. Finally, ketamine potentiates

Table 1. Ketamine pharmacokinetics, based on route of administration

	Intravenous	Intramuscular	Oral	Rectal	Nasal
Induction of general anaesthesia (3)	1–2 mg/kg* 0.5–1 mg/kg**	2–4 mg/kg		8–10 mg/kg	5 mg/kg
Typical recreational dose (single dose, mg) (8)***	50–100	75–125	200–300	No data	60–250
Onset of effect (3)	Seconds	1–5 min	15–20 min	No data	5–10 min
Duration of effect (3)	30–45 min	30–45 min	60–120 min	No data	45–60 min
Bioavailability (%)	100%	93% (9)	17% (9)	25% (10)	25–50% (10)

*Racemic ketamine, **S(+)-ketamine, ***Typical recreational dose is 10–25% of the effective general anaesthetic dose (7).

Citation: Emerging Health Threats Journal 2011, **4**: 7107 - DOI: 10.3402/ehtj.v4i0.7107

gamma-aminobutyric acid (GABA) synaptic inhibition, through weak $GABA_A$ receptor agonism (27, 28), but this is not thought to be clinically significant (3).

Recreational, non-medical ketamine is available to users in powdered, capsule, and liquid formulations. Most recreational use is by nasal insufflation, with ketamine powder insufflated either directly or off the surface of objects such as keys or ketamine spoons or vaporised in solution (8). In tablet form, it is often admixed with other pharmacologically active substances such as amphetamine, caffeine, cocaine, amphetamine, and heroin (8). Importantly, recreational ketamine use often occurs with co-use of other substances, and potentially serious adverse pharmacological and toxicological interactions can occur with concomitant use of either central nervous system depressants (e.g. ethanol, opioids, barbiturates, benzodiazepines) or sympathomimetics (e.g. cocaine and amphetamines) (8).

Epidemiology of recreational use of ketamine

Recreational use of ketamine was first reported amongst those with access to the drug, particularly medical professionals, in 1967 (5). It then spread beyond this group to the community-at-large, firstly in the United States and then internationally, in association with the 'rave' dance sub-culture of the 1980–1990s (7, 29). More recently it has become part of the current 'post-rave' clubbing and youth dance culture, as a mainstream 'club drug' alongside drugs such as 3,4-methylenedioxymethampthetamine (MDMA or 'ecstasy'), cocaine, and gamma-hydroxybutyrate (GHB) (30).

The precise prevalence of recreational, non-medical ketamine use is unknown; small single country studies suggest that the background population use rates of ketamine are low, between 0.1 and 4% of those surveyed (summarised in Table 2) (31–34). In addition, data on the population prevalence rates of ketamine is not routinely collected in most countries and is not included in reports from organisations such as the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the United Nations Office on Drugs and Crime (UNODC). Lifetime and 'recent' recreational use of ketamine is significantly higher in those frequenting the night-time economy (e.g. discotheques, nightclubs, dance/music events; Table 3) (35–38). Four main groups of users are commonly described: regular drug users in the dance music setting, members of the men-who-have-sex-with-men ('gay') club/party scene, injecting heroin users, and self-exploratory people (39). Recreational ketamine use is commonly part of poly-substance use and is taken together with another club drug, ethanol, or stimulant (35, 40).

Geographically, recreational use of ketamine use is seen across the world, but it appears to be most common in East and South-East Asia, potentially because of its relatively low price compared to other psychomimetic drugs, particularly MDMA (41). Global reports of ketamine seizure rose from negligible amounts in 1999 to over 11 metric tonnes in 2007, with nearly all of this in East and South-East Asia, where ketamine seizures exceeded that of heroin (41, 42). Hong Kong reported ketamine as the second-most popular drug of abuse after heroin for the period 2007–2010 (43). Importantly, in the last reported year, 2008, for the first time a substantial minority of seizures (14%) were reported from outside of this region, suggesting a widening of ketamine supply (41).

It is often stated that the bulk of illicitly available ketamine is derived by diversion of legitimate veterinary and medical supplies; however, illicit manufacturing laboratories have now also been reported, particularly in China and South-East Asia (41).

Ketamine-related acute toxicity

The main acute toxicity associated with recreational use of ketamine is related to its psychedelic/hallucinogenic properties. Systemic toxicity with cardiovascular effects can occur, but generally clinical features are related to physical harm, either because of ketamine-induced aggression and agitation or because an individual believes that they can do things without suffering significant injury (e.g. jumping off a building) due to its dissociative features. Any description of acute ketamine toxicity is complicated by the fact ketamine is commonly part of a poly-substance use scenario. In 116 individuals with acute recreational drug toxicity presenting to an Emergency

Table 2. Ketamine use from population surveys, reported by individual country where data has been obtainable

Country, Year	Reference	% Lifetime ketamine use	% Ketamine use in past year	Age range (years)
Australia, 2007	(31)	1.1	0.2	14 to >40
Canada, 2009	(32)	2.2	1.6	12–18
United Kingdom, 2009–2010	(33)	4.0	1.7	16–24
		2.0	0.5	16–59
United States, 2006	(34)	0.1	<0.01	>12

Table 3. Ketamine use in the club and dance music setting, reported by country

Country	Reference	% Lifetime ketamine use	% Recent ketamine use	Comments
Canada	(35)		8.6	Recently = at last rave
Czech Republic	(36)	6.7	0.3	Recently = at last month
France	(36)	16.4		
Italy	(36)	10.8		
Hungary	(36)	20.9		
United Kingdom	(37)	67.8	32.4	Recently = in previous month
Taiwan	(38)		47.0	Based on urine screening of dance club attendees

Department in central London who self-reported ketamine use, 89% had used at least one other recreational drug or ethanol (suggesting ketamine is often part of a polydrug repertoire) (44). It is therefore important in patients presenting with acute toxicity after ketamine use, particularly if systemic features are present, to consider that this toxicity may, in part, be due to the co-ingested drug(s).

Neuro-behavioural effects

Recreational use of ketamine can cause a number of troublesome neuro-behavioural/neuropsychiatric effects. Users may be become agitated, aggressive, paranoid, and display dissociative-type symptoms. The content of hallucinations may be unwanted, which are typically referred to by users as 'falling into the K-hole', and in some cases can be significantly unpleasant. In healthy volunteers, an acute sub-anaesthetic dose of 0.1–0.5 mg/kg ketamine is sufficient to induce schizotypal and dissociative symptoms such as altered perception, as well as impaired performance of tests of vigilance, verbal fluency, word recall (45).

Risk of physical harm

One of the biggest concerns surrounding acute ketamine use is that it reduces awareness of the immediate environment, thus exposing the user to potential physical harm (46). The reduced awareness encompasses a sense of depersonalisation, derealisation, reduced perception of pain, and potentially unconsciousness. This is compounded by users frequently experiencing lack of co-ordination, temporary paralysis, inability to move, blurred vision, and inability to speak (39). As such, users put themselves at risk of significant injury, through jumping from heights, road traffic accidents, drowning, and hypothermia (secondary to incomplete drowning or prolonged environmental exposure (7).

Despite media and public concern about the potential for ketamine to be involved in drug-facilitated sexual assault, it is unusual for ketamine to be detected in this scenario. On screening, only 3 of 1,014 cases in the United Kingdom (47) and 2 of 184 cases from Canada (48) tested positive for ketamine. Drug-driving, on the other hand is more common, and ketamine was associated with 9% of fatal drug-and-alcohol-related single-motor-vehicle collisions in Hong Kong during 1996–2000 (49). During 2007, a single trauma centre in Hong Kong reported 4.5% of drivers involved in non-fatal crashes tested positive for ketamine (50).

Cardiovascular toxicity

During ketamine anaesthetic induction, tachycardia and hypertension precede unconsciousness (1) and this effect is also commonly seen with the sub-anaesthetic doses used for recreational ketamine use. The most common reported cardiovascular effect in patients with acute ketamine toxicity is a self-resolving sinus tachycardia with chest pain and palpitations less commonly reported (44, 51). There have also been isolated reports of acute pulmonary oedema following parental ketamine use, although it is difficult to be certain from these reports whether the pulmonary oedema was due to ketamine or some other factor (52–54). Interestingly, in an *in vitro* model, alveolar S(+)-ketamine reduced alveolar fluid clearance, although the doses required were not clinically relevant (55).

Risk of death from overdose

Ketamine has a wide therapeutic range and the median lethal dose (LD_{50}) in animals is 100 times the average therapeutic intravenous dose (3), which makes death from overdose difficult. Indeed, death and non-fatal emergencies attributed to ketamine use are considered to be very rare (37). When ketamine is reported in post-mortem samples, it is often either alongside another intoxicant or in the setting of trauma. From the forensic literature regarding death following recreational ketamine use, blood ketamine concentrations within the range of 0.1 to 7.0 mg/l have been reported alongside the presence of another co-ingestant such as ethanol, opiates, amphetamine, or cocaine (56–59). Of the 23 deaths in which ketamine was identified in post-mortem samples in the United Kingdom between 1993 and 2006, only 4 were attributed to lone ketamine poisoning (60). Similarly, in

Citation: Emerging Health Threats Journal 2011, **4**: 7107 - DOI: 10.3402/ehtj.v4i0.7107

New York City, of 15 out-of-hospital deaths where ketamine was identified in post-mortem samples of persons identified as recreational drug users, 12 were poly-substance overdoses and 2 died as a result of trauma (58).

Management of acute ketamine toxicity

The management of acute ketamine toxicity is largely supportive and involves removing an individual from excessive auditory and visual stimulation until symptoms resolve. In cases of severe symptoms, particularly agitation/aggression, benzodiazepines may be required (51). Most patients typically improve rapidly following acute ketamine toxicity and in those with significant systemic symptoms and/or prolonged ongoing symptoms, clinicians should consider whether there is an alternative diagnosis contributing to the individual's clinical condition (51).

Chronic toxicity related to recreational ketamine use

Recently, the long-term effects of recreational, non-medical ketamine use have come under scrutiny. We will summarise here the data on associated neuropsychological effects, neurotoxicity, dependence, and urological and gastrointestinal pathology.

Neuropsychological effects and neurotoxicity

Ketamine is associated with both neuropsychiatric symptoms and direct neurotoxicity. As described above, ketamine can cause several acute neuropsychiatric effects. Acute and acute-on-chronic use of ketamine has been shown to be associated with impaired information handling within working memory and episodic memory, as well as semantic processing deficits (61, 62). Men appear to be more affected by these effects than women (63). For up to 3 days following ketamine use, subjects are threefold likelier to report unpleasant dreams (64).

Long-term ketamine users appear to have more pronounced and persistent neuropsychiatric symptoms, generally characterised as schizophrenia-like symptoms. In a recent case-control study comparing frequent ketamine users, defined as use at least four-times-a-week, with infrequent users, abstinent users, poly-drug users, and non-drug users, frequent ketamine use was associated with impairment of working memory, episodic memory, executive function and psychological well-being (65). These frequent users were reported as taking an average of 2.77 g of ketamine an average of 20 days per month. The same group were then followed up for a year, and the frequent ketamine users with increasing ketamine doses were more likely to have cognitive deficits, especially with spatial working memory and pattern recognition memory tasks, and both short- and long-term memory was affected (66). From the same studies, delusional thinking was shown to be correlated positively with the amount of ketamine used by frequent users and persisted despite abstinence (65). A dose-dependent relationship was reported on 1-year follow-up, with frequent users being more delusional than infrequent, abstinent, and non-users, respectively (66). Superstitious conditioning, a form of associative learning, is also more common amongst frequent ketamine users and this process may precede outright delusional thinking (67). Frequent ketamine use is also typified by increased dissociative and depressive symptoms (66), as well as a subtle visual anomaly (68). It is not certain how ketamine causes these effects, but antagonism of the NMDA-R is thought to be important, as is dopaminergic depletion in the prefrontal cortex (3, 26, 69).

Ketamine is also directly neurotoxic. Animal studies have shown that apoptotic neuro-degeneration is induced by NMDA-R antagonists, including ketamine, in the developing rodent brain (70). This effect for ketamine has since been shown to be more marked in older rats and is synergistic with nitrous oxide (71–73); it was ameliorated by $GABA_A$ agonism with benzodiazepines, and prevented by neuronal nitrous oxide synthase antagonism with 7-nitroindazole (73, 74). This last finding implicates endogenous nitrous oxide in ketamine-related neurotoxicity. In monkeys, neuronal death was observed after ketamine anaesthesia administered for 9 hours or more but not for 3 hours duration (75). Recently, evidence for harm in humans following frequent ketamine use has been presented, with bilateral frontal and left temporoparietal white matter degeneration shown on brain magnetic resonance imaging being positively correlated to self-reported ketamine dosages (76).

Tolerance and dependency

There is evidence that ketamine causes a psychological, rather than a physical, dependency. The World Health Organisation's International Classification of Diseases (ICD-10) defines substance dependence as 'a cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state' (77). This definition holds true for frequent, long-term ketamine use. In particular, ketamine use can be uncontrolled, over-prioritised, and linked with tolerance but does not cause a physical withdrawal state.

Anecdotally, ketamine use in humans is characterised by binging, the drug being repeatedly used until a user's supply has been exhausted (78, 79). This phenomenon is also seen in pigeons and monkeys, who repeatedly self-administer freely available ketamine, suggesting that it is

difficult to control ketamine use during a binge (80, 81). Tolerance is considered to be a major factor in the development of dependency (82) and is a well-recognised characteristic of frequent ketamine use, with intranasal doses of up to 130 mg/kg reported (79, 81). Tolerance is likely explained by ketamine auto-induction of metabolism. Ketamine pretreatment doubles its hepatic microsomal metabolism in rats, and both the catalytic activity and protein expression of the rat microsomal cytochrome P-450 system is enhanced by repeated daily ketamine administration (83, 84). Unsurprisingly, frequent ketamine use is associated with increasing doses to achieve the same effect, with a sixfold increase in dosage reported during initiation of chronic use, and frequent users using twice the dose of infrequent users (66, 85).

Urological toxicity

Recently lower urinary tract symptoms (LUTS) of dysuria, increased frequency of small volume micturition, suprapubic pain and, if severe, painful haematuria have been reported amongst long-term ketamine users. There have been no large epidemiological studies, but pilot studies suggest that up to a third of long-term ketamine users may be affected: pooling together the results of three small surveys of frequent users, 50 of 157 ketamine users admitted to LUTS (84–87). In 2007, investigators from Canada linked these symptoms with ulcerative cystitis (88); additionally, those severely affected may also experience obstructive nephropathy (89).

There is evidence from beyond the recreational use setting linking ketamine with urological pathology. In an animal study performed following the reports of human pathology, mice administered intraperitoneal ketamine for up to 6 months demonstrated pathological changes, with mononuclear infiltration occurring throughout the urological tract in the glomeruli, ureters, and bladders (90). Four cases have also been reported from the palliative care setting linking analgesic ketamine use with LUTS (91, 92).

To date, there have been three retrospective case series ($n \geq 10$) published, covering 93 patients reporting chronic urological effects in long-term recreational ketamine users (see Table 4) (86, 93, 94). In all of these, patients self-reported ketamine use in excess of 3 months with ketamine use preceding LUTS. Except for one case, all had either sterile or contaminant-only urinary cultures. Reduced bladder volume was reported in three-quarters (57/77) and hydronephrosis in more than half (38/70) of those who had an appropriate investigation undertaken. Commonly, reduced bladder volume was associated with bladder wall thickening, detrusor instability, and vesicoureteric reflux, which explains the hydronephrosis as potentially a secondary effect of the bladder pathology (86, 93). Alternatively, hydronephrosis could also be a result of either peri-ureteric thickening or intraureteric

Table 4. Summary of three published retrospective case series

Country	*N*	Positive urine culture	Hydro-nephrosis	Reduced bladder volume (≤150 mL)	Raised serum creatinine	Bladder wall thickening	Cystitis on cystoscopy	Abnormal bladder biopsy histology	Peri-ureteric thickening
Hong Kong (86)**	59	2/59	30/59 (on CT)	33/47 (on UDS)	8/59		42/42	12/12	1/59 (on CT)
Taiwan (94)	11	0/11	5/9 (on USS)	10/11 (on USS/UDS)	0/11		5/5	5/5	
United Kingdom (93)	23	1/16	3/12 (on CT/IVU)	14/19 (on CT/US)	0/23	14/19 (on CT/US)	17/17	15/17	2/12 (on CT)
Total	93	3/86	38/70	57/77	8/92	14/19	64/64	32/34	3/71

Citation: Emerging Health Threats Journal 2011, **4**: 7107 - DOI: 10.3402/ehtj.v4i0.7107

obstruction by ketamine-containing gelatinous debris (86, 89, 93). All of those who had cystoscopy had demonstratable cystitis, with abnormal histology being reported in 32 of 34 biopsies. Unusual features were periureteric thickening (3/71) and raised serum creatinine (8/92), with some patients showing ultrasonographic evidence of papillary necrosis (86); it is unknown if this represents a primary renal insult or arises as a consequence of the hydronephrosis.

Histologically, bladder biopsies from patients with ketamine-associated cystitis show a consistent picture of urothelial ulceration, with eosinophilic infiltration of the lamina propria with surrounding reactive urothelial atypia (88, 94, 95). The appearances are similar to carcinoma *in situ*, with nuclear enlargement and disorganisation, high p53 immunoreactivity, and moderate-to-high Ki67 immunoreactivity; importantly, what distinguishes the ketamine-related changes from carcinoma *in situ* is that the ketamine-related biopsies are negative for CK20 (95).

The cause of the bladder pathology is unknown. Given that there are reports of adulterants added to 'street'/illegal ketamine, it is possible that the urinary tract problems are related to the adulterants rather than to ketamine itself. However, in the animal study discussed above, mice were only exposed to intraperitoneal ketamine and still developed mononuclear infiltration occurring throughout the urological tract, in the glomeruli, ureters, and bladders (90). In addition, there are four reported cases from the palliative care setting in patients using pharmaceutical-grade analgesic ketamine who developed LUTS (91, 92). It is likely on the basis of this evidence, that the urinary tract pathology seen is related directly to ketamine and/or its metabolites. Additionally, the bladder is exposed to ketamine and its active metabolites for over a week following a single dose of ketamine (14, 15), which suggests frequent ketamine users would have a prolonged exposure. The evidence for a dose-dependent relationship is strengthened by evidence from a case report of a palliative care patient whose urinary symptoms paralleled the use, discontinuation, reintroduction, and repeat discontinuation of analgesic ketamine (91).

Abstinence of continuing ketamine use is central to managing patients with urological pathology (86, 94, 96). There are no reports of spontaneous resolution of either symptoms or pathology in persistent ketamine users, and both recurrent symptoms and/or worsening pathology are reported in those who return to ketamine use (89, 91). A number of therapies have been explored for the management of ketamine associated urological problems. Some authors have described symptom relief with the use of elmiron (pentosan polysulphate sodium), which is a low molecular weight heparin-like compound that is thought to help increase the glycosaminoglycan layer of the damaged bladder wall urothelium (88). Intravesical hyaluronic acid has also been used (94, 97–99). Hyaluronic acid is a mucopolysaccharide and it is thought that it acts as a urothelial protective barrier. Its use has been described in both general and ketamine-related interstitial and haemorrhagic cystitis (94, 97–99). In one series of six patients with ketamine-related bladder pathology and LUTS, weekly intravesical hyaluronic acid for 1 month resulted in improvement in painful bladder, frequency, and haematuria (94). Surgical intervention, such as augmentation enterocystoplasty or cystectomy with conduit diversion, is generally considered a last resort in patients who have continued symptoms and haematuria despite the above therapies and abstinence from ketamine (93, 94, 100).

Gastrointestinal toxicity

Regular ketamine use is associated with vague abdominal pains of unknown aetiology, colloquially termed 'K-Cramps' (7). Recently, certain authors have described gastric and hepatic pathology in long-term ketamine users investigated for abdominal pains.

In a small retrospective analysis of 37 recreational ketamine users from Hong Kong, typical symptoms of epigastric pain, with or without vomiting, was associated with biopsy-proven *Helicobacter Pylori*-negative gastritis (101). These symptoms were improved by self-reported abstinence, but neither the abstinence nor gastritis resolution was objectively confirmed. In that same analysis, abnormal liver function tests were reported, but no statistical relationship to symptoms was detected (101). Abnormal liver function tests, irrespective of associated pain, have also been reported elsewhere after clinical ketamine use and non-medical ketamine use (89, 101–105). S(+)-ketamine has recently been shown to be directly hepatotoxic in human hepatoma G2 cells *in vitro* and this occurs at concentrations compatible with ketamine use (105). However, this effect has not been shown to cause abdominal pains.

Choledochal cysts, benign cystic dilatations of the common bile duct, in association with abnormal liver function tests have been described in ketamine users from the United Kingdom and Hong Kong (89, 103, 104). One chronic ketamine user from the United Kingdom had a dilated common bile duct that regressed with abstinence but recurred following a return to ketamine use (89). All five patients reported from Hong Kong were diagnosed with choledochal cysts following investigations for recurrent epigastric pain and abnormal liver function tests and improvement in both symptoms and common bile duct dilatation occurred with self-reported abstinence. It is unclear what the mechanism for these effects is.

Conclusion

Recreational, non-medical ketamine use is an important public health issue, with evidence of its increasing use in certain population sub-groups, the youth clubbing scene in particular. In the acute setting, the neuro-behavioural and neuropsychiatric effects of ketamine increase the risk of injury and harm to the individual. In the long-term there is evidence of psychological dependency and strong evidence for deleterious neuropsychiatric and urological effects. Long-term users may develop schizophrenia-type symptoms, have poor psychological well-being, memory difficulties, and are at risk of haemorrhagic cystitis with significant associated lower urinary tract symptoms. More work is still needed to better elucidate the epidemiology of ketamine use and the pathophysiological basis of the chronic neuropsychiatric and urological harms.

Acknowledgements

PD and DW have acted as expert advisers to the UK Advisory Council on the Misuse of Drugs (ACMD) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).

Conflict of interest and funding

The authors have not received any funding or benefits from industry to conduct this study.

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Citation: Emerging Health Threats Journal 2011, **4**: 7107 - DOI: 10.3402/ehtj.v4i0.7107

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Citation: Emerging Health Threats Journal 2011, **4**: 7107 - DOI: 10.3402/ehtj.v4i0.7107