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

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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
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 thalamicocortical 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 subanaesthetic 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 phenacyclidine-binding site of the NMDA-R and prevents neuronal Ca2+ 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 α1- and β2-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* | 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).
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-methylenedioxy-methamphetamine (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             |
| United States, 2006 | (34)      | 0.1                     | <0.01                       | >12               |

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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 coordination, 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 (LD50) 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
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 GABAA 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 intransal 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...
obstruction by ketamine-containing gelatinous debris (86, 89, 93). All of those who had cystoscopy had demonstrable 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.

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References

1. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of Ci-581, a new dissociative anesthetic, in man. Clin Pharmacol Ther. 1965;6:279-91.
2. WHO. WHO model list of essential medications. 16th ed. Geneva: Author; 2010.
3. Sinner B, Graf BM. Ketamine. Handb Exp Pharmacol. 2008;182:313–33.
4. Noppers I, Niesters M, Aarts L, Smith T, Sarton E, Dahan A. Ketamine for the treatment of chronic non-cancer pain. Expert Opin Pharmaacoother. 2010;11:2417–29.
5. Jansen KLR. Ketamine: Dreams and realities. 2nd ed. Sarasota, FL: Multidisciplinary Association for Psychedelic Studies; 2004.
6. White PF, Schulttler J, Shafer A, Stanski DR, Horai Y, Trevor AJ. Comparative pharmacology of the ketamine isomers. Studies in volunteers. Br J Anaesth. 1985;57:197–201.
7. Jansen KL. A review of the nonmedical use of ketamine: Use, users and consequences. J Psychoactive Drugs. 2000;32:419–33.
8. EMCDDA. Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drugs. Luxembourg: Office for Official Publications of the European Communities; 2002.
9. Clements JA, Nimmo WS, Grant IS. Bioavailability, pharmacokinetics, and analgesic activity of ketamine in humans. J Pharm Sci. 1982;71:539–42.
10. Malinovsky JM, Servin F, Cozian A, Lepage JY, Pinaud M. Ketamine and norketamine plasma concentrations after i.v., nasal and rectal administration in children. Br J Anaesth. 1996;77:203-7.
11. Cohen ML, Trevor AJ. On the cerebral accumulation of ketamine and the relationship between metabolism of the drug and its pharmacological effects. J Pharmacol Exp Ther. 1974;189:351-8.
12. Hijazi Y, Boulieu R. Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes. Drug Metab Dispos. 2002;30:853-8.
13. Wieber J, Gugler R, Hengstmann JH, Dengler HJ. Pharmacokinetics of ketamine in man. Anaesthesist. 1975;24:260–3.
14. Parkin MC, Turfus SC, Smith NW, Halket JM, Braithwaite RA, Elliott SP, et al. Detection of ketamine and its metabolites in urine by ultra high pressure liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci. 2008;876:137–42.
15. Adamowicz P, Kala M. Urinary excretion rates of ketamine and norketamine following therapeutic ketamine administration: Method and detection window considerations. J Anal Toxicol. 2005;29:376–8.
16. Irfune M, Shimizu T, Nomoto M, Fukuda T. Ketamine-induced anaesthesia involves the N-methyl-D-aspartate receptor-channel complex in mice. Brain Res. 1992;596:1–9.
17. Zeilhofer HU, Swandulla D, Geisslinger G, Brune K. Differential effects of ketamine enantiomers on NMDA receptor currents in cultured neurons. Eur J Pharmacol. 1992;213:155–8.
18. Bergman SA. Ketamine: Review of its pharmacology and its use in pediatric anesthesia. Anesth Prog. 1999;46:10-20.
19. Shimoyama M, Shimoyama N, Gorman AL, Elliott KJ, Inturrisi CE. Oral ketamine is antinociceptive in the rat formalin test: Role of the metabolite, norketamine. Pain. 1999;81:85-93.
20. Smith DJ, Pekoe GM, Martin LL, Coalgate B. The interaction of ketamine with the opiate receptor. Life Sci. 1980;26:789-95.
21. Bevan RK, Rose MA, Duggan KA. Evidence for direct interaction of ketamine with alpha 1- and beta 2-adrenoceptors. Clin Exp Pharmacol Physiol. 1997;24:923–26.
22. Lundy PM, Lockwood PA, Thompson G, Frew R. Differential effects of ketamine isomers on neuronal and extraneuronal catecholamine uptake mechanisms. Anesthesiology. 1986;64:359–63.
23. Durieux ME. Inhibition by ketamine of muscarinic acetylcholine receptor function. Anesth Analg. 1995;81:57-62.
24. Cohen MG, Chan SL, Bhargava HN, Trevor AJ. Inhibition of mammalian brain acetylcholinesterase by ketamine. Biochem Pharmacol. 1974;23:1647–52.
25. Sato T, Matsuki A, Zsigmond EK, Rabito SF. Ketamine relaxes airway smooth muscle contracted by endothelin. Anesth Analg. 1997;84:900-6.
26. Lindefors N, Barati S, O’Connor WT. Differential effects of ketamine isomers on neuronal and extraneuronal catecholamine uptake mechanisms. Anesthesiology. 1986;64:359-63.
27. Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. Br J Pharmacol. 1983;79:565–75.
28. Irfune M, Sato T, Kamata Y, Nishikawa T, Dohi T, Kawahara M. Evidence for GABA(A) receptor agonistic properties of ketamine: Convulsive and anesthetic behavioral models in mice. Anesth Analg. 2000;91:230-6.
29. FDA. Ketamine abuse. FDA Drug Bull. 1979;9:24.
30. Laidler KAJ. The rise of club drugs in a heroin society: The case of Hong Kong. Subst Use Misuse. 2005;40:1257-78.
31. AIHW (Australian Institute of Health and Welfare). 2008 National drug survey household survey: Detailed findings. Canberra: Author; 2008.

Sarbjeet S. Kalsi et al.
Recreational ketamine toxicity

32. Paglia-Boak A, Mann RE, Adlaf EM, Rehm J. Drug use among Ontario students, 1977–2009: Detailed OSDUHS findings. Toronto, Ontario, Canada: Centre for Addiction and Mental Health; 2009.

33. Hoare J, Moon D. Drug misuse declared: Findings from the 2009/10 British crime survey England and Wales. Home Office Statistical Bulletin. London: Home Office; 2010, p. 1–109.

34. SAMSHA (Substance Abuse and Mental Health Services Administration). The NSDUH report: Use of specific hallucinogens 2006. Rockville, MD: Author; 2008.

35. Barrett SP, Gross SR, Garand I, Pihl RO. Patterns of use and harms associated with non-medical ketamine use. Subst Use Misuse. 2005;40:1525–37.

36. EMCDDA. Annual Report 2006. Selected Issue 3: Development in drug use within recreational settings. Luxembourg: Office for Official Publications of the European Communities; 2006.

37. Dick D, Torrance C. Mixmag drugs survey. Mixmag (The world’s biggest dance music and clubbing magazine). 2010 February, p. 44–53.

38. Tsu AC, Lin HR, Tseng YT, Hu AR, Yeh PC. Profiles of urine samples from participants at rave party in Taiwan: Prevalence of ketamine and MDMA abuse. Forensic Sci Int. 2003;136:47–51.

39. Dillon P, Copeland J, Jansen K. Patterns of use and harms associated with non-medical ketamine use. Drug Alcohol Depend. 2003;69:23–8.

40. Fendrich M, Johnson TP. Editors’ introduction to this special issue on club drug epidemiology. Subst Use Misuse. 2005;40:1179–84.

41. UNODC. United Nations office on drugs and crime: World drug report 2010. Vienna: United Nations Publications; 2010.

42. APAIC. Regional trends: Ketamine. Asia & Pacific Region; 2006 [accessed 2010 November 6]. Available from: http://www.apaic.org/index.php?option=com_content&view=article&id=122&Itemid=135.

43. Anonymous. Central registry of drug abuse: Selected drug abuse statistics [Government Statistics] Hong Kong: Narcotics Division, Security Bureau, The Government of the Hong Kong Special Administrative Region; 2010 [accessed 2010 November 5]. Available from: http://www.nd.gov.hk/th-statistics_list/doc/en/15.pdf.

44. Wood DM, Bishop CR, Greene SL, Dargan PI. Ketamine-related toxicology presentations to the ED [abstract]. Clin Toxicol. 2008;46:630.

45. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Brenner JD, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychopharmacology, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry. 1994;51:199–214.

46. Jansen KL. Non-medical use of ketamine. BMJ. 1993;306:601–2.

47. Scott-Ham M, Burton FC. Toxicological findings in cases of alleged drug-facilitated sexual assault in the United Kingdom over a 3-year period. J Clin Forensic Med. 2005;12:175–86.

48. Du Mont J, Macdonald S, Robard N, Bainbridge D, Aslani E, Smith N, et al. Drug-facilitated sexual assault in Ontario, Canada: Toxicological and DNA findings. J Forensic Leg Med. 2010;17:333–8.

49. Cheng JY, Chan DT, Mok VK. An epidemiological study on alcoholholdings-related fatal traffic crash cases of deceased drivers in Hong Kong between 1996 and 2000. Forensic Sci Int. 2005;153:196–201.

50. Wong OF, Tsui KL, Lam TS, Sze NN, Wong SC, Lau FL, et al. Prevalence of drugged drivers among non-fatal driver casualties presenting to a trauma centre in Hong Kong. Hong Kong Med J. 2010;16:246–51.

51. Weimer AL, Vieira L, McKay CA, Bayer MJ. Ketamine abusers presenting to the emergency department: A case series. J Emerg Med. 2000;18:447–51.

52. Pandey CK, Mathur N, Singh N, Chandola HC. Fulminating pulmonary edema after intramuscular ketamine. Can J Anaesth. 2000;47:894–6.

53. Murphy JL. Jr. Hypertension and pulmonary oedema associated with ketamine administration in a patient with a history of substance abuse. Can J Anaesth. 1993;40:160–4.

54. Tarnow J, Hess W. Pulmonary hypertension and pulmonary edema caused by intravenous ketamine. Anaesth Analg. 1978;77:486–7.

55. Berger MM, Pitzer B, Zugel S, Wieland CW, Vlaar AP, Schultz MJ, et al. Alveolar but not intravenous S-ketamine inhibits alveolar sodium transport and lung fluid clearance in rats. Anesth Analg. 2010;111:164–70.

56. Peyton SH, Couch AT, Bost RO. Tissue distribution of ketamine: Two case reports. J Anal Toxicol. 1988;12:268–9.

57. Moore KA, Kilbane EM, Jones R, Kunsman GW, Levine B, Smith M. Tissue distribution of ketamine in a mixed drug fatality. J Forensic Sci. 1997;42:1183–5.

58. Gill JR. Stajic M. Ketamine in non-hospital and hospital deaths in New York City. J Forensic Sci. 2000;45:655–8.

59. Lalonde BR, Wallage HR. Postmortem blood ketamine distribution in two fatalities. J Anal Toxicol. 2004;28:71–4.

60. Schifano F, Corkery J, Oyefeso A, Tonia T, Ghodse AH. Trapped in the ‘K-hole’: Overview of deaths associated with ketamine misuse in the UK (1993–2006). J Clin Psychopharmacol. 2009;28:114–6.

61. Morgan CJ, Curran HV. Acute and chronic effects of ketamine upon human memory: A review. Psychopharmacology (Berl). 2006;188:408–24.

62. Morgan CJ, Rossell SL, Pepper F, Smart J, Blackburn J, Brandner B, et al. Semantic priming after ketamine acutely in healthy volunteers and following chronic self-administration in substance users. Biol Psychiatry. 2006;59:265–72.

63. Morgan CJ, Perry EB, Cho HS, Krystal JH, D’Souza DC. Greater vulnerability to the amnestic effects of ketamine in males. Psychopharmacology (Berl). 2006;187:405–14.

64. Blagrove M, Morgan CJ, Curran HV, Bromley L, Brandner B. The incidence of unpleasant dreams after sub-anaesthetic ketamine. Psychopharmacology (Berl). 2009;203:109–20.

65. Morgan CJ, Muetzelfeldt L, Curran HV. Ketamine use, cognition and psychological wellbeing: A comparison of frequent, infrequent and ex-users with polydrug and non-using controls. Addiction. 2009;104:77–87.

66. Morgan CJ, Muetzelfeldt L, Curran HV. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: A 1-year longitudinal study. Addiction. 2010;105:121–33.

67. Freeman TP, Morgan CJ, Klaassen E, Das RK, Stefanovic A, Brandner B, et al. Superstitious conditioning as a model of delusion formation following chronic but not acute ketamine in humans. Psychopharmacology (Berl). 2009;206:563–73.

68. Jansen KL. Ketamine—Can chronic use impair memory? Int J Addict. 1990;25:133–9.

69. Narendran R, Frankle WG, Keefe R, Gil R, Martinez D, Silfstein M, et al. Altered prefrontal dopaminergic function in chronic recreational ketamine users. Am J Psychiatry. 2005;162:2352–9.

70. Ikonomidou C, Bosch F, Miksa M, Bittigau P, Voeller K, Dikranian K, et al. Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science. 1999;283:70–4.
71. Beals JK, Carter LB, Jevtovic-Todorovic V. Neurotoxicity of nitrous oxide and ketamine is more severe in aged than in young rat brain. Ann NY Acad Sci. 2003;993:115.

72. Jevtovic-Todorovic V, Carter LB. The anesthetics nitrous oxide and ketamine are more neurotoxic to old than to young rat brain. Neurobiol Aging. 2005;26:947-56.

73. Jevtovic-Todorovic V, Benshoff N, Olney JW. Ketamine potentiates cerebrocortical damage induced by the common anesthetic agent nitrous oxide in adult rats. Br J Pharmacol. 2000;130:1692-9.

74. Wang C, Sadovova N, Patterson TA, Zou X, Fu X, Hanig JP, et al. Protective effects of 7-nitroindazole on ketamine-induced neurotoxicity in rat forebrain culture. Neurotoxicology. 2008; 29:613-20.

75. Zou X, Patterson TA, Divine RL, Sadovova N, Zhang X, Hanig JP, et al. Prolonged exposure to ketamine increases neurodegeneration in the developing monkey brain. Int J Dev Neurosci. 2009;27:727-31.

76. Liao Y, Tang J, Ma M, Wu Z, Yang M, Wang X, et al. Frontal white matter abnormalities following chronic ketamine use: A diffusion tensor imaging study. Brain. 2010;133:2115-22.

77. WHO. International Classification of Diseases (ICD) 10. 2nd ed. Geneva: Author; 2007 [updated 2010 November 5]. Available from: http://apps.who.int/classi
cation of Diseases (ICD) 10.

78. WHO. International Classification of Diseases (ICD) 10. 2nd ed. Geneva: Author; 2007 [updated 2010 November 5]. Available from: http://apps.who.int/classifications/apps/icd/icd10online/index.htm?gf10.htm

79. WHO. International Classification of Diseases (ICD) 10. 2nd ed. Geneva: Author; 2007 [updated 2010 November 5]. Available from: http://apps.who.int/classifications/apps/icd/icd10online/index.htm?gf10.htm

80. Lu Y, France CP, Woods JH. Tolerance to the cataleptic effect of ketamine, part two: A review of problem use and dependence. J Psychoactive Drugs. 2001;33:151

81. Moreton JE, Meisch RA, Stark L, Thompson T. Ketamine self-administration by the rhesus monkey. J Pharmacol Exp Ther. 1977;203:303-9.

82. Nutt D, Lingford-Hughes A, Daglish M. Future directions in substance dependence research. J Neural Transm Suppl. 2003;64:95-103.

83. Marietta MP, White PF, Pudwill CR, Way WL, Trevor AJ. Biodisposition of ketamine in the rat: Self-induction of the N-methyl-D-aspartate (NMDA) receptor antagonists in pigeons: Cross-tolerance between PCP-like compounds and competitive NMDA antagonists. J Pharmacol Exp Ther. 1992;263:499-504.

84. Chan WH, Sun WZ, Ueng TH. Induction of rat hepatic cytochrome P-450 by ketamine and its toxicological implications. J Toxicol Environ Health A. 2005;68:1581-97.

85. Muetzelfeldt L, Kamboj SK, Rees H, Taylor J, Morgan CJ, Curran HV. Journey through the K-hole: Phenomenological aspects of ketamine use. Drug Alcohol Depend. 2008;95: 219-29.

86. Chu PS, Ma WK, Wong SC, Chu RW, Cheng CH, Wong S, et al. The destruction of the lower urinary tract by ketamine abuse: A new syndrome? BJU Int. 2008;102:1616–22.

87. Cottrell A, Warren K, Ayres R, Weinstock P, Kumar V, Gillatt D. The destruction of the lower urinary tract by ketamine abuse: A new syndrome? BJU Int. 2008;102:1178-9.

88. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-associated ulcerative cystitis: A new clinical entity. Urology. 2007;69:810-2.

89. Selby NM, Anderson J, Bungay P, Chesterton LJ, Kolhe NV. Obstructive nephropathy and kidney injury associated with ketamine abuse [case report]. Nephrol Dialysis Transplantation Plus. 2008;1:310-2.

90. Yeung LY, Rudd JA, Lam WP, Mak YT, Yew DT. Mice are prone to kidney pathology after prolonged ketamine addiction. Toxicol Lett. 2009;191:275-8.

91. Gregoire MC, MacLellan DL, Finley GA. A pediatric case of ketamine-associated cystitis. Urology. 2008;71:1232–3.

92. Storr TM, Quibell R. Can ketamine prescribed for pain cause damage to the urinary tract? Palliat Med. 2009;23:670-2.

93. Mason K, Cottrell AM, Corrigan AG, Gillatt DA, Mitchelmore AE. Ketamine-associated lower urinary tract destruction: A new radiological challenge. Clin Radiol. 2010;65:795-800.

94. Tsai TH, Cha TL, Lin CM, Tsao CW, Tang SH, Chuang FP, et al. Ketamine-associated bladder dysfunction. Int J Urol. 2009;16:826-9.

95. Oxley JD, Cottrell AM, Adams S, Gillatt D. Ketamine cystitis as a mimic of carcinoma in situ. Histopathology. 2009;55: 705-8.

96. Shahani R, Stewart RJ. Reply to letter-to-the-editor, Re: Shahani R, Streutker C, Dickson B, et al. Ketamine-associated ulcerative cystitis: A new clinical entity. Urology. 2007;69: 810-2. Urology. 2008;71(5):987.

97. Kallestrup EB, Jorgensen SS, Nording J, Hald T. Treatment of interstitial cystitis with Cystistat: A hyaluronic acid product. Scan J Urol Nephrol. 2005;39:143-7.

98. Lauzazz C, Ahanasiou S, Pitsouni E, Falgas ME. Hyaluronic acid: An effective alternative treatment of interstitial cystitis, recurrent urinary infections and haemorrhagic cystitis? Eur Urol. 2007;51:1534-40.

99. Daha LK, Riedl CR, Lazar D, Holhbrurger C, Pfluger H. Do cytometric findings predict the results of intravesical hyaluronic acid in women with interstitial cystitis? Eur Urol. 2005;57:393–7.

100. Chu PS, Kwok SC, Lam KM, Chu TY, Chan SW, Man CW, et al. 'Street ketamine'-associated bladder dysfunction: A report of ten cases. Hong Kong Med J. 2007;13:311–3.

101. Poon TL, Wong KD, Chan MY, Fung KW, Chu SK, Man CW, et al. Upper gastrointestinal problems in inhalational ketamine abusers. J Dig Dis. 2010;11:106–10.

102. Kimura F, Hashimoto Y, Shimodate Y, Hashimoto H, Ishihara H, Matsuki A. Clinical study on total intravenous anesthesia with droperidol, fentanyl and ketamine (in Japanese). Masui. 1991;40:1371–5.

103. Ng SH, Lee HK, Chan YC, Lau FL. Dilated common bile ducts mimicking choledochal cysts in ketamine abusers. Hong Kong Med J. 2009;15:157.

104. Wong SW, Lee KF, Wong J, Ng WW, Cheung YS, Lai PB. Dilated common bile ducts mimicking choledochal cysts in ketamine abusers. Hong Kong Med J. 2009;15:53-6.

105. Lee ST, Wu TT, Yu PY, Chen RM. Apoptotic insults to human HepG2 cells induced by S(+)-ketamine occurs through activation of a Bax-mitochondria-caspase protease pathway. Br J Anaesth. 2009;102:80-9.

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