ACMD

Advisory Council on the Misuse of Drugs

Ketamine: a review of use and harm

10th December 2013

ACMD

Advisory Council on the Misuse of Drugs

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10th December 2013

Dear Home Secretary and Secretary of State for Health,

On behalf of the Advisory Council on the Misuse of Drugs (ACMD), I am pleased to write and provide you with advice on ketamine. The ACMD last provided advice on ketamine in 2004. The ACMD's present review builds on the evidence base of the 2004 report, particularly new evidence of chronic toxicity to the bladder. The advice covers public health issues and to this extent I am addressing it to the Secretary of State for Health.

Ketamine is widely used in veterinary medicine and in some areas of human medicine as an anaesthetic and analgesic. Ketamine is also a drug of misuse and to give an indication of current levels of misuse, in 2012/13 it was estimated that around 120,000 individuals had misused ketamine. The Crime Survey for England and Wales shows that ketamine misuse is most common in males, in the 20-24 year age group and also that ketamine is often taken in the context of polydrug use; other studies have shown that ketamine use is more common in those who attend nightclubs.

In summary, ketamine misuse can cause a range of physical and psychological harms. There has been an increase in acute ketamine toxicity presentations to hospitals in recent years, effects seen in these presentations are generally short-lived but can include impaired consciousness, agitation, hallucinations and dissociative effects. In addition, there is now good evidence that frequent and heavy ketamine misuse can cause significant toxicity to the bladder, urinary tract and kidneys. This can be associated with severe and disabling symptoms that typically include pain on passing urine, frequency and urgency of urination, blood in the urine and incontinence. Whilst these changes can be reversible with ketamine cessation, there are numerous reports of individuals having to have surgery to remove their bladders because of severe ketamine related bladder damage. At large doses, ketamine can cause acute psychological effects that include severe

dissociation (the 'k-hole') and in frequent, high dose users chronic effects such as impairment in short and long term memory, although it is not yet known whether these effects on the memory are reversible with ketamine cessation. There is some evidence via case reports of ketamine dependence and UK drug treatment services have seen a modest increase in numbers presenting for treatment. The ACMD makes a series of recommendations relating to public health and treatment provision and to this extent I am addressing this letter to the Secretary of State for Health.

There is limited evidence of ketamine causing social harm, especially in comparison to other drugs such as heroin and cocaine, and, for example, evidence from police services of crime associated with ketamine. Case studies presented to the ACMD by ex-users of ketamine and their families and friends, suggest that ketamine misuse can impact negatively on families, social skills and participation in social activities. As described above, large doses of ketamine can lead to dissociative effects which, combined with ketamine's anaesthetic and analgesic effects, can potentially place the user in a position where they are vulnerable to robbery and/or assault.

On the basis of this evidence the ACMD makes two recommendations on ketamine control under the Misuse of Drugs Act and Regulations. First, the ACMD recommends that ketamine be controlled under the Misuse of Drugs Act (1971) as a Class B substance. This was not a unanimous decision but it is a majority recommendation from both the Council and its Ketamine Working Group. Although there is limited evidence of ketamine misuse causing social harm, evidence of physical harm (mainly chronic bladder toxicity but also an increase in acute toxicity) has increased since the ACMD recommended ketamine as a Class C substance in 2004.

Second, the ACMD recommends that ketamine is placed in Schedule II of the Misuse of Drugs Regulations (2001). Although there is limited evidence of organised diversion of ketamine, ketamine is a mainstream drug of misuse with strong evidence of serious harm to regular, high dose misusers. The potential risk of harm if diverted is therefore high. Ketamine is currently a Schedule IV Part 1 drug but many hospitals treat ketamine as a higher schedule drug, in particular instituting safe custody and register requirements, and the Royal College of Veterinary Surgeons Best Practice guidelines state that ketamine should be treated as a Schedule II drug.
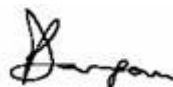
In light of the established use of ketamine in human and veterinary medicine, the ACMD does, however, recommended that the higher schedule is decided on only after consultation with practitioners on the impact of this change on patient and veterinary care.

I would welcome the opportunity to discuss the report and recommendations with you both, and the Minister of State for Crime Prevention and Parliamentary Under Secretary of State for Public Health to whom this letter is copied.

Yours sincerely,

Professor Les Iversen   Dr Paul Dargan
Chair, ACMD   Chair of the ACMD's Ketamine Working Group

Cc:
Minister of State for Crime Prevention, Norman Baker MP
Parliamentary Under Secretary of State for Public Health, Jane Ellison MP

CONTENTS

EXECUTIVE SUMMARY

Background

1. The ACMD reviewed the harms associated with ketamine use in 2004 and recommended that ketamine should be controlled under the Misuse of Drugs Act 1971 as a Class C substance and placed in Schedule IV Part 1 of the Misuse of Drugs Regulations, 2001 (ACMD, 2004). The ACMD also made recommendations on routine screening for ketamine in unexpected deaths and road traffic accidents and that ketamine be included in the British Crime Survey in order to obtain more robust epidemiological data.

2. The ACMD's recommendation to control ketamine was implemented on the 1 January 2006 and ketamine use has been included in the British Crime Survey (now the 'Crime Survey for England and Wales') since the reporting year 2006/7. The Department for Transport includes ketamine in its drug-driving offence proposals consulted on earlier this year [Department for Transport, 2013].

3. Since the ACMD's advice in 2004, the evidence of ketamine misuse and harms has grown and there is particular concern associated with ketamine misuse and chronic toxicity including bladder and other renal tract damage. Reflecting on this, the ACMD was requested in March 2012 by the Home Secretary to review the evidence of the misuse and harms of ketamine and its analogues and provide advice to inform the government's public health response, as well as classification of ketamine.

4. The ACMD established a Ketamine Working Group (21 Mar – 17 Sep 2013) formed of ACMD members and co-opted members (a list of members is included in Annex A) with relevant expertise to carry out the review covering the following areas of evidence:
   - pharmacology;
   - medical and veterinary use;
   - epidemiology of ketamine misuse;
   - physical harm; and
   - social harm.

5. This report summarises the evidence reviewed and the ACMD's consequent conclusions and recommendations to the Government.

Ketamine chemistry and pharmacology

6. Ketamine is a member of a group of compounds known as arylcyclohexylamines. The arylcyclohexylamines include a number of substances with psychoactive properties, including phencyclidine (Class A) and methoxetamine (Class B).

7. These substances produce a wide range of effects mediated by a variety of pharmacological mechanisms but primarily they all act as non-competitive antagonists at glutamate receptors of the N-methyl-D-aspartate (NMDA) sub-type.

Clinical and veterinary ketamine use

8. Ketamine has been used therapeutically as a pharmaceutical agent in a number of areas of both human and veterinary medicine for over 50 years. Studies are under way exploring use of ketamine for treatment-resistant depression, for the treatment of addiction, and it is also being explored experimentally as a pharmacological agent for modelling psychosis.

Human medicine

9. Ketamine is used in a variety of settings, from analgesia in acute and chronic pain to anaesthesia in pre-hospital and in-hospital emergency care in both civilian and military practice.

10. Systematic reviews suggest that there is a need for further research into the role of ketamine as an analgesic in chronic cancer pain (palliative care) and non-cancer pain (Recommendation).

11. Use of ketamine as an analgesic is generally well tolerated but when it is used at high doses it can cause adverse effects including dysphoria, hallucinations, vivid dreams and nightmares. There is emerging evidence that chronic, high dose, therapeutic use of ketamine can cause urological symptoms and bladder damage. It should

be noted that initial doses of ketamine when it is used as an analgesic are lower than the doses reported to be used by those misusing ketamine and lower than those reported to be associated with significant bladder toxicity; however, high-dose clinical use of ketamine as an analgesic can involve doses similar to those reported by individuals who misuse ketamine.

12. Ketamine is used as an anaesthetic in both civilian and military practice, particularly but not exclusively in the pre-hospital environment. It is used for procedural sedation of children in the Emergency Department. Anaesthetic doses of ketamine are generally well tolerated, although some patients experience emergence phenomena including hallucinations and disorientation; there is no potential for bladder toxicity with the single doses of ketamine used in anaesthesia. Ketamine has limited impact on respiratory function and can cause an increase in blood pressure which can be beneficial if it is used as an anaesthetic in patients with major trauma.

Veterinary medicine

13. In veterinary medicine ketamine is widely used in many species; it is the most common anaesthetic used in horses.

Diversion

14. Data on the diversion of ketamine from human or veterinary practice are not collected nationally. However, there have been reports from Controlled Drug Local Intelligence Networks that have reported evidence of diversion of ketamine from health and veterinary settings in some localities. Although ketamine is in Schedule IV Part I, many hospitals treat it as a higher schedule drug with safe custody requirements. The Royal College of Veterinary Surgeons Best Practice guidelines state that ketamine should be treated as a Schedule II drug, although these guidelines are not currently enforceable.

Ketamine misuse: prevalence and patterns of use

15. UK population surveys suggest that ketamine use is more common in males and in the 20–24 age group. There was an increase in life-time, last year and last month ketamine use from 2006/7 to 2010/11 in both adults (16–59) and young people (16–24). More recently, there has been a statistically significant decrease in last month prevalence of ketamine use in adults from 2010/11 to 2011/12 and a statistically significant decrease in last year prevalence of ketamine use in adults and young people from 2011/12 to 2012/13.

16. Along with ecstasy and amphetamines, ketamine is amongst the drugs most likely to be taken simultaneously with other drugs, with nearly half of ketamine users reporting simultaneous polydrug use the last time that they took ketamine.

17. Ketamine use is more common in those who attend nightclubs and there is an association between ketamine use and frequency of attendance at nightclubs and pubs. However, the social acceptability of ketamine consumption varies considerably between and within music cultures and social 'scenes'.

Medical harms

Acute toxicity

18. Available data sources suggest an increase in acute ketamine toxicity in recent years in the UK. There was an increase in access to the National Poisons Information Service concerning ketamine toxicity from 2004 (TOXBASE accesses peaking in 2009 and telephone enquiries peaking in 2010/11). Data from a London Emergency Department showed increasing presentations associated with acute ketamine use from 2006 to 2010 (although many of these presentations involved ketamine in the context of polydrug use).

19. Common effects associated with acute ketamine toxicity include impaired consciousness, agitation, hallucinations, delirium, confusion, dissociative effects, nausea, tachycardia and mild hypertension. These features are generally short-lived and settle within 4-–12 hours; individuals presenting with acute ketamine toxicity usually do not need pharmacological therapy.

Chronic toxicity

20. Ketamine has more recently been recognised as a cause of significant adverse effects within the bladder, urinary tract and kidneys. The severity of urological symptoms and the degree of bladder damage appear to be in direct proportion to the amount of ketamine used, the frequency of usage and the length of use. Some users may take

higher doses of ketamine in an attempt to control bladder pain caused by ketamine use, further increasing the risk of ketamine-related bladder damage.

21. The symptoms associated with ketamine-related bladder damage typically include pain on passing urine, frequency and urgency of urination, blood and matter (e.g. bladder tissue) in the urine and incontinence. These symptoms can be severe and disabling. There is no data collected and available on how common ketamine-related bladder effects are in the UK.

22. Cessation of ketamine gives the best chance of symptomatic relief and improvement in bladder pathological changes. It is vital that symptoms are picked up early by healthcare practitioners in order that support can be provided for ketamine cessation (particularly for those with ketamine dependence) and appropriate analgesia provided for the pain associated with ketamine-related bladder damage (recommendation). The bladder in many cases will heal following ketamine cessation and although some symptoms may persist, these generally become more manageable. However, in some cases severe bladder damage may require surgery including removal of all or part of the bladder. More research is required into the incidence, mechanisms and management of bladder damage caused by ketamine use (Recommendation).

23. Up to one-third of long-term ketamine users experience chronic, severe abdominal ('tummy') pain; this is often referred to by users as 'K cramps'. There are emerging reports of liver toxicity associated with chronic ketamine use.

Deaths

24. Data from the National Programme on Substance Abuse Deaths suggest that the first death in which ketamine was implicated occurred in 1997. From then until 2005 there were less than five deaths per year where ketamine was either found in post-mortem toxicology samples and/or implicated in death. The number of these cases increased until 2009 peaking at 26 and 21 respectively; there was then a decline with the number of cases falling to nine and six in 2012.

25. Data from the Office for National Statistics has shown an increase in deaths in which ketamine was detected in post-mortem samples since 2006 (0–3 per year in 2001–2006 to 7–22 per year in 2007–2012). It is not possible from these data to determine whether ketamine was responsible for the death(s); it is also important to note that there is variation between coroners regarding drug testing in deaths. The new Chief Coroner should promote awareness of the importance of accurately documenting substance-related deaths (Recommendation).

Acute psychological effects

26. Ketamine use is associated with a series of acute psychological effects. At low doses, ketamine induces distortion of time and space, hallucinations and mild dissociative effects. At large doses, ketamine induces 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. This is a desired effect for some users, but for others it can be an unpleasant and frightening experience.

Chronic psychological effects

27. The consequences of ketamine use on cognition have been widely investigated as ketamine acts on the NMDA receptor, which is thought to be involved in learning and memory. Frequent, dependent ketamine users exhibit profound impairments in both short- and long-term memory; however, it is not known currently whether these changes are reversible if users cease ketamine use. Studies suggest that daily/dependent ketamine use may be associated with increased depression, but not infrequent (< 3 times per week) ketamine use. More research is required into the long-term neurological, neurocognitive and psychiatric effects of ketamine use (Recommendation).

Dependence and treatment

28. Without large-scale studies the incidence of ketamine dependence is unknown. However, there are some case reports of ketamine dependence and UK drug services have seen modest increases in requests for treatment of ketamine-related problems. Ketamine presentations rose year on year between 2005-6 and 2010-11, from 114 to 845 but fell slightly in 2011-12 to 751. A small number of specialist drug services offering specific treatment pathways for ketamine users are reporting significant demand from a cohort of patients who are generally using most or every day in amounts of up to several grams of illicit ketamine daily.

29. Treatment services need to be able to respond to ketamine dependence with NICE-recommended psychosocial interventions. There is also a need for joined-up treatment of those who have developed ketamine-related bladder damage – urological interventions should be co-ordinated with psychosocial interventions that promote future abstinence from the drug (Recommendation).

Social harms

Police and border authorities

30. Reports from UK police services suggest increasing ketamine use in many UK regions, but there is limited evidence of crime associated with ketamine and the scale of ketamine supply in the UK by criminal groups is difficult to quantify.

31. There is limited forensic testing of ketamine seizures; results that are available suggest that illicit ketamine is generally of moderate to high purity but may contain other psychoactive substances including cathinones, cocaine and piperazines.

32. The scale of ketamine supply to the UK is unknown due to challenges with identifying border seizures of the drug. Testing at the border should be made more effective by providing the technology to accurately field test at the earliest opportunity (Recommendation).

Social harms

33. There are fewer data available on the social harms associated with ketamine than for other drugs such as heroin or cocaine. Case studies presented by ex-users of ketamine and families/friends affected by ketamine use suggest that frequent ketamine use can impact negatively on families, social skills and participation in social activities.

34. At large doses, ketamine can induce dissociation (the 'K-hole'). The user experiences intense detachment that can be an unpleasant and frightening experience. The company of others (e.g. friends, staff in nightclubs/festivals) can help the user deal with this experience. The dissociative effect of ketamine can potentially place the user in a position where they are vulnerable to robbery, assault and/or rape.

Education and prevention

35. The ACMD is not aware of any evidence-based ketamine education or prevention interventions currently being delivered in the UK. Feasible and relevant ketamine prevention goals might include prevention of onset; increased age of initiation; reduced frequency of dosing and amount used per episode; prevention of transition to injection; cessation of use. Ketamine users should be made aware of the long-term physical risks of using ketamine (Recommendation).

RECOMMENDATIONS

Public health

- Healthcare practitioners, particularly, but not just, GPs, should ask patients presenting with unexplained urinary tract symptoms about ketamine use.
- Users should be made aware of the long-term physical risks of frequent ketamine misuse. Bladder damage and the symptoms associated with it (urinary frequency, haematuria and incontinence) can be significant and disabling and so a strong public health message should be constructed.
- Users and staff in nightclubs and at festivals should be informed that the analgesic, anaesthetic and dissociative effects of ketamine can potentially make users vulnerable to robbery, assault and/or rape. Users should ensure that they have friends with them and staff in nightclubs and at festivals should be aware of these risks associated with ketamine use.

Treatment provision

- Ketamine should be considered as dependence forming for some users and treatment services need to be able to respond to this need with NICE-recommended psychosocial interventions.
- There is a need for joined-up treatment of those who have developed ketamine-induced ulcerative cystitis. Urological interventions should be co-ordinated with psychosocial interventions that promote future abstinence from the drug and provision of appropriate analgesia for the pain associated with ketamine-related bladder damage.

Forensic identification

- The scale of ketamine supply to the UK is unknown due to challenges with identifying border seizures of the drug. Testing at the border should be made more effective by providing the technology to accurately field test.
- The new Chief Coroner should promote awareness of the importance of accurately documenting ketamine and other substance-related deaths.

Research

- It is recommended that research is carried out in the following three areas.
    - The incidence, mechanisms and management of bladder damage caused by ketamine use.
    - The long-term neurological, neurocognitive and psychiatric effects of ketamine use, including 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 urological and liver toxicity.
    - The therapeutic role of ketamine in chronic cancer and non-cancer pain in comparison to other analgesic options.

Control and scheduling

Control

- There is limited evidence of social harm associated with ketamine misuse. However, evidence of medical harm, upon which the ACMD had made its previous recommendation for classification of ketamine as C, has increased. There is some evidence of an increase in acute ketamine toxicity in the UK. However, the main area in which there is evidence of significant medical harm is chronic bladder toxicity. This occurs with chronic, frequent high-dose ketamine misuse and can result in severe symptoms.
- It is recommended that ketamine be controlled under the Misuse of Drugs Act 1971 as a Class B substance; this was not a unanimous decision but it was a majority recommendation from both the Council and the Ketamine Working Group.

Scheduling

- There is limited evidence of organised diversion of ketamine; however, ketamine is a mainstream drug of misuse with strong evidence of serious harm to regular, high-dose misusers, therefore, the potential risk of harm if diverted is relatively high. Many hospitals treat ketamine as a higher schedule drug, in particular instituting safe custody and register requirements; Royal College of Veterinary Surgeons Best Practice guidelines state that ketamine should be treated as a Schedule II drug.

- It is therefore recommended that ketamine is moved to Schedule II. However, in light of the use of ketamine in human and veterinary medicine, it is recommended that the higher schedule is decided on only after consultation with practitioners on the impact of this change on patient and veterinary care.
- It is also recommended that the vial size of pharmaceutical ketamine preparations should be considered. Ketamine is currently supplied in multi-dose vials but usually only a single dose is used. This results in a significant amount of waste of ketamine and the potential for diversion of this unused portion of drug.

MAIN REPORT

KETAMINE CHEMISTRY AND PHARMACOLOGY

Chemistry

1. Ketamine is a member of a group of compounds known as arylcyclohexylamines. Arylcyclohexylamines have structures based on cyclohexylamine with an aryl group (an aromatic ring of some type) attached to the atom of the cyclohexyl ring to which the amine group is also linked. The arylcyclohexylamines include a number of substances which have psychoactive effects, some of which are used as pharmaceuticals while others have appeared as drugs of abuse. These were reviewed as part of the ACMD's report on methoxetamine and related materials (2012).
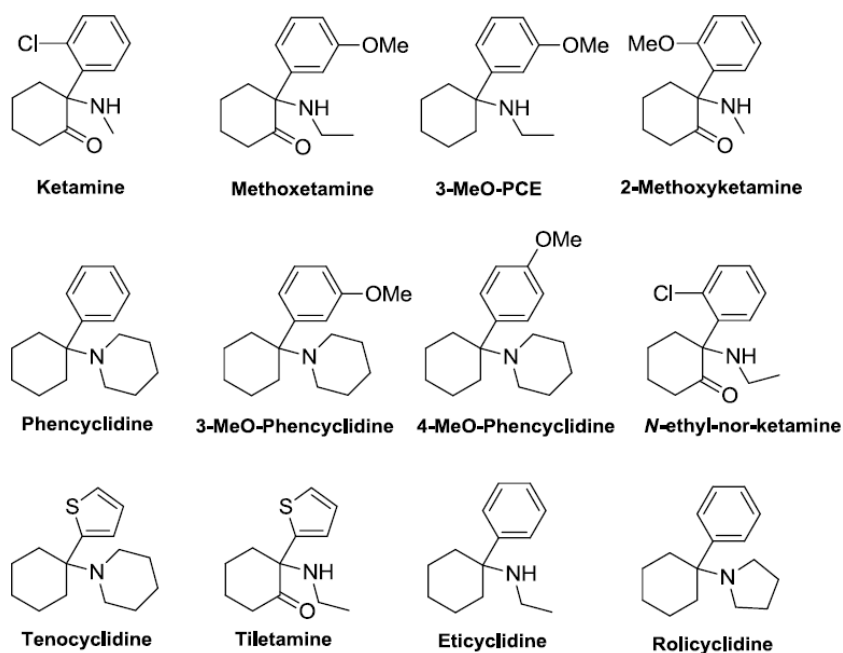

Figure 1 Structures of methoxetamine, phencyclidine, ketamine and other arylcyclohexylamines

Stereochemistry and salts

2. Ketamine is a chiral compound. The S(+) isomer is three to four times more potent than the R(-) isomer as an anaesthetic and as an analgesic and about twice as potent as the racemic mixture (White, 1980; Mathisen, 1995). It also has a higher rate of metabolism. Anticholinergic activity is not stereoselective (White, 1985, Ihnsem, 2001). Most pharmaceutical preparations of ketamine include a racemic mixture but 'Ketanest S' contains only the S(+) isomer. Phencyclidine (PCP), eticyclidine, rolicyclidine and tenocyclidine are not chiral compounds.

3. Pharmaceutical ketamine products usually contain the hydrochloride salt of ketamine. There is very little information on the composition of illicit ketamine as detailed analysis is not routinely commissioned from forensic laboratories but it is probable that seizures consist of racemic mixtures of the hydrochloride salt.

Pharmacology

Ketamine pharmacokinetics

4. Ketamine has high lipid and water solubility and low protein binding and is extensively distributed throughout the body (volume of distribution 3–5 L/kg) (Radonavanovic, 2003).

5. When given orally it undergoes first pass metabolism in the liver where it is transformed into norketamine and then dehydronorketamine (Sinner, 2008). Peak plasma concentrations are reached within a minute intravenously, 5–15 minutes intramuscularly and 30 minutes orally. The duration of action of ketamine is 30 minutes to two hours intramuscularly and 4–6 hours orally (Quibell, 2011).

6. Nasal insufflation of ketamine leads to 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 LSD or 'magic' mushrooms (Moore, 2008). Furthermore, ketamine induces its own metabolism which may lead to users taking higher doses over time.

Ketamine pharmacodynamics

7. Ketamine and related arylcyclohexylamines produce a wide range of effects mediated by a variety of pharmacological mechanisms. Primarily, they all act as non-competitive antagonists at N-methyl-D-aspartate (NMDA) receptors where they bind at the so-called PCP site on the NMDA receptor (Anis, 1983; Roth, 2013). These receptors, which play a critical role in glutaminergically mediated excitatory neurotransmission, are believed to be the principal molecular targets for the anaesthetic action of ketamine and for its psychotomimetic properties. Its reported antidepressant activity has also been attributed to this mechanism in the brain (Zarate, 2006) and its analgesic properties, in part, to the same mechanism in dorsal horn neurons (Quibell, 2011).

8. Systemic administration of NMDA receptor antagonists such as ketamine is known to increase the release of dopamine in the nucleus accumbens region of brain (Matulewicz, 2010), an activity which is typically associated with addiction liability (Cadoni, 2007). In addition to its action on NMDA receptors, ketamine also acts at dopamine D2 and 5-HT$_{2A}$ receptors (Kapur, 2002; Waelbers, 2013). Activation of 5-HT$_{2A}$ receptors is thought to be related to perceptual disorders and hallucinations (Dursun, 1992). At the concentrations employed in human models, ketamine also shows both a stereospecific high-affinity for mu; delta; and for sigma opioid receptors (for a review see Kapur, 2002) and it also affects monoamine transporters (Nishimura, 1999). The complex neurochemical profile of ketamine reflect its actions as a dissociative anaesthetic, psychostimulant and analgesic.

9. Overall, recent studies suggest that ketamine leads to a state of increased glutamatergic transmission, which is linked to psychotic disturbances (Kraguljac, 2013; Sos, 2013). Ketamine also enhances the descending inhibiting serotoninergic pathway and may exert antidepressant effects (Mion, 2013), possibly because of the significance of glutamatergic pathways in depression. Treatment with NMDA receptor antagonists has shown the ability to encourage the formation of new synaptic connections and reverse stress-induced neural changes (Zarate, 2013). However, it has been suggested that there may be a substantial relationship between ketamine antidepressant and psychotomimetic effects. This relationship could be mediated by the initial steps of ketamine action through NMDA receptors (Sos, 2013).

10. Experimentally, ketamine may promote neuronal apoptotic lesions but, in usual clinical practice, it does not induce neurotoxicity. The consequences of high doses, repeatedly administered, are not known. Cognitive disturbances are frequent in chronic users of ketamine, as well as frontal white matter abnormalities (Mion, 2013).

11. Contributing to ketamine's analgesic action is the inhibition of nitric oxide synthase resulting in a decrease in nitric oxide production (Aroni, 2009). Ketamine also binds to opioid receptors but the binding affinity is too low to contribute to analgesic effects (Rowland, 2005) although there are suggestions that the binding to sigma opioid receptors may also play a role in its antidepressant activity (Robson, 2012).

12. Other actions, probably contributing to analgesic activity include blockade of voltage-sensitive calcium channels, sodium channel depression and inhibition of monoamine reuptake (Quibell, 2011; Meller, 1996). Ketamine also possesses anticholinergic activity (antagonist activity at muscarinic acetylcholine receptors) which may also contribute to its psychotomimetic properties (Dunieu, 1995).

Related substances

13. Phencyclidine (PCP) was the first in this series of arylcycloalkylamines to be synthesised. It was marketed in the 1950s and was used as an analgesic/anaesthetic in various surgical procedures but soon fell into disfavour because of its tendency to produce marked and unpleasant behavioural side effects including agitation, delusions and hallucinations. At the time these effects were attributed to its anticholinergic activity and to its structural resemblance to psychotomimetic glycollates and benzilates (Brimblecombe 1975; Neubauer, 1996). There were also suggestions that the effects produced were very similar to symptoms of chronic schizophrenia

(Cohen, 1962). Later, as knowledge of brain neurotransmitters increased, it became apparent that, as for ketamine, the primary pharmacological action of phencyclidine is to act as an NMDA antagonist.

14. Illicit use of phencyclidine began to be reported in the mid-1960s in the USA and has persisted there and in other parts of the world peaking in the late 1970s. During this time many analogues of phencyclidine were synthesised (Roth, 2013) and some appeared as street drugs. The limited information available would indicate that overall their pharmacological profiles are similar to those described for ketamine and phencyclidine. This is certainly the case for methoxetamine and for the 3- and 4-methoxy analogues of phencyclidine which have been shown to bind with high affinity to the PCP-site on the NMDA receptor (Roth, 2013).

Toxicology

15. There have been numerous animal studies that have further elucidated the mechanisms of toxicity of ketamine; these are beyond the scope of this report. An overview of these studies can be found in this book chapter: Li Q, Chan WM, Rudd JA, Wang CM, Lam PYH, Mun Wai MS, Wood DM, Dargan PI, Yew DT. Ketamine. In: Novel Psychoactive Substances: Classification, Pharmacology and Toxicology. Ed: Dargan PI, Wood DM. Academic Press 2013, ISBN: 978-0124158160.

Current control of ketamine and its analogues

16. In 1979 phencyclidine (PCP, sometimes referred to as 'angel dust') was added to Class A of the UK Misuse of Drugs Act 1971 following outbreaks of abuse, primarily in the USA. It was made a Schedule II material under the Misuse of Drugs Regulations, because at that time it was thought that there may be some medical applications. Although it is not currently in use as a pharmaceutical, it remains in Schedule II.

17. In 1984 three other psychoactive arylcyclohexylamines related to PCP (eticyclidine, rolicyclidine and tenocyclidine) were added to Class A of the Misuse of Drugs Act 1971 as named compounds following reports of misuse, again primarily in the USA. All three were added to Schedule I of the Misuse of Drugs Regulations.

18. In January 2006 ketamine was added to Class C of the Misuse of Drugs Act as a named compound following increased evidence of abuse in the UK. It was placed in Schedule IV (part 1) of the Misuse of Drugs Regulations.

19. In February 2013 a clause containing two generic definitions was added to both the Misuse of Drugs Act and the Misuse of Drugs Regulations to control two groups of arylcyclohexylamines. These generic controls covered a further range of materials related to PCP as well as methoxetamine and a range of methoxetamine-related materials. Methoxetamine and other psychoactive derivatives of ketamine and PCP were beginning to be offered for sale on 'legal high' websites. The generic controls were constructed so as to limit their scope to materials which were known, or expected, to produce psychoactive effects. All materials covered by these controls were added to Class B of the Misuse of Drugs Act 1971 and to Schedule I of the Misuse of Dugs Regulations.

20. These 2013 generic controls excluded a number of materials through the wording '…any compound (not being ketamine, tiletamine or a compound for the time being specified in paragraph 1(a) of Part 1 of the Schedule)'; the wording of the exclusion clause within the Regulations is slightly different, but the effect is the same. This meant that ketamine remained in Class C, Schedule IV (Part 1), while tiletamine, a pharmaceutical with very little evidence of abuse, was specifically excluded from control and those materials falling within the scope of the new generics, but already listed by name, remained within Class A (eticyclidine, PCP, rolicyclidine and tenocyclidine) and Schedule I or II. There are no known new structural analogues of ketamine that are available in the UK that are not covered by this 2013 Generic.

21. Thus, different arylcyclohexylamines are currently controlled within Classes A, B and C and in Schedules I, II and IV (Part I).

CLINICAL AND VETERINARY USE OF KETAMINE

22. Ketamine has been used therapeutically as a pharmaceutical agent in a number of areas of both human and veterinary medicine for over 50 years, in particular as an analgesic and anaesthetic. Studies are underway exploring the use of ketamine for treatment-resistant depression, for the treatment of addiction and it is also being explored experimentally as a pharmacological model of psychosis.

Ketamine use as an analgesic and in palliative care

23. Ketamine is a dissociative anaesthetic with strong analgesic properties. Its analgesic effect is likely to be due to its NMDA receptor blocking activity, and in particular, effects at the calcium channel at the NMDA receptor (Hewitt 2000; Visser 2006). It is used clinically in sub-anaesthetic doses (typically < 100-200 mg/day) for treating neuropathic, inflammatory or ischaemic pain. In higher doses approaching anaesthetic doses, it may be useful for treating terminal uncontrolled overwhelming pain and procedure-related pain unresponsive to standard treatments. Although these uses of ketamine are outside the terms of the UK marketing authorisation for the proprietary product, it may be used in these clinical situations when judged by the prescriber to be in the best interest of the patient on the basis of best available evidence. Ketamine use is generally only initiated by specialists in pain or palliative care (Visser, 2006, Palliative Care Guideline).

24. Ketamine is available in the UK as a racemic mixture in vials for parenteral use containing 200 mg, 500 mg or 1 g of ketamine solution. As noted below, initial doses of ketamine are generally much lower than this and so there can be substantial wastage of unused ketamine from these preparations. An oral solution can be obtained as a special order from Martindale or prepared by a local pharmacy from the parenteral preparation.

25. Ketamine is generally administered orally (PO), by intravenous injection (IV) or by subcutaneous injection (SC)/continuous subcutaneous infusion (CSCI); it can also be administered by intramuscular injection (IM), sublingually (SL), intranasally (IN) and per-rectum (PR) (Visser, 2006, Palliative Care Guideline).

26. Ketamine is used in a wide range of doses, depending on the indication (Visser, 2006, Palliative Care Guideline). For analgesia initial oral doses are generally 2-25 mg three to four times a day, increased to 40-60 mg four times a day. Intravenous doses for analgesia are typically 2.5-5 mg as required and 0.5-1 mg/kg to cover procedures associated with severe pain, or where conscious sedation is required. Subcutaneous doses are typically 2.5-25 mg, with continuous subcutaneous injection (CSCI) generally given at a dose of 50-100 mg/24hours, increased gradually if required to 600 mg/24 hours. The upper limits of these doses are similar to the doses reported to be used in a typical session by those who misuse ketamine (in one study 31% of users report using less than 0.125 g; 35% between 0.25 g and 0.5 g; 34% more than 1 g; and 5% more than 3 g per typical session (Winstock, 2012).

Cancer pain and use of ketamine in palliative care

27. Ketamine is used in sub-anaesthetic doses, often as 'burst' subcutaneous, continuous subcutaneous infusion or intravenous therapy prior to conversion to oral therapy in opioid-tolerant cancer pain (Visser, 2006); early clinical audit data suggested that this was effective (Jackson, K., 2001). Since then a number of studies have been published – a 2012 Cochrane Review of the use of ketamine in cancer pain found seven randomised controlled trials (RCTs) and 32 case reports/series (Bell, 2012). Only two RCTs were of sufficient quality to be included; these suggested that ketamine as an adjuvant to morphine improves the effectiveness of morphine in the treatment of cancer pain. Hallucinations were common in the ketamine groups (40% in one study). The overall conclusion of this Cochrane Review was that there is insufficient evidence to assess the benefits and harms of ketamine as an adjuvant to opioids for the management of cancer pain.

28. Amongst the 32 case reports/series in the Cochrane Review of ketamine use in cancer pain, the majority (28/32, 88%) described improved pain control with ketamine (Bell, 2012). In general, adverse effects were not reported as severe and in only two reports ketamine was withdrawn because of significant 'adverse cognitive effects'. Commonly reported adverse effects were sedation and hallucinations.

29. A randomised controlled trial of subcutaneous ketamine for cancer pain published more recently showed that there was no difference in pain control with ketamine use; however, adverse effects were significantly more common in the ketamine group (Hardy, 2012).

Chronic non-cancer pain

30. A review of controlled studies investigating use of ketamine in chronic non-cancer pain identified 29 controlled trials with a total of 579 patients (Bell, 2009). The conclusion of this systematic review was that ketamine can provide short-term relief of refractory neuropathic pain in some patients but that adverse psychotomimetic and urological effects limit its use in many patients and therefore long-term use of ketamine for chronic non-cancer pain should only occur in the context of a controlled trial with a focus on optimal dose, route of administration, and duration of treatment.

Acute post-operative pain

31. A Cochrane Review undertaken in 2005 and updated in 2010 evaluated the literature on the effectiveness and tolerability of ketamine for the management of acute post-operative pain in adults (Bell, 2010). Thirty-seven randomised controlled trials were identified including a total of 2,240 patients. Twenty-seven of these 37 studies showed that ketamine given in the peri-operative period reduced requirements for rescue analgesia, morphine requirements in those also treated with morphine and decreased post-operative nausea and vomiting. In this setting, low dose short-term use of ketamine is well tolerated with no potential for urological effects; adverse effects reported include hallucinations in 7.4%, 'pleasant dreams' in 18.3% and nightmares in 4% (Bell, 2010; Elia, 2005).

Ketamine for procedures

32. Ketamine can be used as an analgesic and/or sedative for painful procedures e.g. dressing changes in burns patients or those with severe pressure ulcers, or to allow patients to be positioned for epidural or other procedures. There is a high incidence of dysphoric effects at high doses (e.g. 0.5 mg/kg IV, 1.5 mg/kg IM) used in this setting.

33. Ketamine is particularly used in paediatric burns patients in combination with midazolam for 'conscious sedation'; a recent observational study has shown that it is generally effective and well-tolerated in paediatric burns patients (O'Hara, 2013). Ketamine (1 mg/kg intravenously) is recommended by the College of Emergency Medicine for analgesic sedation for children who need a painful or frightening procedure as part of their emergency care (CEM).

Adverse effects of ketamine as an analgesic

34. Dysphoric effects and hallucinations are reported quite commonly, particularly at higher doses (Mercadante, 2000; Visser, 2006; Palliative Care Guideline). They are likely to be more common in anxious patients. Benzodiazepines (midazolam 2.5 mg subcutaneously or diazepam 5 mg orally) or haloperidol (0.5-2.5 mg orally or subcutaneously) may be required and are generally effective (Visser, 2006; Palliative Care Guideline). Some consider using haloperidol prophylactically to prevent ketamine-related dysphoric effects and hallucinations (Palliative Care Guideline). Patients may also experience vivid dreams and nightmares. A history of psychosis is generally considered a contraindication to the use of ketamine (Palliative Care Guideline).

35. There are five reports of significant bladder effects related to therapeutic use of ketamine as an analgesic for individuals with chronic pain at doses of 240 mg-1 g/day in adults and 8 mg/kg/day in a child (Storr, 2009; Gregoire, 2008; Shahzad, K., 2012). In the most recent report, a 52-year-old male who had been using oral ketamine at a dose of 240 mg/day for three years for chronic back pain developed severe bladder damage that did not settle when the ketamine was stopped; the patient required a cystectomy for management of his severe bladder damage (Shahzad, 2012).

36. In a 2013 survey of UK palliative care specialist doctors and nurses, 16% (54/340) reported seeing unexplained urinary tract symptoms (not related to urinary tract infection) in patients receiving ketamine and 9% (29/312) reported seeing unexplained liver function tests and/or abdominal pain in patients receiving ketamine. In a previous survey conducted in 2011 by the same group, 16 of 164 (9%) reported seeing unexplained urinary tract symptoms in patients receiving ketamine and these occurred at total daily doses of ketamine $\leq$ 500 mg in 13 cases and > 500 mg in three cases. (Personal communication Dr Andrew Wilcock, Nottingham University Hospital NHS Trust)

37. There are also reports of abnormal liver function tests associated with therapeutic use of ketamine (Dundee, 1980; Noppers, 2011). In one series, 14/34 patients anaesthetised with ketamine had abnormal liver function tests (Dundee, 1980); the other report described three patients receiving ketamine by intermitted intravenous infusion who developed abnormal liver function related to ketamine which settled within two months of stopping ketamine (Noppers, 2011).

Anaesthetic use of ketamine

38. This section focuses on ketamine use as an anaesthetic both in military and civilian medical practice. It is most commonly used in the pre-hospital setting and within emergency medicine and major trauma.

History

39. The first descriptions of the medical use of ketamine as an anaesthetic were in the British military in 1971 (Barry, 1971). Further articles describing the use of ketamine paralleled operational deployments made by British military units. Ketamine has also been used in major civilian incidents, including the response to the 2005 London Underground bombings.

Clinical issues

40. Ketamine is an intravenous anaesthetic agent that has significant analgesic properties in sub-anaesthetic doses. It produces a 'dissociative anaesthesia' – profound analgesia with a light sleep. The typical anaesthetic dose is 1-2 mg/kg intravenously (duration of action ~ 5-10 minutes) or 10 mg/kg intramuscularly (duration of action ~ 20-30 minutes) (Electronic Medicines Compendium).

41. Ketamine is a stable preparation requiring no special storage conditions and with a shelf life of up to five years. It is available in various concentrations from 10 mg/ml to 100 mg/ml.

42. In military practice, ketamine is currently used throughout the entire military chain of evacuation, from the point of wounding, through the field hospital and on to the receiving hospital in the UK. In addition to its use as an anaesthetic for emergencies such as field amputation, it has been very useful for treating pain that responds poorly to opiates, such as pain associated with nerve injury. All doctors joining the Army are given a full day of training that focuses on the treatment of pain (Davey, 2012) and on anaesthesia; ketamine use is one of the sections covered on this course.

43. In civilian practice ketamine is most commonly used as an anaesthetic in the pre-hospital setting. In the Emergency Department ketamine is particularly used for paediatric sedation for children requiring sedation for painful or frightening procedures (CEM); less commonly it is used in adult patients in the Emergency Department for 'dissociative sedation' (RCA/CEM). In addition to its use as an anaesthetic in the pre-hospital environment, ketamine may also be used as an analgesic, for example in major trauma (Jennings, 2011).

44. Ketamine increases blood pressure (Tweed, 1972) and is therefore often considered the anaesthetic of choice in trauma patients with haemodynamic compromise (Morris, C., 2009; Jensen, 2010). Previously ketamine was contraindicated in traumatic brain injury because of concerns that it increased intracranial pressure (Prabu, 2004); however, more recent studies have shown no evidence to suggest that ketamine use is associated with harm in patients with traumatic brain injury (Hughes, 2011). Ketamine use is associated with a lower risk of respiratory depression and relatively preserved airway reflexes compared to other anaesthetic agents; however, it is still important that facilities for airway support are available when ketamine is used at anaesthetic doses (RCA/CEM; Jensen, 2010).

45. In the UK, ketamine use can only be initiated by authorised prescribers. Whist it may be administered by paramedics, a prescriber must authorise its use. In an emergency situation a doctor can request ketamine to take with them for use in the pre-hospital situation as they are allowed to possess controlled drugs. Specific disaster procedures are in place to allow supply of ketamine for major trauma incidents. Within the military ketamine is only handled by registered physicians; it is not carried by nurses or combat medical technicians.

Concerns and adverse effects

46. Emergence phenomena (e.g. disorientation, hallucinations) are common and can be reduced with concomitant opioid or benzodiazepine use. In the military setting these emergence phenomena can cause challenging behaviour and this is always taken into account when using it – ensuring weapons are made safe and casualties closely monitored.

47. Urological problems are not a problem with single-dose use of ketamine for anaesthesia.

Ketamine and depression

48. Major depression remains a leading cause of disability in the world, affecting an estimated 350 million people worldwide, with 1 in 20 people reported to have had an episode of depression in the previous year (WHO). Up to one-third of those with depression are resistant to drug and other therapies (Rush, 2006; Shelton, 2010). There is therefore a need for new strategies for managing depression and new antidepressant treatments.

49. Several studies have now shown that a single, sub-anaesthetic dose of ketamine can produce clinical improvement within hours in treatment-resistant unipolar depressed patients (Berman, 2000; Zarate, 2006) including those with electroconvulsive-therapy-(ECT)-resistant depression (Ibrahim, 2011; Aan het Rot, 2012). Furthermore, three studies with individuals with treatment-resistant bipolar depression have also shown some effectiveness (Diazgranados, 2010; Ibrahim, 2011; Zarate, 2013). However, it is notable that all of these studies have been in patients with severe, treatment-resistant depression and describe the use of ketamine by the intravenous route.

50. Not all treatment-resistant depressed patients respond to ketamine and in those that do, the length of the antidepressant effect following one or two doses is variable and only lasts hours to days (Krystal, 2013). There are limited data on the longer-term antidepressant effect of ketamine.

51. Studies to date have administered one or two doses of ketamine over time. Some (e.g. Oxford group presentation to the ACMD by Rupert McShane) are exploring whether 'top-up' dosing might prolong the antidepressant effect. The effects of multiple dosing should be monitored if repeated dosing is to be a strategy in the treatment of depression. Further research is clearly needed to determine the optimum treatment strategy and ketamine is currently only used within research studies for patients with severe treatment-resistant depression and not as a 'mainstream' antidepressant.

52. At present most research has used intermittent or single-dose intravenous dosing of ketamine making it less likely to be applicable to the management of most patients with depression. However, there is an on-going clinical trial of intranasal ketamine (Clinicaltrials.gov: NCT01304147). It is important to note that some studies have suggested that ketamine misuse may be associated with an increased risk of depression and so it is important that this is addressed in any future studies investigating longer-term ketamine use for the management of depression.

53. Ketamine has recently been shown to be associated with a decrease in suicidal ideation (Machado-Vieira, 2012). Because ketamine has analgesic properties, it has been used to treat depression in the context of chronic pain in patients with cancer (Thangathurai, 2010; Zanicotti, 2012).

Ketamine and addiction

54. A series of studies in Russia by Krupitsky provide some preliminary evidence that psychotherapy combined with three doses of ketamine in recently detoxified alcoholics may reduce 12-month relapse rates in alcohol dependence from 76% to 34%. Three isolated doses (1.5-2.0 mg/kg bolus IM) of ketamine were given alongside sessions of psychotherapy before and after the administration of the drug to 111 recently detoxified alcohol-dependent patients. In a control group of 100 similar recently detoxified alcohol-dependent patients, 24% were abstinent after one year compared with 66% of those who had undergone ketamine therapy. The same group have also researched heroin dependence treatment and suggest some efficacy of single doses of ketamine alongside psychological treatment (Krupitsky, 2007).

55. More research is needed in this area. The studies of treatment-resistant depressed patients noted above suggest added efficacy for those with comorbid alcohol dependence or a family history of alcoholism. Ketamine appears more effective in individuals with a family history of alcoholism (Phelps, 2009; Luckenbaugh, 2012). A study of depressed patients who had comorbid alcohol dependence showed that another NMDA receptor antagonist (memantine) had efficacy (Muhonen, 2008).

Ketamine as a pharmacological agent for modelling psychosis

56. In healthy individuals, a single sub-anaesthetic dose of ketamine produces a transient psychosis-like experience. In those with schizophrenia, a single dose will produce symptoms that closely imitate that individual's own symptoms in the acute phase of the illness (Lahti, 2001). These observations have led to the ketamine model of psychosis and the search for glutamatergic treatments of the psychosis/schizophrenia.

57. Some research is now giving single doses of ketamine to healthy volunteers to provoke psychotomimetic symptoms resembling schizophrenia and then administering newer anti-psychotic medications to test their potential efficacy. These studies have the potential to test new anti-psychotic therapies in a more productive and reliable way than rat models of psychosis (Doyle, 2013; De Simoni, 2013).

Ketamine use in veterinary medicine

58. At the time of writing there are four authorised veterinary medicinal products (VMPs) containing ketamine; these are all solutions for injection. One is authorised in the UK as well as 12 other European Member States (mutually recognised authorisation), and the remaining three hold UK national authorisations (VMD, 2013).

59. These products can either be used as a sole agent in cats and non-human primates for restraint/minor surgical procedures, or they may be used in combination with other VMPs for induction of anaesthesia in cats, dogs, horses, donkeys, cattle, pigs and non-human primates.

60. Ketamine is the VMP most commonly used for induction of anaesthesia in horses both in the field and in hospital/clinic-based veterinary practice. It is administered by intravenous (IV) injection only, at a dose rate of 2.2 mg/kg bodyweight following IV detomidine, romifidine or xylazine (VMD, 2013; Mason, 2004). It is estimated that 90% or more equine anaesthetics rely on ketamine.

61. A benefit of ketamine use in horses is that cardiovascular parameters are well maintained; however, this may be somewhat blunted by administration of other VMPs. The recovery from ketamine-based anaesthesia is considered to be good and superior to recovery from inhalational anaesthetics (Hall, 2003; Mason, 2004; Taylor, 1982).

62. In farm animal practice (food-producing species), ketamine is authorised for administration to cattle, at an IV dose of 2-5 mg/kg bodyweight following IV/intramuscular (IM) xylazine. In pigs, an IM dose of 15-20 mg/kg bodyweight is administered, in combination with IM azaperone (VMD product information database 2013). Use of ketamine in cattle and pigs as would be expected is significantly less common than in horses.

63. A benefit of ketamine use with farm animals is that procedures are often being conducted 'in the field' with limited monitoring equipment available. The properties of ketamine make it advantageous to other VMPs in these circumstances.

64. In dogs, ketamine is authorised for use at an IM dose of 5-7.5 mg/kg bodyweight following IM medetomidine ± IM butorphanol or 10-15 mg/kg bodyweight following IM xylazine (VMD product information database 2013).

65. In cats, ketamine is authorised for administration IM as a sole agent at a dose of 11 mg/kg bodyweight for minor restraint, or 22-33 mg/kg bodyweight for minor surgery (pre-medication with acepromazine may be used) or when more restraint is required. When used in combination with other VMPs in cats, the recommended IM dose reduces to 2.5-7.5 mg/kg bodyweight administered following IM medetomidine ± IM butorphanol, and reduces further with IV administration to 1.25-2.5 mg/kg bodyweight. Alternatively, an IM/subcutaneous (SC) dose of 10-22 mg/kg bodyweight may be administered following IM/SC xylazine (VMD, 2013). Use of ketamine in cats is more common than in dogs, cattle and pigs but much less than in horses.

66. Other injectable anaesthetic agents (e.g. propofol, alfaxan) are authorised as VMPs and commonly used in dogs and cats. While these agents may offer advantages over ketamine in some situations, there are cases where ketamine cannot easily be substituted, e.g. cats in respiratory distress that require imaging procedures and cannot remain still or animals that are too small for endotracheal intubation. In these cases ketamine is beneficial because even though it may produce mild, dose-dependent respiratory depression, laryngeal and pharyngeal reflexes are reasonably well maintained.

67. In addition to the above, the Veterinary Medicines Regulations make provision for veterinary surgeons to use their clinical judgement to use authorised medicines in a manner beyond the scope of the authorisation, when there is no suitable VMP. This is termed 'cascade use' and allows other legitimate uses of ketamine, outside the scope of what is specified with the authorised product (VMD veterinary medicines guidance note 13 2013) – for example, use in another target species such as in rabbits, hamsters, goats or wildlife where almost all cases are anaesthetised using ketamine.

68. As a prescription only medication, ketamine is only ever authorised for administration by a veterinary surgeon or under the direct supervision of a veterinary surgeon (e.g. administration by a veterinary nurse or 'darts man' using a dart gun for wildlife). The pattern of use is almost exclusively a 'one-off' administration. There is no known indication at present for chronic use of ketamine in veterinary practice.

69. Increased sensitivity, especially to acoustic stimuli in the recovery period after ketamine use, is noted in veterinary practice. The dissociative nature of the agent does mean that when used for a shorter duration (as seen with smaller animals requiring minor procedures), recovery must be in a non-stimulatory environment for the animal and veterinary staff's safety, to avoid injury to either the animal or veterinary staff.

KETAMINE MISUSE – PREVALENCE, PATTERNS AND FEATURES OF USE

Data sources

70. This section describes available data on ketamine misuse prevalence from the UK. The Crime Survey for England and Wales (CSEW, formerly British Crime Survey (BCS)) includes ketamine and is the most reliable general population estimate of drug use because of its high quality methodology and sampling procedure (ketamine is included in the Scottish Crime and Justice Survey but not in the Northern Irish Drug Use Prevalence). However, one notable criticism of the CSEW (along with other household surveys) is that it is likely to underestimate use in sub-populations such as young people, students, and those in the criminal justice estate. Hence general population figures should be considered alongside data from specific target groups. However, targeted surveys that have been conducted in the UK have typically used convenience sampling (i.e. non-probabilistic or non-random designs), meaning that data obtained from these types of survey cannot be generalised to the wider population, do not allow insight into time trends, and are only valid for the population studied (i.e. the data cannot be generalised to the general population). The *Smoking, drinking and drug use among young people* survey reports robust generalisable estimates for 11- to 15-year-olds in England.

General population surveys

Crime Survey for England and Wales (all data and figures from 2011/12 and 2012/13 sweep) (Home Office 2012 and Home Office 2013)

71. The graphs below (Figures 2–4) show ketamine prevalence in adults (16–59) and young people (16–24) recorded by the BCS/CSEW since 2006/07. There was a statistically significant fall in last month prevalence in adults only from 2010/11 to 2011/12 and in last year prevalence in adults and young people from 2011/12 to 2012/13. In terms of the demographic profile of the average ketamine user, the CSEW indicates that ketamine users are more likely to be male than female, single, most likely to come from the 20–24 age group, unemployed or a student and Chinese or mixed race (Home Office, 2013).

72. Analysis of simultaneous polysubstance use patterns indicates that, along with ecstasy and amphetamines, ketamine is amongst the drugs most likely to be taken simultaneously with other drugs, with nearly half of ketamine users reporting simultaneous polydrug use the last time that they took ketamine. Although base numbers were small (n=50), for 48% of ketamine users their most recent ketamine-use episode included use of another drug (40% drugs other than cannabis, 8% cannabis only). Seventy-four per cent of the most recent episodes mentioned alcohol, and 77% of episodes included alcohol and other substances (Home Office, 2012).

73. In terms of past year polysubstance use (not necessarily simultaneous), the BCS for 2009/10 (Hoare, 2010) provides data on past year ketamine users' use of other illicit drugs in the past year. Past year ketamine users are more likely than users of any other illicit drugs to have used other illicit drugs in the past year. Only 3% of past year ketamine users report that they did not take any other illicit drugs in the past year. For the other 97% of past year ketamine users, the drugs they were most likely to have taken in the past year were cannabis (86%), followed by ecstasy (85%), and powder cocaine (77%). Therefore, when looking at past year use, as well as when looking at most recent use, national surveys suggest that ketamine use is more likely than many other illicit drugs to be associated with the use of other drugs.
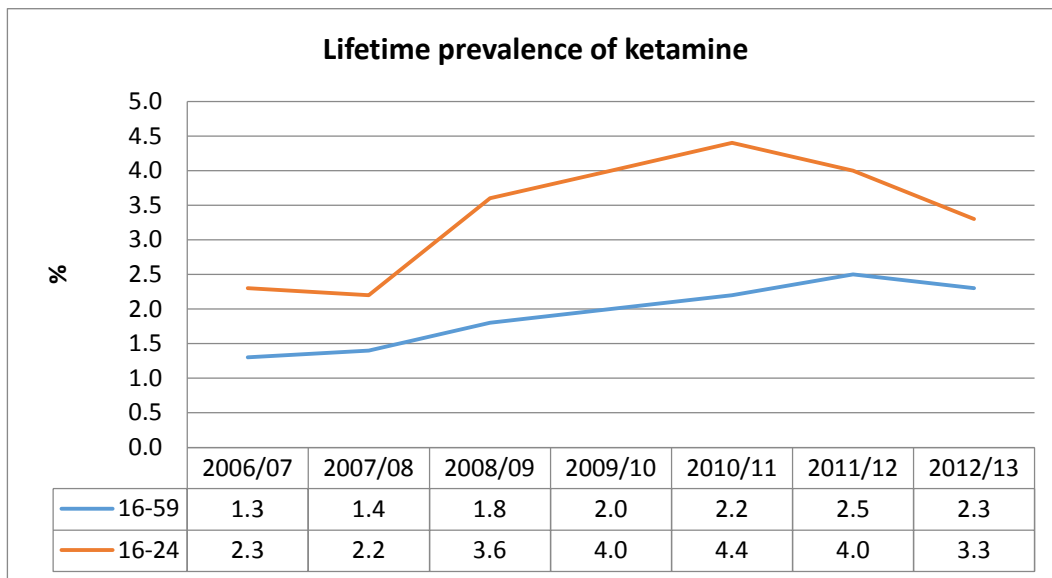
Figure 2 Lifetime prevalence of ketamine use in England and Wales (Crime Survey for England and Wales 2012/13)
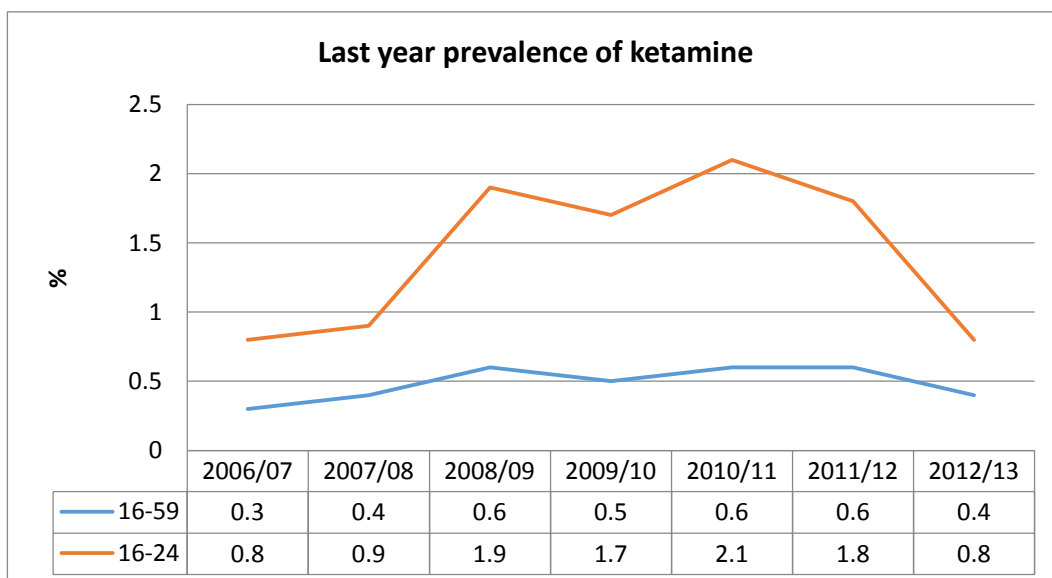

Figure 3 Last year prevalence of ketamine use in England and Wales (Crime Survey for England and Wales 2012/13)
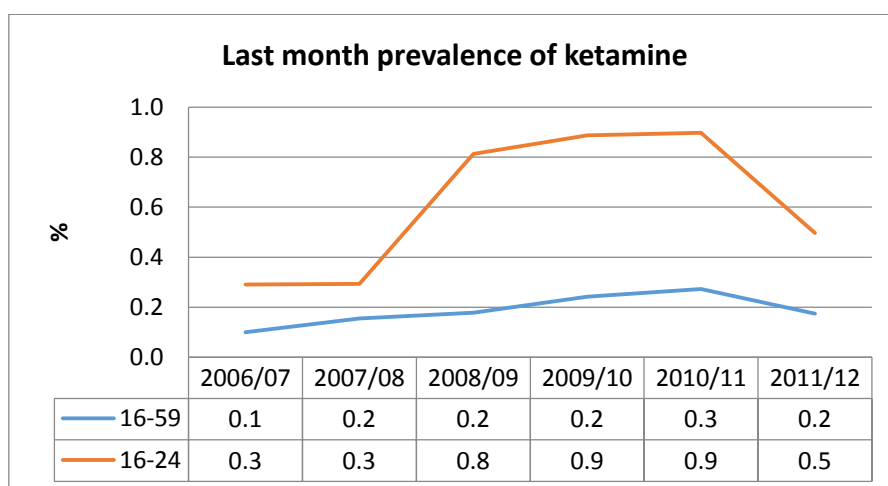

Figure 4 Last month prevalence of ketamine use in England and Wales (Crime Survey for England and Wales 2011/12)

	Lifetime ketamine use	Last year ketamine use	Last month ketamine use
Adults (16–59y)	738,000 (661,000–816,000)	120,000 (89,000–152,000)	57,000 (37,000–76,000)
Young people (16–24y)	218,000 (165,000–271,000)	54,000 (27,000–81,000)	33,000 (15,000–51,000)

Table 1 Estimates of the absolute numbers of people using ketamine in lifetime and last year (2012/13) and last month (2010/11) (Crime Survey for England and Wales)

Scottish Crime and Justice Survey

74. In 2012, lifetime ketamine use was reported by 1.2% of the adult (aged 16 and over) population, 0.3% in the previous year, and 0.1% in the previous month (Scottish Government Social Research, 2012).

School surveys

England

75. The *Smoking, drinking and drug use* among young people survey, conducted with English school children aged 11–15, included ketamine in its most recent sweep (2011)). Thirty-five per cent of children reported having heard of ketamine (31% in 2005) and 0.5% reported using it in the previous year. Use has remained relatively stable since 2005 (Figure 5). Use increased with age; 0.3% in 13-year-olds to 1.1% in 15-year-olds. The median age of initiation was 15 (3% of all 11- to 15-year-olds).

76. Two per cent of all children aged 11–15 reported being offered ketamine in 2010; this has remained stable since 2005. Six per cent of male 15-year-olds and 5% of females reported having been offered ketamine in 2010.

Last year prevalence of ketamine

	2005	2006	2007	2008	2009	2010	2011
All	0.4	0.5	0.4	0.7	0.6	0.5	0.5
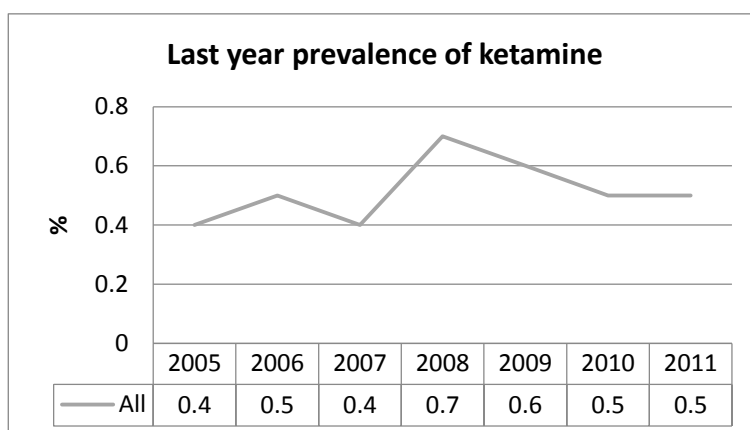
Figure 5 Last year prevalence of ketamine use in 11- to 15-year-olds in England (The Smoking, drinking and drug use among young people survey)

Scotland

77. The Scottish Schools Adolescent Lifestyle and Substance Use Survey (SALSUS) reported on ketamine use in 13- and 15-year-olds for the first time in 2010 (Scottish Government, 2011). Two per cent of 15-year-old and 1% of 13-year-old boys, and 1% of 15-year-old and 0% of 13-year-old girls reported use of ketamine in their lifetime. One per cent of both 13- and 15-year-old boys, and 0% of 13- and 15-year-old girls reported use of ketamine in the previous year. One per cent of both 13- and 15-year-old boys, and 0% of both 13- and 15-year-old girls reported use of ketamine in the previous month. Three per cent of 15-year-old boys and 1% of girls reported being offered ketamine. In 13-year-olds the respective proportions were 1%.

ESPAD

78. The 2011 pan-EU substance use survey ESPAD (www.espad.org) conducted every four years (including the UK) in 15/16-year-olds does not include ketamine.

Data from studies using convenience samples

Stonewall survey of men's health

79. The 2011 Stonewall health survey (n=6,861; aged 16–85) estimated that 8% of gay or bisexual men (living in England, Scotland, or Wales) reported use of ketamine in the previous year (Guasp, 2011).

Mixmag/Global Drugs Survey

80. One of the largest sub-population drug use surveys is the annual Mixmag/Global Drugs Survey (http://globaldrugsurvey.com/); this survey has previously targeted those who are frequent attenders of nightclubs or dance venues, but more recently has also included others through recruitment in the popular press. In the 2013 survey (data collected 2012-13) 50.6% of UK respondents (n= 7,700) reported lifetime use of ketamine, and 31.5% in the previous month. Ninety-six per cent reported that they usually ingested the drug by insufflation, and 42% reported that they usually drank alcohol during the same use episode (not clearly defined). Price paid was £20/gram, with 16% reporting having purchased ketamine over the Internet.

81. Data from 2012 indicated that 47.8% of UK respondents self-reported lifetime use, 24.5% in the previous 12 months, and 19.8% in the previous month. Forty per cent of respondents who self-identified as regular clubbers reported use in the previous month. However, as samples are independent and not drawn from a sampling frame, it is important not to infer trends in prevalence.

Ketamine use by nightclub customers

82. National surveys such as the British Crime Survey and more recently the Crime Survey for England and Wales indicate that there is an association between ketamine use and frequency of attendance at nightclubs and pubs. For example, last year use of ketamine was over 20 times higher among those who had visited a nightclub four or more times in the past month (6.6%) compared with those who had not visited a nightclub in the past month (0.3%) (Home Office, 2012). Last year use of ketamine was around 15 times higher among those who had visited a pub nine or more times in the past month (3%) compared with those who had not visited a nightclub in the past month (0.2%).

83. Ketamine use varies considerably between and within different dance clubs, dance 'scenes' and regions, however. A series of convenience sample surveys of drinking and drug use by over 650 bar and club customers conducted in the Manchester night-time economy in the 2000s found that self-reported ketamine use was higher in the 'gay friendly' night-time economy and in dance clubs playing hard dance, funky house and trance music, and lowest in 'straight' bars and in dance clubs playing drum and bass (Measham, 2009).

84. An ongoing study of South London gay clubbers (2010 to date) has collected data from the same gay dance clubs in July of each year. Surveys were conducted in July 2010 (Measham, 2011a), July 2011 (Wood, 2012) and July 2012 (Wood, 2013) with convenience samples of 308, 315 and 330 attendees respectively. Self-reported ketamine use was very high amongst gay clubbers compared to the general young adult population and very similar between the 2010, 2011 and 2012 data collection periods: 57%, 60% and 67.1% reported lifetime use in 2010, 2011 and 2012 respectively; 46%, 49% and 43.6% reported past year use in 2010, 2011 and 2012 respectively; 30%, 35% and 24.4% reported past month use in 2010, 2011 and 2012. Fourteen per cent and 13% reported having taken and/or intending to take ketamine on the fieldwork night in 2010 and 2011 respectively.

85. A further distinction exists regarding at what point and where in the clubbing 'night out' ketamine consumption occurs. A qualitative study of ketamine users in Manchester concluded that ketamine use was more popular both at nightclub 'after parties' and at 'chill out' house parties that were seen as subject to less scrutiny and allowed users to have a greater control over the context to their consumption (Moore, 2008). Furthermore, some users actively sought out the more introspective or 'semi-social' rather than sociable aspects of the ketamine experience after an evening out socialising.

86. Despite the much higher prevalence of ketamine use amongst clubbers than non-clubbers, the social acceptability of ketamine consumption varies considerably between and within music cultures and social 'scenes'. For example, a qualitative study of ketamine users in south west England noted that its use was more popular amongst groups following 'alternative' lifestyles, such as 'free party' ravers, travellers and squatters (Riley., 2008). Furthermore, for both users and non-users that they interviewed, ketamine use was seen as potentially socially divisive even within a cultural or social group because of the dissociative and anaesthetic

effects leading to a perceived vulnerability or loss of control that might obligate others to intervene and 'babysit' them.

87. The type of nightlife patron also seems important in determining ketamine prevalence (Measham, 2009). When Measham and colleagues (Measham, 2011b) investigated ketamine use in more 'mainstream' UK nightlife – participants were surveyed on main thoroughfares in Lancashire town/city centres in the UK in autumn 2010 – they found self-reported ketamine lifetime use of 16%, 9% in past year, 5% in past month and 1% taken and/or planning to take on the fieldwork night. A similar study conducted in mainstream nightclubs in the same Lancashire towns/city centres just over a year later in spring 2012 found similar levels of ketamine use, with self-reported lifetime ketamine use of 18%, past year use of 11%, past month use of 3%, and 0% reporting use (already taken and/or planned) on the fieldwork night (Measham, 2012).

Dose and frequency of ketamine use by nightclub customers

88. In a follow-up survey to the 2009 Mixmag survey, 1,285 individuals with ketamine use in the previous year were asked about the typical amounts of ketamine used per session and the maximum number of days of consecutive use (Winstock, 2012). Thirty-one per cent reported using less than 0.125 g; 35% between 0.25 g and 0.5 g; 34% more than 1 g; and 5% more than 3 g per typical session. The mean number of maximum number of consecutive days of use was 3.5, with 11% reporting ever using ketamine on seven or more days consecutively. Seventy per cent used ketamine 1–4 days per month 16% 5–8 days per month and 13% used nine or more days per month.

Diversion

Human medicine

89. In December 2005 a change to the Misuse of Drugs Act 1971 made Ketamine a Class C controlled substance and placed it in Schedule IV part 1 of the Misuse of Drugs Regulations 2001. Specific controlled drug prescription requirements and safe custody requirements do not apply to this schedule. However, many hospital pharmacy services treat ketamine as a higher schedule drug, in particular instituting safe custody and register requirements. It is reported that this works well, is not too onerous and does not impact negatively on ketamine use in hospitals.

90. There is no recording at a national level of diversion of ketamine from legitimate use in human medicine. However, there are well-documented cases during the last five years from a number of hospitals and veterinary practices of diversion of ketamine; these are currently only collected at a local level and not collated nationally.

91. The Health Act 2006 and The Controlled Drugs (Supervision of Management and Use) Regulations 2006 that were introduced following the Shipman Enquiry brought in additional governance arrangements and sharing of information between health and social care professionals in local intelligence networks. Information about diversion of ketamine could, and has been, shared through these networks. The concerns reported in the early days were mainly from veterinary practice. Through improved governance, greater awareness and sharing of information there are now fewer reported concerns.

92. Ketamine is currently supplied in multi-dose vials but usually only a single dose is used, this results in a significant amount of waste of ketamine and the potential for diversion of this unused drug portion.

93. There are anecdotal reports from clinicians working in drug dependence clinics of patients reporting that they have sourced ketamine from the human and veterinary medicine supply chain.

Veterinary medicine

94. The veterinary medicines supply chain involves three parties: from manufacturers to registered wholesale dealers and finally veterinary practices, which are mainly clinical practices but may also be academic and commercial research laboratories. Medicines would not be imported directly by veterinary practices. Inspections of each party are carried out every 3–4 years by the MHRA or VMD and the Home Office in the case of research establishments.

95. Royal College of Veterinary Surgeons Best Practice guidelines state that ketamine should be treated as a Schedule II drug under the Misuse of Drugs Regulations 2001, although these guidelines are not currently enforceable because ketamine is in Schedule IV part 1 of the Misuse of Drugs Regulations 2001.

96. The VMD issues non-mandatory guidance on the handling of veterinary medicines based on the Veterinary Medicines Regulations set out in the EU Directive 2001/82/EC, as amended. However, controlled drugs must be handled in accordance with Home Office regulations. With regards to ketamine, the guidance recommends it be stored in a secure, locked cabinet and its use recorded in a register. Products on the market for veterinary medicines have a shelf-life of 2–3 years and 28 days once the packaging is opened. Due to the well-known potential for ketamine misuse, the guidance recommends witnessed destruction of unused or out-of-date ketamine is good practice e.g. placing an injectable solution in sawdust or cat litter, or by using a denaturing kit. All of the veterinary ketamine medicines are prescription only and some guidance is also given on prescribing.

97. A report run by the Inspection and Investigation Team at the VMD for the period January 2013 to May 2013, identified that 316 veterinary practices have been inspected and at 85 of those premises, a minor 'deficiency' was cited against 'Ketamine register'. This has been interpreted to mean that either an informal register was not being kept or that the register was not clearly auditable or that the locked cabinet was not secure. However, not all inspectors report a lack of an informal register as a deficiency as this is currently not required for Schedule IV drugs. The VMD inspectors also report that a greater proportion of deficiencies are found within equine veterinary practice (either exclusive equine practice or mixed practice), or when the medicine is stored in multiple locations (e.g. may be kept in a veterinary surgeon's car with ambulatory practice, as well as being stored in the practice). Although it is necessary for the medicine to be transported to various sites in these practices, this can affect the audit trail without a register being kept.

98. When veterinary ketamine medicines are used in food-producing species, there is a legal requirement to maintain records and traceability from manufacturer to the animal receiving the medication. Legal action can be taken in cases of non-compliance.

Illegal supply

99. There is relatively little information available on the routes of supply of illegal ketamine. On the basis of the available data, the primary source country for ketamine importations to the UK is India, with most importations being made by fast parcel post and airfreight. Seizures mostly range between 1–5 kg and are commonly discovered in food stuffs and beauty preparations (SOCA ketamine report). It is not clear based on currently available data what the source of these ketamine importations are within India.

100. In February 2011, India added ketamine to the list of psychotropic substances controlled under its Narcotic Drugs and Psychotropic Substances Act 1985. This had the effect of significantly increasing the penalties associated with attempts to illegally transport ketamine out of India.

101. There are challenges in identifying ketamine seized at the UK border and estimating the scale of its supply to the UK. Until the diversification of the UK drug market with the emergence of new psychoactive substances (NPS), established drugs such as cocaine, heroin and ketamine could be reliably identified using immunoassays and colormetric tests. Now that the UK drug market is more diverse, including new variations of established drugs, these testing methods are a less reliable way of identifying ketamine. Providing alternative technology to accurately field test for ketamine at the UK border would improve intelligence on the scale of ketamine supply to the UK.

MEDICAL HARMS

Acute physical harms and treatment

Background

102. Similar to most other recreational drugs, there is no single source providing data on the acute toxicity associated with the use of ketamine. Therefore, it is necessary to combine data from a number of sources to build a picture of the acute toxicity associated with the use of ketamine (Wood, 2012). These sources include:

- user reports from surveys and Internet discussion forums;
- poisons information services;
- case reports and case series; and
- data from Emergency Departments.

103. Most of the data on the acute toxicity of ketamine has been published since the ACMD 2004 review of ketamine.

User self-reports and surveys

104. The largest published user survey was a cross-sectional survey of 100 ketamine users undertaken in Sydney, Australia between January 1998 and October 1999 (Dillon P, 2003). The mean age of starting ketamine use was 25.8 ± 4.8 years; 58% had used more than ten times and 35% had used more than 20 times.

105. Overall, 35% identified that 'health risks' were an issue related to the use of ketamine. Using pre-defined physical and psychological effects, individuals were asked whether they had experienced these effects and whether they were positive or negative effects. Increased heart rate (17% individuals), temporary paralysis (16%), lack of co-ordination (14%), blurred vision (21%) and feeling no pain (7%) were generally considered to be positive effects. 'Increased breathing' (11% individuals), difficulty breathing (2%), nausea (9%), vomiting (3%) and convulsions (<1%) were always considered to be 'negative effects'.

106. Psychological effects that users associated with the desired effects of ketamine (separation from the environment, separation from the body, auditory and visual hallucinations, 'unusual thought content', euphoria, enhanced colour vision, absence of time and novel body sensations) were generally classified as 'positive effects'; only 20% reported that these effects were unwanted and severe. Although 38% reported that they had had to "deal with someone else who had suffered badly after ketamine use". The risk of developing a 'K-hole' was reported to be greater with increased use of ketamine, particularly in those who had used ketamine more than 20 times.

Poisons Centre Data

107. The clinical effects of acute ketamine toxicity are usually short-lived. In a prospective observational study of 20 calls to the Connecticut Poisons Control Centre, 50% of patients were asymptomatic by the time they were evaluated in the Emergency Department (ED). Those that had ongoing symptoms at the time of ED presentation complained of anxiety (40%), palpitations (15%), chest pain (10%), confusion (5%), vomiting (5%) and memory loss (5%). Physical examination findings were tachycardia (60%), altered mental status (30%), slurred speech (15%), hallucinations (15%), nystagmus (15%), mydriasis (15%) and hypertension (10%). Eighteen patients were discharged directly from the ED after an observation period of <5 hours (Weiner, J., 2000).

108. The UK National Poisons Information Service (NPIS) reported that ketamine was the sixth and tenth most common recreational drug in terms of TOXBASE accesses and telephone calls to NPIS in the 2011/12 financial year (see Figure 6). For both TOXBASE accesses and telephone calls to NPIS, there was an increase in the percentage of overall activity related to ketamine from 2004, peaking in 2010/11 for TOXBASE accesses and 2009/10 for telephone calls to NPIS. No data were available on the clinical effects of acute ketamine toxicity reported to NPIS (NPIS, 2011/12).
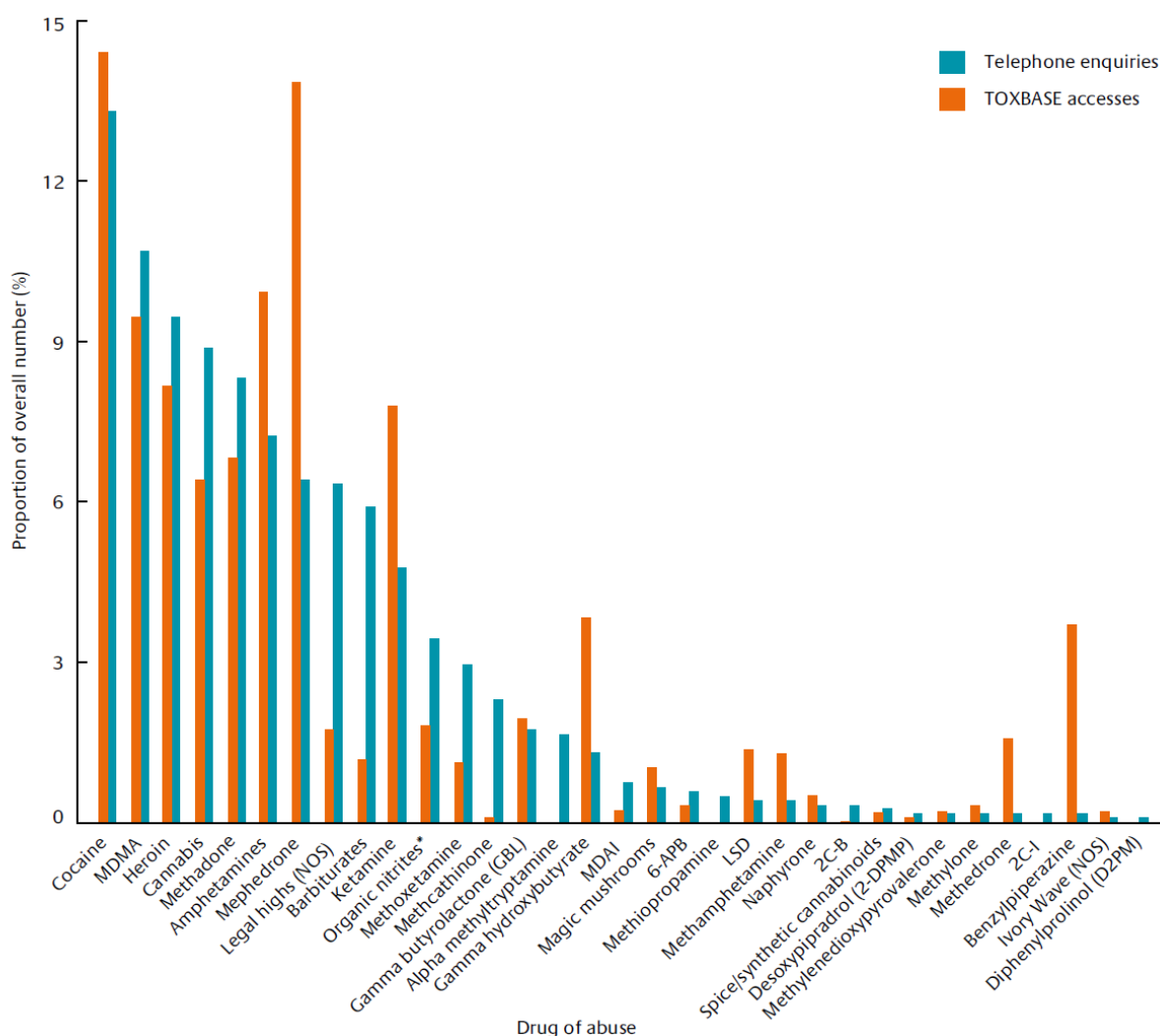
Figure 6 – Telephone enquiries to the UK National Poisons Information Service (NPIS) and TOXBASE Accesses 2011/12 concerning recreational drugs (Graph from the 2011/12 NPIS Annual Report)

Emergency Department Data

109. Data on presentations to a large South London Emergency Department demonstrated increasing presentations associated with acute ketamine use from 58 in 2006 to 81 in 2010 (Wood, 2013).

110. In a case series of 116 presentations associated with ketamine use to the same South London Emergency Department in 2006 (n=58) and 2007 (n=58), only 13 (11.2%) related to lone ketamine use. Other co-used substances included ethanol (38.8%), GHB/GBL (47.3%), cocaine (19.0%) and MDMA (52.6%). Thirty-eight point eight per cent had hypertension (systolic BP >140 mmHg) and 29.3% had tachycardia (heart rate ≥100 bpm); these may in part be due to co-used drugs. There was no difference in the frequency of agitation/aggression between all patients (25.0%) and those with lone ketamine use (23.1%). Overall length of hospital stay was short (mean length of stay of 11.2 hours (range 0.3 -– 61.5 hours). No lone ketamine patients were admitted to critical care (Wood, 2008).

111. Data from the US Drug Abuse Warning Network (DAWN) in 2010 showed that although the number of Emergency Department presentations relating to the use of ketamine were much lower than other drugs such as cocaine, between 2005 to 2010 there was a three-fold increase in ketamine presentations (2005 ketamine 303 -vs- cocaine 483,865; 2010 ketamine 915 -vs- cocaine 488,101) (DAWN).

112. The largest ED case series with acute ketamine toxicity is a series of 233 presentations between July 2005 and June 2008 from Hong Kong. Unlike the data in the UK series, most reported using lone ketamine (co-used substances included alcohol (24, 10%), MDMA (15, 6%), methamphetamine (14, 6%), benzodiazepines (10, 4%),

cocaine (9, 4%) and zopiclone (9, 4%)). Toxicological screening was undertaken in 126 (56%) and in 72% of these cases ketamine was the only substance detected (Ng, 2010).

113. Symptoms reported included impaired consciousness (106, 45%), dizziness (28, 12%), agitation/irritability (10, 4%), hallucinations (10, 4%), muscle cramp (4, 2%), seizures (2, 1%), chest pain/discomfort (13, 6%), palpitations (12, 5%), abdominal pain (49, 21%), nausea and/or vomiting (23, 10%), dysuria (20, 9%), urinary frequency/urgency (8, 3%), dyspnoea (17, 7%). Six (3%) individuals presented with physical injury following the use of ketamine. Clinical features on examination included tachycardia (HR >100 bpm) in 91 (39%), hypertension (not defined) in 93 (40%), hyperthermia (not defined) in 32 (14%) and abdominal tenderness in 41 (18%).

114. Similar to other reports, the majority (72%) were managed and discharged directly from the ED. There were no deaths related to the use of ketamine; five patients were admitted to the intensive care unit, but from the information provided it is likely that the reason for admission related to co-used substances.

115. There are several reports of pulmonary oedema related to both medical and recreational use of ketamine, although this has not been reported in the large ED case series; it is unclear what the mechanism is for this, but animal models suggest ketamine increases alveolar fluid uptake (Tarnow, 1978; Pandey, 2000).

Acute harms treatment

116. Generally individuals presenting with acute ketamine toxicity do not need pharmacological therapy and reassurance and observation is all that is required. In individuals with troublesome hallucinations or agitation a single dose of a benzodiazepine e.g. oral diazepam may be required.

Chronic physical effects, harms and treatment

Ketamine and chronic urological and renal effects of ketamine

117. Ketamine has only relatively recently been recognised as a cause of significant effects within the bladder, urinary tract and kidneys. Isolated case reports documenting bladder symptoms and a form of 'cystitis' associated with prolonged recreational usage of ketamine began to appear in 2006-2007 mainly from Hong Kong, Canada and the United Kingdom (Shahani, 2007; Chu, 2007; Chu, 2008; Cottrell, 2008; Cottrell, 2008; Selby, 2008).

Ketamine and the bladder

118. The symptoms associated with ketamine-related bladder damage typically include pain on passing urine, frequency and urgency of voiding, blood and matter (e.g. bladder tissue) in the urine, and incontinence (Chu, 2008; Cottrell, 2008). These symptoms can be severe and disabling. The urine is usually sterile, in other words there is no evidence of infection (Chu, 2007; Chu, 2008].

119. There have been no studies investigating the incidence of ketamine-related bladder damage in the UK. However, a number of studies have investigated how common bladder symptoms are amongst recreational and/or dependent ketamine users.

  - In a follow-up interview study to the 2010 Mixmag survey, 1,285 individuals who had self-reported use of ketamine in the last year were asked about lower urinary tract symptoms (Winstock, 2012). In this group 26.5% (340) reported at least one urinary tract symptom (pain in lower abdomen 11.3% (145), burning or stinging when passing urine 8.1% (104), needing to pass urine more frequently 17.4% (224), incontinence 3.3% (43) or blood in the urine 1.5% (19)).

  - Another study looked at urinary tract symptoms in 30 frequent (> four times per week), 30 infrequent (two times per month to four times per week) and 30 ex-ketamine users (Muetzelfeldt, 2008). Twenty per cent of frequent users, 6.7% of infrequent users and 13.3% of ex-users reported 'cystitis or bladder problems'.

  - Finally, in a questionnaire study of 48 ketamine users in Bristol, 26 (54%) of whom were daily users, 36 (75%) reported urological symptoms (Weinstock, 2013).

120. The severity of urological symptoms and the degree of bladder damage appear to be in direct proportion to the amount of ketamine used, the frequency of usage and the length of use. In the Mixmag 2010 follow up study, higher doses (1 g ketamine or more during a typical session) were associated with higher rates of all urological symptoms (Winstock, 2012). In the Bristol study, all eight (100%) individuals using more than 5 g of ketamine daily reported urological symptoms, whereas urological symptoms were only present in ten (50%) of those reporting use of 0-2 g of ketamine daily (Weinstock, 2013).

121. However, some taking lower doses or even therapeutic doses can develop urological symptoms. There are five reports of significant bladder effects related to therapeutic use of ketamine as an analgesic for individuals with chronic pain at doses of 240 mg-1 g/day in adults and 8 mg/kg/day in a child (Storr, 2009; Gregoire, 2008; Shahzad, 2012). In the most recent report, a 52-year-old male who had been using oral ketamine at a dose of 240 mg/day for three years for chronic back pain developed severe bladder damage that did not settle when the ketamine was stopped; the patient required a cystectomy for management of his severe bladder damage (Shahzad, 2012).

122. The changes that occur in the bladder are a direct result of ketamine and its metabolites being excreted via the kidneys into the urine and coming into direct and prolonged contact with the bladder lining (Cottrell, 2008). This initially results in inflammation and ulceration of the bladder lining, which can result in bleeding into the bladder. Prolonged exposure can result in damage to nerve endings, resulting in persistent bladder pain and fibrosis (scarring) of the bladder. Ultimately, the bladder becomes severely scarred and will shrink; at this stage the damage may be irreversible (Tsai, 2009; Cottrell, 2008). Individuals with this severe bladder damage need to pass urine frequently, often having to void every 15-30 minutes, and experience severe bladder pain and blood in the urine (Tsai, 2009; Cottrell, 2008).

123. Cystoscopy findings in those with ketamine-related bladder problems include inflammation and ulceration of the bladder wall, haemorrhage and infiltration of the bladder wall with inflammatory cells. In more advanced cases, significant scarring and shrinkage of the bladder wall will be seen (Tsai, 2009; Cottrell, 2008; Chu, 2008).

124. Removing the insult to the bladder by cessation of ketamine gives the best chance of symptomatic relief and improvement in bladder pathological changes. The bladder in many cases will heal and although some symptoms may persist, these generally become more manageable (Tsai, 2009). In the 2010 Mixmag survey, 108 (51%) of 251 individuals who stopped ketamine reported that their urological symptoms improved. However, a proportion of users, despite stopping the drug, will have persistent symptoms (Personal Communication Prof David Gillatt).

125. One major problem is control of the bladder pain whilst healing occurs; some users may take higher doses of ketamine in an attempt to control this pain further increasing the risk of ketamine-related bladder damage. An appropriate analgesic regime, generally including opiates, is often necessary to treat bladder pain in these individuals (Wood, 2011; Weinstock, 2013).

126. If cessation of ketamine is not possible, and in those with severe symptoms, a variety of methods of symptom control may be used including anticholinergic drugs to reduce frequency/urgency, amitriptyline as an anticholinergic, and sedatives and analgesics (Weinstock, 2013). Bladder protective agents such as hyaluronic acid may help in some cases, although the data to confirm this are limited (Kalsi, 2011). Bladder distension under anaesthetic may play a role although this generally only gives a temporary relief of symptoms.

127. Severe frequency/urgency, persistent bladder pain and incontinence may all be indications for surgical intervention in association with reduced bladder capacity. This usually involves major surgery including removal of all or part of the bladder and replacement with an intestinal segment (Chung, 2013). As those affected may be in their twenties this is a drastic step with potential long-term sequelae including renal problems, continence issues and cancer.

Upper urinary tract and kidney damage

128. The lining of the renal pelvis in the kidneys and the ureters (the drainage system of the kidneys), is the same as that of the urinary bladder. They are therefore exposed to the same potential damage by being bathed in urine containing ketamine and its metabolites.

129. Transit of urine through the upper tracts is, however, more rapid than the bladder which acts as a storage vessel. Therefore damage in the upper tract is less frequently seen. However, scarring and narrowing of the ureters is well documented in frequent, high-dose ketamine users and can be seen at its early stages radiologically in a large percentage of those with ketamine-related bladder damage (Mason, 2010). In one series of 59 individuals with ketamine-related bladder problems, 51% had hydronephrosis (abnormal swelling of the kidneys); this was bilateral in 44% and unilateral in 7%; 13% also had papillary necrosis (Chu, 2008). Hydronephrosis can also occur as the result of smooth muscle relaxation (Lo, 2011).

130. Ultimately, if obstruction is prolonged and not relieved the end result may be renal failure. Ketamine users with bladder symptoms should therefore have imaging of their upper urinary tract and measurement of renal function. Those with obstruction, with or without symptoms, require surgical or radiological intervention to drain the kidneys and correct the blockage if this does not resolve.

Other chronic effects of ketamine use

131. Up to one-third of long-term ketamine users experience chronic, severe abdominal ('tummy') pain; this is often referred to by users as 'K cramps' [Muetzelfeldt, 2008; Erowid Ketamine]. There are internet discussion forum reports of users taking higher doses of ketamine to control this pain [Erowid Ketamine] In a series of 233 Emergency Department presentations with acute ketamine toxicity, 49 (21%) had abdominal pain (Ng, 2010).

132. It is not clear what the cause of this abdominal pain is. In one series of 37 ketamine users, abdominal pain was associated with Helicobacter pylori negative gastritis (Poon, 2010). However, as discussed below, there is the potential that in some individuals this pain may relate to ketamine effects on the liver and/or gallbladder.

133. There have been a number of reports of abnormal liver function associated with ketamine use. In an Emergency Department series of 233 acute ketamine toxicity presentations in Hong Kong, 35 (15%) had abnormal liver function (Poon, 2010). In some of the reports of ketamine-related liver effects, dilatation of the common bile duct (similar in appearance to choledochal cysts) was found on ultrasound and/or CT imaging of the liver (Poon, 2010; Ng, 2009; Wong, 2009). There are no data to be able to determine whether, like the urological effects of ketamine, these effects may be dose-related. It appears that generally the common bile duct dilatation and liver function tests improve with ketamine cessation (Poon, 2010; Ng, 2009; Wong, 2009).

134. There are also reports of abnormal liver function tests associated with therapeutic use of ketamine (Dundee, 1980; Noppers ,2011). In one series, 14/34 patients anaesthetised with ketamine had abnormal liver function tests (Dundee, 1980); the other report described three patients receiving ketamine by intermitted intravenous infusion who developed abnormal liver function related to ketamine which settled within two months of stopping ketamine (Noppers, 2011).

135. The cause of these ketamine-related liver effects is poorly understood. Data from an in vitro study in human hepatoma G2 cells have suggested that S(+) ketamine is directly hepatotoxic (Lee, 2009). However, the finding of common bile duct dilatation suggests a mixed aetiology with an obstructive component.

Fatalities

Office for National Statistics (ONS) Drug-Related Deaths Data

136. The number of deaths in which ketamine has been mentioned on the death certificate in England and Wales, split by year of death registration, is shown in Figure 7. It is not possible from these data to determine whether ketamine was responsible for the death(s). It is also important to note that there is variation between coroners regarding drug testing in deaths.
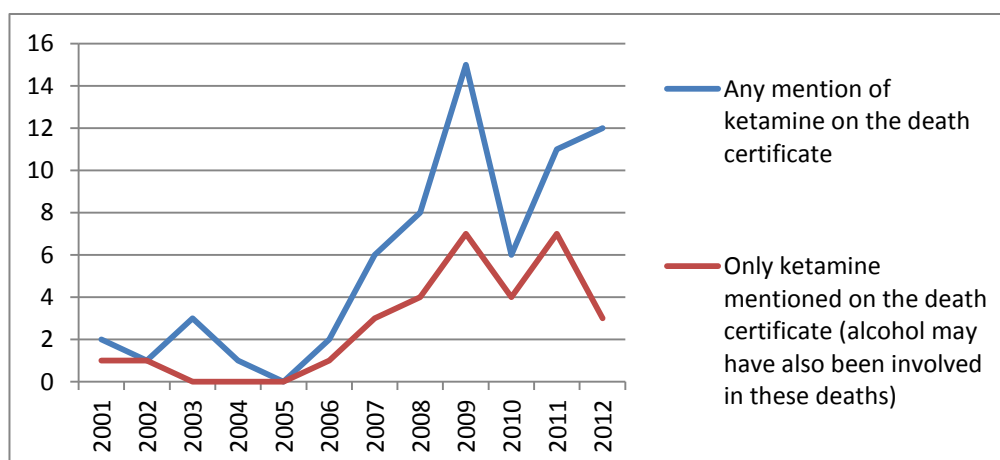

Figure 7 Number of deaths per year in England and Wales in which ketamine has been mentioned on the death certificate (Office for National Statistics)

137. The majority of these deaths have been in individuals aged less than 30 years – Table 2 below gives a breakdown of the deaths in which ketamine was mentioned on the death certificate by age at the time of death.

Age group	2007	2008	2009	2010	2011	2012
All ages	6	8	15	6	11	12
Under 30	3	6	9	5	8	6
30-39	1	1	4	1	1	4
40–49	0	0	2	0	2	2
50 and over	2	1	0	0	0	0

Table 2 Number of deaths where ketamine was mentioned on the death certificate (England and Wales), by age group (Office for National Statistics)

National Programme on Substance Abuse Deaths (np-SAD)

138. The National Programme on Substance Abuse Deaths (np-SAD) receives information on a voluntary basis from UK coroners relating to inquests involving drug-related deaths (Ghodse, 2013). The np-SAD database was examined to April 2013 to identify deaths involving ketamine. Cases where ketamine was present at post mortem but had been administered by health professionals for medical purposes were excluded.

139. The first death in which ketamine was implicated was in 1997. From then until 2005 there were fewer than five deaths per year where ketamine was either found in post-mortem toxicology samples and/or implicated in death. The number of these cases increased until 2009, peaking at 26 and 21 respectively; there was then a decline with the number of cases falling to nine and six in 2012.

140. Of the 93 deaths in the np-SAD database, 86% are male and mean age at death was 30.9 (range 15.8 – 60.6) years. The majority were employed (60%), had a history of previous drug use (75%) and lived with others (54%). Drowning occurred in nine instances and there were three road traffic accidents where use of ketamine may have impaired judgement.

141. Although in most cases ketamine was detected together with alcohol and/or other drugs (70/93), there are 23 cases where ketamine was the sole substance implicated in the cause of death.

142. The principal (n=70, 75%) underlying cause of death was accidental poisoning not solely relating to ketamine. In the remaining 23 cases it is not possible to be certain whether ketamine was the cause of death.

Acute psychological effects, harms and treatment

Acute psychological effects of ketamine

143. 'Emergence phenomena' associated with ketamine include delusions, hallucinations, delirium and confusion, and sometimes 'out-of-body' and 'near-death' experiences. These phenomena led to ketamine being withdrawn from mainstream anaesthetic use with humans. 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 (Siegel, 1978) but use remained rare in Europe until the 1990s when it appeared on the 'rave' and nightclub scene, initially as an adulterant in ecstasy tablets (Dalgarno, 1996).

144. 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' (Muetzelfeldt, 2008).

145. 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. This is a desired effect for some users, but for others it can be an unpleasant and frightening experience.

146. Acute pleasure associated with taking the drug may underpin the reinforcing properties of many recreational drugs (e.g. Robinson, 1993). Acutely, ketamine increases extracellular dopamine (DA) concentrations in the rat

striatum and prefrontal cortex (Moghaddam, 1997) and nucleus accumbens (Makulewicz, 2010); some PET studies in humans have shown that it elicits striatal DA release (Breier, 1997; Smith, 1998; Vollenweider, 1997).

147. Ketamine also interacts with μ-opioid receptors and non-opioid σ-receptor sites (Kapur, 2002), 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 (Jansen, 2001). S+ ketamine has a much greater affinity for the NMDA-receptor, and R-ketamine has a greater opioid action.

148. Acute reinforcing effects in animals and humans: Preclinical findings suggest clear similarities between ketamine and other addictive drugs in a wide range of behavioural paradigms. Rats will self-administer ketamine (Marquis, 1989; Winger, 2002), show conditioned place preference (Suzuki, 2000) and locomotor sensitisation following repeated doses has been observed (Meyer, 2007; Trujillo, 2008; Wiley 2008). Furthermore, ketamine substitutes for ethanol in drug discrimination paradigms in rats (Harrison, 1998; Shelton, 2004). Humans dependent on alcohol show enhanced NMDA receptor function (Krystal, 2010) and in recently detoxified alcoholics, ketamine produces ethanol-like subjective effects including a 'high' (Krystal, 1998).

149. Studies with healthy volunteers have found that intravenous (IV) ketamine increases subjective ratings of 'high' (Krystal, 1999) and this relates to its abuse potential. In one study, sub-anaesthetic doses (0.4 mg/kg and 0.8 mg/kg] or placebo were given IV to healthy, ketamine-naive volunteers (Morgan, 2004a). 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.

150. Despite anecdotal reports of a high risk of accidental injury whilst acutely intoxicated with ketamine, largely due to the dissociation and analgesia (e.g. Lilly, 1978; Moore, 1978), there are sparse scientific data on this risk. Because ketamine is a powerful analgesic, the intoxicated user is more vulnerable to injury. One case study reported a hospital worker who had injected ketamine collapsing with their face on an electric fire and suffering third-degree burns (Jansen, 2001). In a study of 90 ketamine users, 13% reported being involved in an accident as a direct result of taking ketamine and 83% knew someone who had (Muetzelfeldt, 2008).

151. An important public health and safety message is therefore that those acutely intoxicated with ketamine should not be left alone because of the risk of accidents. It is also important for staff working in settings where ketamine may be used (e.g. night-time economy and festivals) to be aware of the risks and vulnerability associated with the dissociative and analgesic effects of ketamine.

Chronic psychological effects, harms and treatment

Depression

152. Increased depression (assessed with the Beck Depression Inventory) in both daily users and ex-ketamine users was found over the course of one year in a longitudinal study (Morgan, 2010) 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.

Subclinical psychotic symptoms

153. Studies with infrequent (>1 per month < 3 times per week) and daily ketamine users assessing sub-clinical psychotic symptomatology have found that scores on measures of delusions, dissociation and schizotypy are higher in daily ketamine users compared to infrequent and in infrequent users compared to poly-drug controls who do not use ketamine (Curran, 2000; Morgan, 2010).

154. Morgan *et al*. (Morgan 2012) 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 (Narendran, 2005) and despite anecdotes (e.g. Jansen, 2001; Lilly, 1978) there is little evidence of any link between chronic, heavy ketamine use and diagnosis of a psychotic disorder. Nevertheless, John Krystal at Yale has reported that he feels that there are numerous cases of ketamine-induced psychosis in psychiatric hospitals in Hong Kong (personal communication).

Cognitive impairment

155. 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 the principal action of ketamine is at the NMDA receptor, the consequences of ketamine use on cognition have been widely investigated. In humans, a single dose of ketamine induces marked, dose-dependent impairment in working and episodic memory which would impact profoundly on users' ability to function (Morgan, 2006; Fletcher, 2006). In mice, impaired fear memory (decreasing fear in a fear conditioning paradigm) has been found after four but not two weeks of daily injection of 5 mg/kg ketamine (Amann, 2009).

156. Several studies have examined cognitive function in infrequent and frequent ketamine users (e.g. Curran, 2000; Curran, 2001; Morgan, 2009; 2004b; 2006a; 2006b; Narendran, 2005). Overall, recreational ketamine use does not appear to be associated with long-term cognitive impairment. However, the most robust findings are that frequent, dependent ketamine users exhibit profound impairments in both short- and long-term memory (for review see Morgan and Curran 2006). It is not known currently whether these changes are reversible if users cease ketamine use.

157. Many studies have been cross-sectional and cannot address causation. However, in a longitudinal study, frequent ketamine use caused impairment in visual recognition and spatial working memory that correlated with changes in level of ketamine use over 12 months (Morgan, 2010). Other impairments in planning and frontal function have been observed but appear to be unrelated to measures of ketamine use (Morgan, 2009).

Neurological changes

158. Increased D1 receptor binding in the right dorsolateral prefrontal cortex of ketamine users has been reported, indicating upregulation of dopaminergic receptors (Narendran, 2005).

159. White matter abnormalities have been observed in dependent ketamine users compared to controls (Liao, 2010). Reduced fractional anisotropy correlated with the degree of ketamine use in the bilateral frontal and left temporoparietal regions. There were also small changes in the temporal region that may relate to the drug's impairment of episodic memory. Similar changes have been observed in other drug-dependent populations (Nestler, 2005) suggesting that these may not be specific effects of ketamine. However, more recent studies comparing 16 ketamine users with16 poly-drug-using controls found white matter abnormalities in the right hemisphere in ketamine users compared with controls (Edward Roberts, 2013).

Educational and professional achievement

160. Dependent ketamine users in the UK are often part of sub-cultures, such as the traveller and free party scenes that may have limited interest in participating in mainstream society (Newcombe, 2008; Riley, 2008). 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.

161. An interview study of 100 recreational users found that 20% perceived employment-related problems to result from their ketamine use (Dillon, 2003). Morgan *et al*. (2010) found that frequent/daily users had spent significantly fewer years in education than infrequent or non-users.

Dependence and treatment

Dependence

162. There are some case reports of ketamine dependence in the literature (e.g. Hurt, 1994; Jansen, 1990; Moore, 1999; Pal, 2002), and reports from surveys of ketamine users (Muetzelfeldt, 2008; Winstock, 2012). However, there have been no large-scale studies, and so the incidence of ketamine dependence is unknown.

163. 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 dependence (Muetzelfeldt, 2008). 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. Other reported features of dependence include salience of use and continued use despite harmful consequences (Muetzelfeldt, 2008).

164. In a follow-up survey to the 2009 Mixmag survey, 1,285 individuals with ketamine use in the previous year were assessed for dependence using DSM-IV criteria that were operationalised to give a proxy measure for dependence (Winstock, 2012). Based on these criteria, 17% (218) were considered as dependent on ketamine.

165. The need for increasing doses is one index of a substance's dependence forming potential. Studies with rats (Cumming, 1976) and monkeys (Bree, 1967) as well as children undergoing anaesthesia (e.g. Byer, 1981) have convincingly demonstrated the rapid development of tolerance with repeated ketamine dosing. This may be due to induction of liver enzymes (Livingston Waterman, 1978). It is also possible that that it reflects neuronal adaptations in receptor numbers or receptor sensitivity.

166. Tolerance is associated with frequent use with significant and rapid increases in dose reported in some studies. Frequent ketamine users report escalating doses over time, with one study finding a 600% increase from first use to current use (Morgan, 2008). Objective data from hair analyses showed a doubling of ketamine concentrations in hair over a year in infrequent ketamine users (Morgan, 2010). Frequent ketamine users' hair did not change, but they were probably already using maximal amounts.

167. Craving seems to be a key problem in frequent users: 28 of the 30 daily users in a study by Morgan *et al*. (2008) 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 characterised by anxiety, shaking, sweating and palpitations when they stopped using.

168. A few published case studies also show craving and somatic and psychological aspects of anxiety as withdrawal symptoms (Blatchut, 2009; Critchlow, 2006; Lim, 2003).

169. There is currently little evidence about physiological withdrawal from ketamine users (Morgan, 2011). However, a psychological withdrawal syndrome including anxiety, drug craving, tremulousness and palpitations have been described (Critchlow, 2006; Morgan, 2008; Blachut, 2009).

170. Critchlow (2006) provided a detailed description of ketamine discontinuation in a single patient as follows:
    - 1–4 hours after cessation: craving and drug hunting;
    - 4–8 hours after cessation: anxiety, shaking, sweating, palpitations, low mood, great effort required to resist craving; these symptoms were decreased by alcohol consumption;
    - 24–48 hours after cessation: tiredness, low appetite and low mood; at this point the patient would 'take to bed for 24 hours and wake feeling recovered'.

171. A small number of cases report more severe symptoms on ketamine cessation including nightmares and psychosis which were relieved by further ketamine use (Lim, 2003).

Treatment of dependence

172. UK drug services are describing modest increases in requests for treatment of ketamine-related problems. Ketamine presentations rose year on year between 2005-6 and 2010-11, from 114 to 845 but fell slightly in 2011-12 to 751 (National Treatment Agency for Substance Misuse 'Club drugs: emerging trends and risks', 2012).

173. A small number of specialist drug services offering specific treatment pathways for ketamine users, in areas of anticipated higher need, are reporting significant demand from a cohort of patients who are generally using most or every day in amounts of up to several grams of illicit ketamine (Personal Communication, Dr Owen Bowden Jones and Dr Luke Mitcheson).

174. There is little evidence relating to the treatment of ketamine dependence other than case reports (Critchlow, 2006).

175. In the absence of a clear evidence base, it has been suggested that accepted evidence-based psychological interventions such as relapse prevention be used as for other illicit drugs (Maxwell, 2003; Winstock, 2012) and symptomatic prescribing for discontinuation symptoms (Critchlow, 2006,; Krystal, 1998) be considered.

176. The Department of Health published UK guidelines on drug treatment (DH, 2007) which provide a comprehensive basis for the delivery of drug treatment including the delivery of psychosocial interventions in community, in-patient and residential settings. The UK guidance does incorporate summaries of, and refers to, the current relevant NICE guidance on drug misuse treatments (NICE, 2007). Of particular relevance for ketamine treatment, the current established guidance recommends the availability of a range of evidence-based psychosocial interventions.

177. There are high levels of co-morbidity of mental health problems in drug treatment populations (Weaver, 2003) and early data from small clinic samples suggest high rates of mental health co-morbidity in individuals with ketamine dependence (Personal Communication, Dr Owen Bowden Jones),

SOCIAL HARMS

Information from the police and border authorities

178. Reporting from ACPO (Association of Chief Police Officers) during 2012 showed that ketamine use had increasingly become a problem in many UK regions. In the south west of England, Neighbourhood Beat Managers noted it rising in popularity. In the south east, an increase was noted in the availability and use of ketamine and linked party drugs to the re-emergence of a 'rave' culture in the area. In London, there was an increase in ketamine use among young people; it seemed no longer confined to the niche nightclub market but was spreading into the wider drugs market.

179. During the second quarter of 2012, the number of UK police seizures of ketamine was twice that for the preceding quarter at 162.

180. The scale of ketamine supply in the UK by criminal groups is difficult to quantify. The low number of groups identified by Organised Crime Group Mapping compared to the increasing identification of ketamine use around the UK does not currently correlate. Groups supplying Class A drugs are more likely to attract a higher threat score on the data than those supplying Class C drugs such as ketamine.

181. According to the OCGM tracker, criminal groups involved in the supply of ketamine represent less than 1% of all crime groups identified.

182. The wholesale price for ketamine has increased from GBP 4,500 per kg in 2012 to GBP 5,250 in March 2013. This is a rise of GBP 750 per kg. The street price of ketamine at £10–£20 per gram is broadly similar to the street prices of amphetamine and mephedrone. Ketamine is cheaper than cocaine, which for normal street purity ranges sells for between £30 and £50 per gram. A dealer purchasing one kilogram of ketamine for approximately £5,000 should be able to double their money by selling it on for at least £10,000 (at £10 per gram). The profit margins for mephedrone are broadly similar. Profits for amphetamine are normally greater, as unlike ketamine and mephedrone, amphetamine is normally bulked with adulterants to increase the amount of powder (which lowers the purity).

Adulterants and purity of illicit ketamine

183. A small number of samples taken from UK seizures of ketamine during the first quarter of 2012 had been mixed with other substances including cocaine, mephedrone, 4-methylethcathinone (4-MEC) and a mixture of piperazines. During the second quarter of 2012, ketamine purity in 12 UK seizures of ketamine was found to be in the range of 76–100%. Analysis by the Home Office Forensic Early Warning System of ketamine samples encountered at UK Summer music festivals since 2011 showed only 17 of the 106 ketamine samples to be mixtures. The substances most frequently used in a mixture with ketamine were benzocaine and MDMA; also seen were 4-MMC (4-methylmethcathinone), paracetamol, methoxetamine, cocaine and amphetamine.

184. In the Netherlands, there have been reports of ketamine being mixed with methoxetamine. Similar findings have been noted in Spain with ketamine mixed with both mephedrone and methoxetamine. Reports from users have pointed out that the effects of taking these substances are more unpleasant than those of ketamine.

185. A small number of samples taken from seizures of ketamine during the first quarter of 2012 had been mixed with other substances including cocaine, mephedrone, 4-methylethcathinone and a mixture of piperazines (SOCA ketamine report).

Case studies

Published literature

186. An interview study of 100 recreational users found that 20% perceived employment-related problems to result from their ketamine use (Dillon, 2003). In another study, frequent/daily users of ketamine had spent significantly fewer years in education than infrequent or non-users (Morgan, 2010).

Personal communications from ex-users and families and friends affected by ketamine use

187. Ketamine users report headaches associated with frequent ketamine use. In addition, they report memory loss with consequences such as losing money, keys and forgetting their home address.

188. Families of ketamine users report negative impact on the family related to ketamine use. Examples include the breakdown of family relations because of stealing, mood swings and aggression. In some cases this has led to family break up and users seeking a home with foster care.

189. Other reports include ketamine use leading to social exclusion, with long-lasting impact on social skills and decreased participation in social activities. Others report negative financial impacts of a regular ketamine habit, for example failing to pay mortgage or rent and falling behind with or having to take time off work.

190. Some personal reports explained that the ease of purchasing ketamine was a significant factor when a user was trying to reduce ketamine use and recover.

Evidence presented by Matt Southwell to the ACMD Ketamine Working Group (05-10-2013)

191. An individual using ketamine can often look strange or 'odd' to others around them who have not taken ketamine because of the dissociative effects. When ketamine first came onto the UK market, users tended to take ketamine in groups. Since then, younger users have started taking ketamine in groups where a variety of drugs are being used and their odd appearance is more noticeable and can be viewed as sociably unacceptable.

192. The effects of ketamine can be perceived as letting the user opt out or not deal with life and often the reality is that regular ketamine users will become socially excluded.

The 'K-hole' and vulnerability in some social settings

193. At large doses, ketamine can induce dissociation (the 'K-hole'). The user experiences intense detachment that can be an unpleasant and frightening experience. The company of others (e.g. friends, staff in nightclubs/festivals) can help the user deal with this experience.

194. The dissociative effect of ketamine can also place the user in a position where they are vulnerable to robbery, assault and/or rape. Users may also be less conscious of the number of sexual partners they have, which may in turn have consequences for their sexual health.

INTERVENTIONS

Education and prevention

195. Feasible and relevant ketamine prevention goals might include prevention of onset; increased age of initiation; reduced frequency of dosing and amount used per episode; prevention of transition to injection; cessation of use. Ketamine users should be made aware of the long-term physical risks of using ketamine.

196. There are a number of websites (international, national and local) dedicated to providing information about ketamine. Some of these are moderated and reviewed (e.g. FRANK, Know the Score, DAN); others are not, and contain information from users which may not present an accurate and comprehensive picture.

197. The evidence base in drug prevention suggests that provision of drug-related information, whilst it clearly has value in sharing knowledge, does not in itself deliver significant levels of early behaviour change and might in some cases produce some negative effects (Chowdry, 2013).

198. The ACMD is not aware of any evidence-based ketamine education or prevention interventions that are currently being delivered in the UK. A number of organisations and individuals provide training to professionals on ketamine, some of which do include elements on education and prevention. There are also a number of sources of general evidence-based guidance on drug education and prevention programmes; these include: the Department for Education (DfE) funded Centre for Analysis for Youth Transitions repository of impact studies (http://www.ifs.org.uk/centres/caytRepPublications); howdrythe DfE funded Alcohol and Drug Education and Prevention Information Service (ADEPIS) http://mentor-adepis.org/; the European Commission funded Drug Prevention Quality Standards (http://www.emcdda.europa.eu/publications/manuals/prevention-standards) and in the resources offered by Dartington Social Research Unit (http://dartington.org.uk/).

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ANNEX A THE ROLE OF THE ACMD AND ITS MEMBERS

Role of the ACMD

The ACMD was established as an independent expert advisory body under the 1971 Misuse of Drugs Act and its remit is to keep under review the drug situation in the United Kingdom and to advise Government Ministers on measures to be taken for preventing the misuse of drugs or for dealing with the social problems connected with their misuse. This includes providing recommendations on the following matters if considered appropriate based on the evidence before it:

a) for restricting the availability of such drugs or supervising the arrangements for their supply;

b) for enabling persons affected by the misuse of such drugs to obtain proper advice, and for securing the provision of proper facilities and services for the treatment, rehabilitation and after-care of such persons;

c) for promoting co-operation between the various professional and community services which in the opinion of the Council have a part to play in dealing with social problems connected with the misuse of drugs;

d) for educating the public (and in particular the young) in the dangers of misusing such drugs and for giving publicity to those dangers; and

e) for promoting research into, or otherwise obtaining information about, any matter which in the opinion of the Council is of relevance for the purpose of preventing the misuse of such drugs or dealing with any social problem connected with their misuse.

ACMD members

• Ms Gillian Arr-Jones	Pharmacist
• Mr Martin Barnes	Chief Executive, DrugScope
• Mr Simon Bray	Commander, Metropolitan Police, and training and development lead
• Dr Roger Brimblecombe	Pharmacologist
• Ms Annette Dale-Perera	Strategic director, addiction and offender care, Central North West Thames NHS Foundation Trust
• Dr Paul Dargan	Consultant Physician and Clinical Toxicologist, Guys and St Thomas' NHS Foundation Trust and Reader in Toxicology, King's College London
• Professor Simon Gibbons	Professor of Medicinal Phytochemistry, UCL School of Pharmacy; Professor of Medicinal Phytochemistry and Head of the Department of Pharmaceutical and Biological Chemistry at the UCL School of Pharmacy
• Ms Sarah Graham	Director, Sarah Graham Solutions – addictions therapist
• Professor Raymond Hill	Neuropharmacologist
• Professor Leslie Iversen CBE	Retired professor of pharmacology at the University of Oxford
• Ms Kyrie James	Judge, First Tier Tribunal (Immigration and Asylum Chambers); solicitor-advocate (non-practising)
• Mr Nigel Kirby	Deputy Director, Planning and Risk, National Crime Agency
• Mr David Liddell	Director of the Scottish Drugs Forum
• Professor Fiona Measham	Professor of Criminology in the School of Applied Social Sciences at Durham University
• Mrs Jo Melling	Director, Oxfordshire Drug and Alcohol Action Team
• Mr Graham Parsons	Pharmacist
• Mr Richard Philips	Independent consultant in substance misuse
• Mr Howard Gray Roberts	Retired Deputy Chief Constable, Nottinghamshire Police
• Professor Fabrizio Schifano	Consultant psychiatrist (addictions), CRI Hertfordshire Drug and Alcohol Recovery Services
• Professor Harry Sumnall	Professor in substance use, Liverpool John Moores University
• Mr Arthur Wing	Consultant and manager (freelance and interim)

ANNEX B THE ROLE OF THE KETAMINE WORKING GROUP AND ITS MEMBERS

ACMD Ketamine Working Group members

ACMD members

- Dr Paul Dargan — Consultant Physician and Clinical Toxicologist, Guys and St Thomas' NHS Foundation Trust and Reader in Toxicology, King's College London
- Mr Nigel Kirby — Deputy Director, Planning and Risk, National Crime Agency
- Professor Fiona Measham — Professor of Criminology in the School of Applied Social Sciences at Durham University
- Professor Harry Sumnall — Professor in Substance Misuse, Liverpool John Moores University
- Ms Gillian Arr-Jones — Pharmacist
- Commander Simon Bray — Metropolitan Police, and training and development lead
- Dr Roger Brimblecombe — Pharmacologist
- Ms Annette Dale-Perera — Strategic director, addiction and offender care, Central North West Thames NHS Foundation Trust

Co-opted members

- Dr Dominic Aldington — Consultant in Pain Medicine, Royal Hampshire County Hospital
- Dr Owen Bowden Jones — Consultant Psychiatrist and Lead Clinician for Club Drug Clinic Addictions Directorate, Central and North West London NHS Foundation Trust
- Professor Valerie Curran — Professor of Psychopharmacology, University College London
- Baroness Ilora Finlay — Baroness Finlay of Llandaff, Professor of Palliative Medicine, Cardiff University School of Medicine
- Professor David Gillatt — Professor of Urology, University of Bristol
- Dr Rutendo Manyarara — Veterinary Assessor (Pharmaceuticals), Veterinary Medicines Directorate
- Dr Luke Mitcheson — Consultant Clinical Psychologist, Head of Addictions Psychology and Lead Psychologist for Lambeth Addictions, South London and Maudsley NHS Foundation Trust
- Mr Ric Treble — Scientific Advisor, LGC
- Dr Mike White — Former Forensic Intelligence Adviser
- Dr David Wood — Consultant Physician and Clinical Toxicologist, Guys and St Thomas' NHS Foundation Trust and Senior Lecturer, King's College London

Ketamine Working Group Terms of Reference

1. The Ketamine WG was established by the Advisory Council on the Misuse of Drugs 21 March 2013. The WG will be dissolved once the ACMD has provided advice to the Home Secretary on the misuse and harms of ketamine.

2. The WG's functions shall be:
   - to gather and assess evidence on the misuse and harms of ketamine; and
   - to present this to the ACMD as a report that will inform an ACMD decision on any advice to the Government regarding ketamine misuse and harms.

3. The WG is to be chaired by Dr Paul Dargan with administrative support provided by the ACMD Secretariat.

4. The membership of the WG is set out in Annex A. All ACMD members and co-opted members to the WG should be familiar with and work according to the ACMD Code of Practice.

5. Experts and stakeholders external to the ACMD will be invited to give presentations where relevant and/or submit written evidence. Much of the evidence gathering is scheduled to take place on 10th May 2013.

6. The WG has four planned meetings, including an evidence-gathering session. The WG may hold further meetings as required.

ANNEX C LIST OF CONTRIBUTORS

Individual sections of the report were drafted by Working Group members. All Working Group members had the opportunity to comment on early and final drafts of the report.

The following individuals and organisations gave oral evidence, research papers and written representations and shared information with the ACMD.

- Dr Ian Back, Consultant in Palliative Medicine, Y Bwthyn and Royal Glamorgan Hospital Cwm Taf Health Board, Wales
- Dr Rupert McShane, Consultant psychiatrist, Oxford Health NHS Foundation Trust and Honorary Senior Clinical Lecturer
- Dr Celia Morgan, Senior Lecturer at Exeter University and honorary Reader in Psychopharmacology at University College London
- Mat Southwell, Partner Coact
- Shielmor Twomey – founder, Ketamine Awareness-Caleb's Campaign 2010
- Vicky Unwin, mother of Louise Cattell, who drowned in her bath after taking ketamine; Ambassador for the Angelus Foundation and campaigner for drug education to be made part of the National Curriculum
- Dr Andrew Wilcock, Macmillan Reader in Palliative Medicine and Medical Oncology, Nottingham University Hospital NHS Trust, Nottingham
- Professor David Yew, Dr med (habil), DSc, PhD. Emeritus Professor of Anatomy and Research Professor of the Institute of Chinese Medicine, Chinese University of Hong Kong