Novel Psychoactive Treatment UK Network

NEPTUNE

Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances

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Inspiring Improvement

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Chapter 4

Ketamine and methoxetamine

Drug type: depressant/dissociative

4.1. 'Dissociative' drugs

'Dissociative' drugs can distort perceptions of sight and sound and create feelings of detachment or dissociation from the self and the environment; however, these mind-altering effects are not hallucinations. Dissociative drugs, such as ketamine and phencyclidine, were initially developed as anaesthetics for surgery, but then became used for recreational purposes.

Ketamine hydrochloride is one of the dissociative drugs most commonly used for recreational purposes in the UK. The recreational use of ketamine analogues has also been reported; these include methoxetamine ((RS)-2-(ethylamino)-2-(3-methoxyphenyl) cyclohexanone) and 3-MeO-PCE (N-ethyl-1-(3-methoxyphenyl) cyclohexanamine. Methoxetamine is the ketamine analogue that is most extensively discussed here, because the evidence suggests it is more widely used for recreational purposes than other analogues and because the evidence base is large than it is for other analogues. Other dissociatives include, but are not limited to, phencyclidine (PCP or 'Angel Dust'), the 3- and 4-methoxy analogues of phencyclidine – namely 1-[1-(3-methoxyphenyl) cyclohexyl]piperidine and 1-[1-(4-methoxyphenyl)cyclohexyl]piperidine – N-ethyl norketamine, N-ethylketamine, tiletamine, dextromethorphan – and nitrous oxide (discussed in Chapter 5). N-ethyl norketamine, currently a so-called legal high, has effects similar to ketamine is sold mainly on the internet. More recently, new substances have appeared on the market: diphenidine, which is 1-(1,2-Diphenylethyl) piperidine, and methoxphenidine, which is 1-[1-(2-methoxyphenyl)-2-phenylethyl-piperidine; these, like ketamine and its analogues, are all NMDA receptor antagonists.

Methoxetamine was at a point one of the more popular ketamine analogues. As it is not included in the Crime Survey for England and Wales (CSEW), it is not possible to determine how prevalent its use is in the UK. There is anecdotal evidence, however, that it is limited and that it has decreased in recent years. There was also a reduction in National Poisons Information Service (NPIS) activity relating to methoxetamine, following it becoming subject to a temporary class drug order in April 2012, with calls and TOXBASE® enquiries becoming infrequent.[1] It is likely that these reductions resulted from 'market forces', reflecting the fact that users may not like the effect of these drugs.

4.2. Street names

Street names for ketamine at the time of publication include: K, Ket, Special K, Kit-Kat, Cat Valium, Super K, Vitamin K. Cornflakes, Cereal and Level.

Street names for methoxetamine at time of publication include: M-ket, K-max, Mexxy, MXE powder, Special M and METH-O.

Other names for both may be used locally.

4.3. Legal status

Ketamine is currently a Class B drug under the Misuse of Drugs Act 1971 and is placed in Schedule 2 of the Misuse of Drugs Regulations 2001.

Methoxetamine was the first drug to be subject to a temporary class drug order (TCDO), in April 2012. It is now a Class B drug under the Misuse of Drugs Act 1971 (Schedule 1).

4.4. Quality of the research evidence

In comparison with other club drugs, the international evidence on the management of the acute and chronic harms related to the use of ketamine is relatively wide and includes studies of healthy volunteers and animal studies.

The evidence on ketamine analogues is very limited, in contrast. Evidence on the management of methoxetamine's acute and chronic harms, especially where there was analytic confirmation of its use, is very limited and confined to a few case reports.

4.5. Brief summary of pharmacology

Ketamine is a predominantly sedative drug, but its complex neurochemical profile reflects its actions as a dissociative, anaesthetic, psychostimulant and analgesic substance.[2]

Ketamine is part of the arylcyclohexylamine group of compounds, which act primarily as non-competitive antagonists at glutamate receptors of the N-methyl-D-aspartate (NMDA) sub-type. It also acts at dopamine D2 and 5-HT_{2A} receptors and the activation of 5-HT_{2A} receptors is thought to be related to perceptual disorders and hallucinations. Ketamine also shows affinity for mu, delta, and sigma opioid receptors and affects monoamine transporters.[2]

Ketamine is a non-competitive NMDA receptor antagonist that acts as a dissociative anaesthetic with analgesic and amnestic properties. It is a derivative of phencyclidine (PCP), and both are arylcyclohexylamines. Like PCP, ketamine stimulates the vital functions of heartbeat and respiration, though it is less toxic and shorter acting than PCP, which is a Class A drug.[3]

The term 'dissociative' suggests that sensory loss and analgesia, as well as amnesia, are not accompanied by actual loss of consciousness.[4] As a dissociative anaesthetic, ketamine has the capacity to induce narcosis and narcosis-like states in which consciousness appears to be separated from the body.[5] Its use can lead to a trance-like cataleptic state, unconsciousness, amnesia and deep analgesia, but with intact ocular, laryngeal and pharyngeal reflexes.[6] Ketamine impairs psychomotor performance in a dose-dependent fashion.

Ketamine has a plasma half-life of 2–4 hours.[7] Peak plasma concentrations are reached within a minute when ketamine is injected intravenously, 5–15 minutes when injected intramuscularly or snorted,and 4–6 hours when taken orally.[8,9]

Enzyme kinetic studies have shown that for ketamine the initial metabolic steps in humans (N-de-ethylation) are catalysed by CYP2B6 and CYP3A4. Therefore, caution should be addressed when co-administered orally with CYP3A4 and CYP2B6 inhibitors (such as ritonavir and cobicistat).[10,11]

Methoxetamine, which is 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexanone, or 3-MeO-2-Oxo-PCE, is an analogue of ketamine. Its analogues are 1-[1-(3-methoxyphenyl)cyclohexyl]-piperidine (methoxyphencyclidine; 3-MeO-PCP) and N-ethyl-1-phenylcyclohexylamine (eticyclidine).

Methoxetamine first appeared in 2010 and was synthesised as a close structural analogue of ketamine in order to elude the classification of ketamine while retaining its psychoactive properties.[12] Because of its structural similarities to PCP and ketamine, it has been assumed that the effects of methoxetamine are similar.[13]

Methoxetamine is both a dopamine reuptake inhibitor and an NMDA receptor blocker; its affinity for the NMDA receptor is comparable to or higher than that of ketamine. In addition, methoxetamine (in addition to PCP and its analogues) has affinity for the serotonin transporters.[14]

Methoxetamine has been marketed to drug users as much more powerful and as having longer-lasting effects than ketamine (these characteristics derive from its N-ethyl group). It has also been claimed that it is a 'bladder-friendly' alternative to ketamine, although there is no evidence to support this (or indeed to refute it). There are also indications that methoxetamine has a shorter half-life than PCP, but longer than ketamine, and that the psychoactive effects should be anticipated to last longer than would be expected for ketamine.[13] Although the group modification, from 2-chloro to 3-methoxy, seems to give methoxetamine lower levels of analgesic and anaesthetic properties than ketamine, it may be responsible for a half-life that is longer than that of ketamine.[4]

4.6. Medical uses of ketamine

Ketamine is used as an anaesthetic and a powerful analgesic, particularly in paediatric, emergency medicine and veterinary medicine, and is considered as a safe battlefield anaesthetic due to its pharmacological profile. It also has a medical role in the management of pain in both humans and animals.

A number of studies have investigated the role of ketamine in treatment-resistant depression and major depressive disorders.[15–17] Experimental studies are being conducted on the use of ketamine as a pharmacological agent for modelling psychosis. The Advisory Council on the Misuse of Drugs (ACMD)has recommended the need for further research into the role of ketamine as an analgesic in chronic cancer pain (palliative care) and non-cancer pain.[1]

There are currently no clinical or non-clinical uses of methoxetamine. However, as an analogue of ketamine, it could be of pharmaceutical interest for treatment-resistant depression if it were to show rapid antidepressant properties similar to those of ketamine.[14,18]

4.7. Prevalence and patterns of use

4.7.1. Prevalence of use in the UK

The recreational use of ketamine has been characterised by the EMCDDA as having 'potential for more widespread diffusion',[19] although currently its use in Europe is still relatively low, lower than that of ecstasy,[19] and is concentrated among particular sub-groups. In the UK, ketamine use escalated in the 1990s on the 'rave scene', first as an adulterant of ecstasy, before becoming increasingly mainstream.[20]

Measurement of the use of ketamine by the British Crime Survey (BCS; which is now the Crime Survey for England and Wales, CSEW) started in 2006/07, when it was suggested that it had been used in the past year by 0.3% of 16–59-year-olds. In 2013/14, ketamine use in the past year was reported by 0.6% of the adult population (aged 16–59 years), a statistically significant increase from 0.4% in 2012/13.[21]

The CSEW in 2013/14 estimated that 1.8% of people between the ages of 16 and 24 years (a total of around 100,000) had used ketamine in the previous year. In the 16–59 age group, it was estimated that 200,000 people had used done so (0.6%), with ketamine being the sixth most commonly used substance (Table 4.1).

Table 4.1. *Prevalence of ketamine use as found in the Crime Survey for England and Wales, 2013/14*

Age group and use	Prevalence
16–24-year-olds reporting ketamine use in past year, 2013/14	1.8%
16–59-year-olds reporting ketamine use in past year, 2012/13	0.6%

There was a statistically significant increase in past-year use of ketamine among all adults from 2012/13, when it was used by 0.4% of adults, to 2013/14. This was also the case among the 16–24-year age group, with an increase from 0.8%.

Ketamine use is higher among some sub-cultures, lifestyles and occupations.[22] These include clubbers,[20,23–30] 'travellers', 'free party scene',[31,32] gay men and MSM[27,28,33–35] young injectors, self-exploratory people[28] and workers in the medical field.[36,37] In a 2011 survey in a gay-friendly club, 10% reported it as their favourite drug and intended to use it on the night of the survey.[38]

Ketamine is associated with 'clubbing', as well as post-club 'chill-out', when it is used for extending clubbing experience and as part of the drugs repertoire or stages in clubbing.[39] Of the respondents to the Global Drug Survey 2013 survey (2012/13 data) 50.6% reported lifetime use of ketamine and 31.5% use in the past month.[40]

However, despite the association of ketamine with clubbing and post-clubbing use, a study has reported that the most commonly endorsed settings were home or a friend's house or somewhere else familiar.[41] In addition, there is some evidence that its use in clubs varies significantly within the different dance 'scenes' and regions. In surveys of the users of the night-time economy and clubs, it was shown that ketamine use was highest use in gay-friendly clubs, dance clubs playing 'hard dance' music, 'funky house' and 'trance' music and lowest in 'straight' (heterosexual) bars and those playing 'drum and bass' music.[42]

The 2011/12 CSEW reported that ketamine users generally have high rates of simultaneous poly-use, with 48% using another drug the last time they used ketamine (third highest after methadone users, at 58% and ecstasy users, at 49%). Ketamine users were also more likely, compared with the users of any other illicit substance, to have used (concurrently) other drugs in the past year and past month.[43]

There is some evidence from the UK that initiation in ketamine use may take place at a slightly older age than for other substances, and that it is possible more experienced users add ketamine to their poly-use repertoire.[39]

Research carried out in the US, England and Australia suggests that ketamine users tend to be white, male, under 30 years old, urban and moderately well educated.[20,28,33,44] In the UK, the CSEW also indicates that ketamine users are more likely to be male, single, in the 20–24-year age group, unemployed or a student. Differences between the various sub-groups have been shown. For instance, Morgan et al.[45] found that frequent and daily users had spent significantly fewer years in education than infrequent or non-users.

Ketamine is typically used intranasally, by insufflation. It is rarely injected. A study conducted in Scotland, for example, found that ketamine was injected by only 0.9% of users.[46]

No population data are available on the use of methoxetamine in the UK, but a 2012 ACMD report stated that there was some evidence of its use in England, Scotland and Wales. It is not clear how much it is used or whether geographic differences exist.[47] However, and as mentioned above, there is anecdotal evidence that the use of methoxetamine has become negligible.

4.7.2. Ketamine use and high-risk sexual and injecting behaviours

Like other club drugs, ketamine is used as part of a socially active lifestyle and is associated with elevated, even pronounced, sexual health risks.[48] The Global Drug Survey showed that, compared with the general population, clubbers are more socially active, have more concurrent partners, use condoms less consistently and have higher rates of sexually transmitted infections.[48]

Ketamine is associated with an increased incidence of unsafe sex among gay men.[49,50–52] A US study of gay and bisexual men attending 'circuit parties' in three cities found that over 60% had used ketamine at parties in the past year and unsafe sexual behaviour was associated with frequent ketamine use.[51] One study suggested that ketamine use (as well as GHB use) was associated with unprotected anal intercourse with regular partners, whereas methamphetamine was associated with unprotected anal intercourse with casual partners.[35]

Ketamine is rarely injected (typically being taken intranasally) but some use by injection has been reported. Laukenau et al. studied young ketamine injectors in US cities and described two types of ketamine injectors, with different demographic profiles: experienced injecting drug users (IDUs), who injected a number of drugs and who tended to be homeless youth and homeless travellers;[53,54] and new IDUs, who initiated injecting with ketamine and tended to have stable housing and who associated with others who used ketamine.[54]

The injecting of ketamine in the UK has not been systematically documented. There is some anecdotal evidence from the few UK treatment centres that provide treatment pathways to ketamine users that a minority of users inject this drug (intravenously and/or intramuscularly). There is also some anecdotal evidence which suggests that it is possible that a minority of older injecting opiate drug users also inject ketamine.[55]

US studies have found 'hidden' populations of ketamine injectors in US cities but it is not possible to determine whether those findings are relevant to the UK. A 2002 study among ketamine injectors found that a slight majority had injected other substances prior to injecting ketamine for the first time (56%) but a large minority (44%) began their injecting career with ketamine. The median age at first injecting ketamine (18 years) was slightly older than injecting other drugs (17 years). Most ketamine injectors were poly-users: 56% had used one or more additional drug before, during or after their last ketamine injection, while 44% had not.[54]

In interviews with ketamine injectors, subjects reported the advantages of injecting over snorting: sniffing aggravated the nasal passage and injecting produced a 'cleaner' high. Those who developed tolerance from sniffing found that injecting was a more potent and reliable mode of ingestion.[54] Most reported that the main reason for injecting was to achieve the 'k-hole' (where the user experiences feelings of detachment and perceptions appear divorced from reality), which was more reliably achieved and intensely experienced by injecting.[54] Among those who injected ketamine only, intramuscular injecting was more common than intravenous injecting.

Injecting ketamine was shown to be associated with high-risk behaviours. Multiple injections were typical, for example 8 to 10 injections over several hours.[54] Multiple injecting of any substance has health implications.[54]

4.8. Routes of ingestion, dosing and frequency of dosing

4.8.1. Ketamine

Illicit ketamine in the UK is mainly in powder form, typically sold in gram doses. It is less frequently available as a liquid, in which form it is possibly diverted from pharmaceutical supplies. Illicit ketamine for recreational use is often sold as a powder of fine crystal and is crushed for insufflation. It is usually white or transparent but can also be off-white or brown. Doses for recreational use are known as 'bumps' and are often measured as the quantity of powder that fits on the tip of a domestic key, a method therefore known as 'keying'. Ketamine is sometimes sold in tablet form (in which form it is on occasion falsely sold to users as ecstasy). Ketamine is sometimes dissolved for injecting and then has a faster and more potent effect.

Ketamine is rarely taken orally, as it will then be metabolised into norketamine, which produces a sedative effect rather than the desired psychedelic effect. It can also be smoked, used rectally[56,57] or swallowed in a wrap of paper.

The onset of the effects of ketamine is likely to occur approximately 5 minutes (but up to 30 minutes) after insufflation, the most common form of use. Effects occur in a matter of seconds or minutes after injection, smoking and smoke inhalation. This rapid onset of effect is thought to increase its potential for misuse. The effects themselves are generally short-lived, typically lasting 1–4 hours,[58] depending on dose, tolerance, individual factors and other drugs ingested. This short duration of effect may promote bingeing; ketamine users in a session will typically self-administer several doses in order to maintain psychotropic effects over time,[59] until supplies are exhausted.[60,61] On the other hand, the short duration of effects may also increase its appeal over longer-lasting hallucinogens.[39]

A typical recreational dose is approximately 10–25% of the effective general anaesthetic dose.[6] Single doses for intranasal use vary widely.[6,61,62] A follow-up of the Mixmag survey looked at both typical amounts used in a 'session' and the number of days of consecutive use. It reported that just under a third of respondents (31%) used less than 0.125 g; just over a third (35%) used between 0.25 g and 0.50 g, and 34% used more than 1 g per session. Five per cent reported using more than 5 g in a typical session. The mean number of maximum days of consecutive use was 3.5 days, with 11% reporting using ketamine on seven or more consecutive days. Seventy per cent used ketamine 1–4 days per month, 16% 5–8 days and 13% 9 or more days per month.[63]

The small number of specialist treatment services offering specific treatment to ketamine users report that most of their patients use ketamine most days or every day and use up to several grams per day.[1] The highest dose noted in a series of 60 patients attending three clinical urology centres for a ketamine-related urological syndrome was 20 g per day.[64]

4.8.2. Methoxetamine

Methoxetamine is generally sold as a white crystal powder, but can be found in tablet form. It is generally used by insufflation, but can be used rectally, by sublingual application and by injection (intramuscular mainly, but also intravenous).[13,65] It is also used orally, usually swallowed in a cigarette paper, or as tablets.

The range of doses reported is 20–100 mg for oral administration and 10-50 mg for intramuscular injection.[4,13,65] The effects of methoxetamine were described as lasting 1–3 hours[65] by one report, but drug user websites investigated by Corazza et al. stated that the duration of action of methoxetamine ranges from 5 to 7 hours when insufflated, less (approximately 1 hour) when administered by intramuscular injection.[58] The onset of the effects of methoxetamine have been described to start 10–20 minutes after ingestion,[65] but can be delayed by 30–90 minutes after insufflation.[4] This could have serious implications, as users may ingest a second dose thinking that the first dose was inadequate. The effects after intramuscular injection are faster, with onset after approximately 5 minutes.[58] Compulsive re-dosing has also been described.[58]

Powders and tablets sold as methoxetamine have been found typically to include a range of other compounds and adulterants, including mephedrone, caffeine and cocaine.[47]

4.9. Desired effects for recreational use

4.9.1. Ketamine

The mind-altering effects of ketamine make it attractive to some drug users, along with its lack of hangover, short duration and relatively low cost. One of the earliest studies on the recreational use of ketamine found that users perceived it as a safe and potent hallucinogen with short duration of action and an equal balance of positive and negative effects.[66]

According to Teltzrow et al., ketamine has characteristic subjective effects which differ according to individual and setting of use.[67] Overall, however, it can produce a range of experiences, depending on dose:[68]

- At low doses, ketamine produces distortion of time and space, visual and auditory hallucinations and mild dissociative effects.[69] It also has stimulant-type properties.[70]
- At high doses, it produces more severe dissociation, known by some users as the 'k–hole', where the user experiences feelings of intense detachment and perceptions appear completely divorced from reality.[69]

Ketamine has been described as able to induce a 'raft' of intense experiences, including some that can be characterised as positive and negative psychotic-like features.[71] Ketamine can act like a stimulant at low doses and can cause potent psychedelic experiences in moderate or high doses. It is dissociative inasmuch as it causes users to feel both sedated and separate from their bodies.[54] Ketamine exhibits features of

a hallucinogenic drug and its use leads to alterations in mood and thought content. The combination of effects of ketamine has been described by some as 'alcohol-like intoxication, cocaine-like stimulation, opiate-like calming, and cannabis-like imagery'.[72]

Moore et al. referred to the 'playful' effect of ketamine, in that it leads to improved moods and a child-like state. The intensity of ketamine was also emphasised.[39] Its effects include euphoria, depersonalisation and derealisation, feelings of universal empathy and experiencing synaesthesia (combinations of sense experiences such as sound and colour).[73] Ketamine users also report that it enhances creativity and that it is used to manage the 'come-down' from other drugs, such as stimulants.

Ketamine users often experience floating sensations, sensory distortions and transcendental phenomena, such as mystical insight, spiritual trips, revelations or alternative realities.[69] Ketamine is sought by some because it induces a 'separate reality', 'near death', 'lack of fear of death' and out-of-body experiences.[74] States similar to those reported as near-death experiences have been described and include altered perceptions of time, a strong sense of detachment from the physical body and a sense of peace and joy.[75]

There are individual variations in motivations to use ketamine, as well as in what constitutes desired or unwanted effects. These have been described by a study as revolving around axes of sociability and intensity, with control over effect being an important concept. The voluntary versus involuntary entry into the k-hole[39] is a salient example: for some it is too intense; for others it is a desired journey or place. Interviews with users suggest that the dose is a key point of control, which users associate with the possibility of negative or positive consequences of ketamine use. It has been reported that some users 'test' doses of ketamine to assess the strength of batches[39] and then adjust doses for desired effects. Self-administration of titrated ketamine is attempted by users to achieve the desired amount of dissociative sensation, hallucination and transcendental experience.[66]

In addition to dose, frequency of use and past exposure have been self-reported as influencing the experience. In a study of recreational users, 58% interviewed said they had experienced the k-hole and that this was related to increased exposure to the drug (more than 20 times).[28]

Ketamine is also used for self-medication for depression and studies are currently being conducted to examine its possible antidepressant action. There is also anecdotal evidence that it is also used as self-medication for sleep and anxiety. Anecdotal evidence also suggests that it is commonly used by MSM for some forms of anal sex ('fisting') because of its anaesthetic and muscle-relaxing effects.

4.9.2. Methoxetamine

Reports from users suggest that methoxetamine produces ketamine-like effects. It has been marketed as much more powerful and longer-lasting than ketamine (but less so than PCP).[4,13] Although the effects have been described as broadly similar to, albeit more intense than, those of ketamine, there may be individual variations. One

patient implied that the clinical effects of methoxetamine were subjectively very different from his previous ketamine use.[76]

The effects and dosage of methoxetamine are linked to mode of ingestion. Typically, it works as a short-acting mood enhancer, with powerful visual hallucinogenic and dissociative properties. The desired effects include euphoria, empathy, 'cosiness', intensification of sensory experiences, especially while listening to music, a mild to strong sense of dissociation, distortion of the sense of reality, vivid hallucinations, introspection and brief antidepressant effects.[4] There is one report of the use of methoxetamine as an analgesic for self-medication for chronic foot pain.[77]

An 'm-hole' has been described by users, typically referring to a subjective state of dissociation, which mimics the out-of-body experiences of near-death experiences,[75,78] and is often accompanied by feelings of derealisation, depersonalisation and disorientation, as well as vivid hallucinations.[4]

4.10. Mortality

No deaths have been reported associated with the medical use of ketamine. In terms of recreational use, fatalities solely linked to ketamine toxicity are relatively rare. Ketamine-related deaths have been reported in adults after intravenous doses of 500–1000 mg.[79,80]

A study by the National Programme for Substance Abuse Deaths (NPSAD) identified 23 deaths in the UK from 1993 to 2006 where ketamine was mentioned in the death certificate or coroner's report. However, ketamine was used on its own in only four of these cases, suggesting the particular risk is posed by poly-drug use and drug interaction. Nonetheless, the four fatalities associated with ketamine on its own have led some to question the high safety profile often attributed to ketamine.[78]

One of the limitations of the data on drug-related mortality was highlighted by the authors of the NPSAD study: the fact that even if ketamine was recorded in the post-mortem examination, this did not necessarily mean that it had contributed directly to the death. The four deaths from ketamine alone could, for instance, have been associated with the increased likelihood of accidents caused by the drug's dissociative effects.[78] The effects of ketamine, notably a reduced awareness of risk, a reduced perception of pain, a lack of coordination, a temporary paralysis and an inability to speak, would indeed put users at significant risk of injury or accidents. Although it has been argued that the highest risk of mortality from ketamine is through accidental death when intoxicated,[57,81] there is little scientific evidence to support this at present.[82]

4.11. Acute ketamine toxicity*

In comparison with other drugs, ketamine in itself has a wide margin of safety,[82] but it is often co-ingested with other substances, which increases both its associated harms and those of other substances. It is also gives rise to a greater risk of accidents (see section 4.11.3) and chronic use can lead to urological problems, which can be severe (see section 4.14.4).

Ketamine is characterised by its ability to cause unconsciousness, amnesia and analgesia, while sparing airway reflexes and maintaining haemodynamic stability.[6] Coughing and swallowing reflexes are maintained with minor suppression of the gag reflex, even when a user is very intoxicated, thus reducing the potential risk for users, if ketamine is used on its own.[82]

The Morgan and Curran review suggests the lack of severe acute physical health consequences, with no adverse outcome reported from large overdose, where no other substances are co-ingested.[82] The main features of acute intoxication associated with ketamine are related to its psychedelic, dissociative and hallucinogenic properties.

In humans, a single dose of ketamine induces dose-dependent impairments in working and episodic memory, which can have a profound effect on the user's ability to function.[83] Ketamine is associated with direct neurotoxicity and can cause acute neuropsychiatric effects, such as agitation or ketamine-related psychotic states. Generally, clinical features are related to physical harm (e.g. agitation or accidents, and behaviours resulting from dissociative effects), but systemic toxicity with cardio-vascular effects can occur and can be severe.

Ketamine stimulates the cardiovascular system, leading to increased heart rate, cardiac output and blood pressure,[82] and this will present a risk for people with hypertension or severe cardiac disease, and people at risk of stroke and raised intracranial pressure. Risks are increased with co-ingestion of stimulants[82] and should be emphasised in harm reduction messages (section 4.16).

4.11.1. Features of acute ketamine toxicity

The reported acute effects of ketamine use are summarised in Box 4.1.

Case reports provide some insight into how common these ketamine-related effects are. In a study by Ng et al.[92] which reviewed 233 cases of presentations to an emergency department, the most common presenting symptoms were: impaired consciousness (45%), abdominal pain (21%), lower urinary tract symptoms (12%) and dizziness (12%). The most common physical symptoms included high blood pressure (40%), tachycardia (39%), abdominal tenderness (18%) and chest discomfort and palpitations (11%). However, no patient had serious cardiovascular complications (e.g. myocardial infarction or significant arrhythmias). In that study, 46% of patients

* SPC data ketamine hydrochloride for injection can be found (for Ketalar) at http://www.medicines.org.uk/emc/medicine/12939/SPC/Ketalar+Injection/#PRODUCTINFO. SPC states that respiratory depression may occur with overdosage.

Box 4.1. *The reported acute effects of ketamine use*

Dermatological
Transient rash, predominantly in face and neck

Gastrointestinal
Nausea
Vomiting

Neurobehavioural effects/psychiatric effects[66,83,84]
Hallucinations (visual and auditory)
Slurred speech
Dizziness
Numbness
Confusion
Blurred vision
Insomnia
Decreased sexual motivation
Cognitive impairment
Aggression
Paranoia and display of dissociative-type symptoms
Ataxia
Acute dystonia (one report)
Agitation (agitated patients are at risk of other effects including hyperthermia, rhabdomyolysis, self-injury, enhanced perception, depersonalisation, movement disorders and confusion)
Paralysis and muscle rigidity
Ketamine-related psychotic states (typically short-lived with complete resolution).[71,85] Among patients with schizophrenia stabilised on an antipsychotic, however, ketamine can cause a relapse of psychotic symptoms,[86] which are idiosyncratic to those each individual exhibited during the acute phase of their illness[87,88]
Delirium
Polyneuropathy
Seizures
Convulsions

Cardiovascular and respirator[89–91]
Self-resolving sinus tachycardia (most commonly reported)
Hypertension (common)
Chest pain
Palpitation
Transient major Brugada ECG patterns (one case report)
Raised intracranial pressure
Pulmonary oedema
Respiratory depression
Cardiac and respiratory arrest Increased muscle tone and activity may produce hyperpyrexia

had a period of altered consciousness at some point after ketamine ingestion. This effect of ketamine was short-lived, however; only 14% of the patients had a score on the Glasgow Coma Scale of less than 15 when examined in hospital. Among patients who had blood tests performed, leukocytosis (in 36%) and a raised creatinine kinase level (in 32%) were the most common abnormalities, whereas 16% had abnormal liver function test results and 3% had abnormal renal function test results. Most of the patients were managed solely in the emergency department (72%) and 85% had no or only minor complaints.[92]

There are few reports (albeit they are increasing in number) of methoxetamine use with analytical confirmation of the use of the substance.[13,93] The effects of methoxetamine are dose dependent and include mild euphoria, hallucinations, disorientation, confusion, vertigo, analgesia, numbness, anxiety, tachycardia, hypertension, nausea, vomiting, diarrhoea, insomnia, agitation, sweating, catatonia and hypertonia; as well as elevated creatine kinase.[13] Opiate-like effects have been described by a user (quoted by Rosenbaum et al.[65]), as well as respiratory depression, antidepressant effects and amelioration of phantom limb pain. Cognitive impairment has also been reported.[47] Partial amnesia to preceding events was noted in one report.[77]

Methoxetamine can cause rapid-onset neurological impairment; reversible cerebellar impairement has also been reported.[94] A case series on the effects associated with methoxetamine use reported cerebellar ataxia, incoordination, dysarthria and nystagmus.[76] Cerebellar signs were reversible in all cases observed, but recovery could extend over several days.[76] Nystagmus and tremor have been reported.[13,93,95]

A report of three presentations with confirmed methoxetamine consumption at an emergency department shows that acute effects include ketamine-like dissociative/catatonic symptoms, as well as features of sympathomimetic activation, with marked tachycardia and hypertension and agitation or aggression.[93,96]

Methoxetamine seems to have more severe side-effects than ketamine.[58] It has greater effects than ketamine in terms of hypertension and other stimulant-like effects, including agitation, tachycardia and cerebellar features, such as ataxia.[47] People have presented at hospital with methoxetamine intoxication with impaired consciousness. One report of three cases mentioned a patient presenting to hospital with a score on the GCS of 13, another 10 and the third 7.[76]

Corazza et al. cite a report of a fatality following an unconfirmed intravenous injection of both methoxetamine (8–100 mg) in addition to 400 mg of 5,6-methylenedioxy-2-aminoindane (MDAI).[58]

4.11.2. Acute withdrawal

For withdrawal see section 4.13.2.

4.11.3. Poly-drug use: complicating factors for acute toxicity

Acute ketamine toxicity is often complicated by poly-drug use, which is common. In one study of attenders at an emergency department, 89% of self-reported ketamine users stated that they had used another drug and/or alcohol.[89] It is therefore recommended that when people present with acute toxicity after ketamine use, clinicians consider the possible impact of other drugs ingested.[6] Poly-drug use has also been implicated in death (section 4.10).

4.12. Management of ketamine-related acute harms

4.12.1. Identification and assessment of acute toxicity

Diagnosis of acute ketamine intoxication in an ED setting should be made on clinical assessment and the recognition of the clinical effects of ketamine, also taking into account the common co-ingestion of a number of substances, including alcohol.

A case series of US ED presentations suggested that the diagnosis of ketamine should be considered when people (especially young people) present with agitation, tachycardia and either visual hallucinations or nystagmus, although the absence of the latter two findings does not rule out the possibility of ketamine misuse. The authors also recommend that if symptoms are not improving, they should investigate other drugs co-ingested or another differential diagnosis.[90]

Because the onset of the effects of ketamine intoxication are rapid and are generally short-lived, people will typically develop the adverse effects in the setting where the drug was ingested, in night clubs for example, and symptoms may resolve before they reach hospital. Indeed, some clubs provide a room or area where unwell users of club drugs are initially assessed and managed prior to transfer to hospital, if required.[97] Wood et al. analysed the patient presentations, one such facility over a five-month period in 2008/09. Of the 173 presentations for recreational drug toxicity, 37.9% were for ketamine, which was the second most frequently mentioned drug, after GHB/GBL. However, the authors stated that ketamine was not as commonly seen in the emergency department where they worked.[98]

Information on presentation to the hospital EDs resulting from ketamine toxicity is limited. In the UK, ketamine was the seventh most frequently searched for drug in TOXBASE® enquiries in 2012/13, at 2933 enquiries, but this was a 14.2% reduction from the previous year. A reduction was also noted in telephone enquiries over the same period.[99]

4.12.2. Clinical management of acute toxicity

No antidote exists for ketamine overdose. The effects of ketamine are not reversed by naloxone and no other agents are available to reverse the effect on humans.[7] Activated charcoal is not necessary after ketamine acute intoxication, unless there is evidence that a co-ingestant may be contributing to the patient's symptoms or, in the case of a large ingestion, if the patient presents very early.

Most patients will improve rapidly following acute ketamine toxicity.[6] Although randomised controlled trials and other robust studies are not available, there is consistency in case reports and series that patients are best managed with:

- standard supportive care, with special attention to cardiac and respiratory functions, as the effects of the drug are usually short-lived;[6,90,100]

For up-to-date guidance on the management of ketamine acute toxicity, it is recommended that information be sought from the National Poisons Information Service (NPIS), specifically the NPIS 24-hour telephone service and the poisons information database TOXBASE®:

http://TOXBASE.org/Poisons-Index-A-Z/K-Products/Ketamine/

It is recommended that relevant clinicians and departments are registered to receive these facilities.

Non-UK readers should consult their local or national guidelines.

- benzodiazepines, where the patient is agitated;
- consideration of other causes for clinical presentation, for example co-ingestion of other psychoactive drugs, head injury, hypoglycaemia etc.
- removal of the person from auditory and visual stimulation until symptoms resolve has been recommended. A quiet environment, with minimum of external stimuli, may prevent excessive agitation.[6]

Observation of the patient until vital signs and mental state have normalised is also recommended. If symptoms fail to improve within an hour of presentation, the diagnosis and the management should be reviewed. [6,90]

Profoundly obtunded (altered level of consciousness) patients may require airway support, intravenous fluids and titrated benzodiazepine therapy if they are agitated, hyperthermic or show overt sympathomimetic signs.[92]

As for ketamine, in the management of acute methoxetamine intoxication observation and symptom-directed supportive care[13] are recommended; cardiovascular and respiratory support is sometimes needed. Oral diazepam and midazolam have been prescribed.

For up-to-date guidance on the management of methoxetamine acute toxicity, it is recommended that information be sought from the National Poisons Information Service (NPIS), specifically the NPIS 24-hour telephone service and the poisons information database TOXBASE®:

http://www.toxbase.org/Poisons-Index-A-Z/K-Products/Methoxetamine/

It is recommended that relevant clinicians and departments are registered to receive these facilities.

Non-UK readers should consult their local or national guidelines.

4.12.3. Outcome of treatment for acute toxicity

A study of presentations at a Hong Kong ED[92] reported that most of the patients (197/233; 85%) developed no, or only minor, complications. The majority (168/233; 72%) were safely managed in the emergency department with supportive measures, including intravenous fluid and benzodiazepines for agitation. The five patients requiring management in an intensive care setting had all co-ingested other drugs that could have contributed to their clinical status.[92]

4.13. Harms associated with chronic ketamine use

4.13.1. Ketamine dependence

There is evidence that the administration of NMDA receptor agonists, such as ketamine, increases the release of dopamine in the nucleus accumbens, which is typically associated with addiction liability.[101] There are case reports of ketamine dependence,[37,68,102,103] but a lack of large studies, so the incidence is not known. It can be argued that the ICD-10 criteria for 'dependence syndrome' can be applied in some cases of chronic ketamine use.

Frequent ketamine use is associated with tolerance. Animal studies[104,105] and human studies (children undergoing anaesthesia[106]) have shown a rapid development of tolerance with repeated ketamine dosing. A study of Australian recreational ketamine users found that 22% reported physical tolerance to ketamine.[28] Frequent users of recreational ketamine report escalating dose, with one case report of a 600% increase from dose at first use[61] and another a reported 760% increase from the initiation dose.[41] Also of concern among frequent users are the compulsive patterns of behaviour: bingeing or using without stopping until supplies run out.[41]

There are no reports of methoxetamine dependence, but withdrawal has been described by users. Corazza et al. investigated through their analysis of drug user websites the effects of the chronic methoxetamine use. Withdrawal symptoms were described and included low mood and depressive thoughts, cognitive impairment for many hours, as well as insomnia and suicide attempts.[4]

4.13.2. Ketamine withdrawal

There is conflicting evidence on the existence of a specific ketamine withdrawal syndrome following cessation of ketamine use but a specific ketamine withdrawal syndrome has not yet been described.[82] In a study of 30 daily users, 28 reported having tried to stop taking ketamine but failing; all reported ketamine cravings as the reason for failure. The study also found that 12 of the 30 daily users reported withdrawal symptoms – anxiety, shaking, sweating and palpitations.[61] Other studies also reported craving and somatic and psychological symptoms (e.g. anxiety) of ketamine withdrawal.[73,107,108]

Clinical experience suggests that ketamine withdrawal does exist. Although ketamine rarely produces serious withdrawal symptoms, the marked drug tolerance and psychological dependence might contribute to the difficulty in abstaining.[109]

It has been argued that in cases of sustained and heavy use, the existence of a ketamine withdrawal syndrome must be considered. [73] Although ketamine has a short half-life, metabolites are present for some hours and may be responsible for continuing symptoms.[73] In addition, the symptoms of acute withdrawal may be short-lived and therefore not identified.[110] However, case reports have described somatic and psychological aspects of anxiety as withdrawal symptoms.[73,107,108] One case report mentioned withdrawal symptoms such as 'chills', autonomic arousal, lacrimation, restlessness, nightmares and psychological craving, with further ketamine use to relieve these symptoms.[108] Another described in detail the effects of discontinuation of use on one patient, which included craving and drug hunting, anxiety, shaking, sweating, palpitations, tiredness, low appetite and low mood.[73]

4.13.3. Other harms of chronic use of ketamine

4.13.3.1. Ketamine-induced damage to the urinary tract

Ketamine use is associated with damage to the urinary system, which can be in the form of severe and in some cases irreversible bladder damage. This has been referred to as ketamine-induced ulcerative cystitis,[82] although some have argued that it would be more appropriate and concise to describe it as ketamine-induced uropathy.[111] The mechanism of damage from ketamine is not yet clear but the effects, which are not specific to the bladder, are most likely to result from direct toxicity of ketamine or its metabolites. Damage can affect the entire urinary tract.[64]

The urological syndrome associated with ketamine use can lead to severe clinical symptoms:[64] a small, very painful bladder, dysuria, painful haematuria, urge incontinence, frequent and urgent urination, nocturia, obstruction of the upper urinary tract, papillary necrosis,and hepatic dysfunction.[64,111–113] Auxiliary examination showed cases of patients with symptoms including the following: sterile pyuria, contracted bladder (involving chronic inflammation with ulceration), erythematous swelling, necrotic mucosa, thin epithelium with neutrophilic and lymphoplasma cell infiltration in bladder mucosa, collagen and adipose tissue and bladder wall fibrosis with or without vesico-ureteric reflux and involvement of the upper urinary tract.[111]

Cystoscopic inspection of the bladder also often shows a denuded urothelium, which, in the most severe cases, may slough off as intact sheets of cells. There are reports of young patients at an end-stage of the disease process who required cystectomy (bladder removal) and reconstruction, [64] with a serious impact on life expectancy.

It has been reported that 20–30% of ketamine users suffer from lower urinary tract symptoms.[41,112] A study assessing the prevalence of urinary symptoms in a large cohort of non-treatment-seeking ketamine users found that harms to the urinary tract are dose related and are particularly common among regular and dependent users. Urinary symptoms are associated with an increased frequency of use and increased

amount used per session.[1] However, the duration and/or amount of ketamine used to induce lower urinary tract symptoms is not known.

The time of onset of lower urinary tract symptoms following ketamine misuse varies from a few days to a few years following the onset of use, with the severity being in part determined by the chronicity of use. Up to 100% of those using more than 5 g per day report urinary symptoms.[114] Because of the severe bladder pain, users frequently self-medicate for severe pain with ketamine, as the only effective means of pain relief they know, thus perpetuating the damage to their urinary tract.[64]

Studies of patients in chronic pain and palliative care receiving ketamine suggest individual variations, with some individuals are more susceptible than others to ketamine-related urological damage.[64] Some series have reported a slight male predominance, but this is insignificant and not universally reported.[115] At the present time, it would seem that ketamine-induced vesicopathy does not exhibit any gender bias.[112]

There is also a link between chronic ketamine use and kidney dysfunction. Hydronephrosis secondary to stenosis (narrowing) of the ureter seems to be an emerging health problem associated with frequent and high-dose ketamine use.[82] Chu et al.[112] reported in their study of ketamine-induced ulcerative cystitis that 51% of patients presented with unilateral or bilateral hydronephrosis. Four patients also showed papillary necrosis and this led to renal failure in one. Patients presenting with a history of ketamine use and urological symptoms need to have their kidneys imaged to rule out ureteric strictures.

Methoxetamine was marketed as more 'bladder friendly' than ketamine. However, there is emerging evidence from an animal study that exposure to methoxetamine can induce changes in the kidney and bladder after daily use, suggesting that chronic use of methoxetamine in humans may be associated with similar lower urinary tract symptoms, as those described for chronic ketamine use.[116]

4.13.3.2. Gastrointestinal toxicity

People with prolonged and heavy use of ketamine have reported intense abdominal pain, referred to by users as 'k-cramps'.[41] The Ng study of presentations to EDs reported that 21% of ketamine patients presented with abdominal pain and 15% had abnormal liver function.[92]

Little is currently known about ketamine-induced abdominal pain. A small number of case reports[113,117,118] have reported colic-like, upper gastric pain in young ketamine users who also presented with abnormal liver function. CT scans showed dilation of the common bile duct, mimicking cholecystitis. These symptoms appear to resolve once the patient stops using ketamine. In one UK case, a person had a dilated common bile duct that regressed with abstinence but recurred following a return to ketamine use.[117] It has been postulated that biliary tree dilation might be related to dysfunction of the sphincter of Oddi, but the exact pathophysiology remains unknown.[92,113,117,118]

4.13.3.3. Diabetic ketoacidosis (DKA)

Ketamine can precipitate DKA in type 1 diabetes. The metabolic acidosis can be severe and has, in some cases, been associated with rhabdomyolysis.[119–138]

4.13.3.4. Drug interaction in HIV treatment

The use of ketamine raises general issues of adherence to antiretroviral regimens. As a substrate of the CYP450 system (specifically 3A4), ketamine may interact with certain antiretroviral medications, particularly the protease inhibitors with CYP450 inhibitive properties.[139] Also, its cardiovascular effects may be deleterious among any patients with underlying heart disease or lipid abnormalities.

4.13.3.5. Neurobehavioural, psychiatric and psychological effects

4.13.3.5.1. Cognitive impairment and memory impairment

Overall, studies have shown that infrequent ketamine users do not appear to experience long-term cognitive impairment. However, there is evidence that frequent ketamine users do have profound impairments of their short-term and long-term memory, although many studies have been cross-sectional and hence unable to address causation.[82]

Neuropsychological harms appear to be related to frequency and quantity of dosing. Cognitive impairment and long-term psychological effects can result from prolonged use.[45] Ketamine is associated with direct neurotoxicity and can cause acute neuropsychiatric effects. One longitudinal study showed that frequent ketamine use impaired visual recognition and spatial working memory; the degree of impairment was correlated with changes in the level of ketamine use over 12 months.[81] Acute and acute-on-chronic use has been associated with impaired information handling within working memory and episodic memory, as well as deficits in semantic processing,[83,140] with men more affected than women.[141]

A case control study found that frequent ketamine use is associated with impairment of working memory, episodic memory, executive function and psychological well-being.[142] One-year follow-up with the same group showed the frequent users on increasing doses were more likely to have cognitive deficits, especially with spatial working memory and pattern recognition memory tasks, with both short-term and long-term memory affected.[45]

One study has shown that delusional thinking was positively correlated with the amount used by frequent users and persisted despite abstinence.[142] A dose-dependent relationship was found at one-year follow-up, with frequent users more delusional than infrequent, abstinent and non-users.[45]

Taking ketamine regularly has detrimental effects on memory function which last beyond the acute effects of the drug. Research suggests frequent use of ketamine produces long-lasting impairments in episodic memory and aspects of retrieval from semantic memory, which goes beyond ingestion.[59]

A three-year longitudinal study of people who had ceased or reduced ketamine use reported that some may continue to experience drug-related symptoms three years later. This is particularly in relation to impairment of episodic memory which was still present three years later and possibly also attentional functioning. Schizotypal symptoms and perceptual distortion may also continue after ketamine cessation.[143]

Research on infrequent users (defined as taking ketamine more than once a month but less than three times per week) and daily ketamine users found that scores on measures for delusion, dissociation and schizotypy were higher in the daily users.[20,45] Morgan et al. found that daily ketamine users had patterns of symptoms similar to individuals in the prodromal phase of schizophrenia.[45] Long-term ketamine users have more pronounced and persistent neuropsychiatric symptoms, generally characterised as schizophrenia-like symptoms. However, there is no evidence of clinically significant positive or negative psychotic symptoms among infrequent users.[144] There is also little evidence of a link between chronic heavy use of ketamine and diagnosis of a psychotic disorder.[82]

4.13.3.5.2. Depression

Frequent use of ketamine is typified by increased dissociative and depressive symptoms[45] (as well as subtle visual anomalies[103]). Morgan et al.'s longitudinal study[45] found increased levels of depression in both daily users and ex-ketamine users over the course of one year, but not among infrequent users. However, the depression was not at clinical levels and the increase was not correlated with changes in ketamine use.[82]

In contrast, there is some evidence that ketamine may be of therapeutic use for the management of treatment-resistant depression,[15,16,145] as well as post-traumatic stress disorder.[146] A recent large clinical trial testing the efficacy of intravenous ketamine in mood disorders reported that it was associated with a rapid and large antidepressant effect at 24 hours, significantly superior to midazolam. Ketamine appears to possess rapid antidepressant effects independent of its transient psychoactive effects.[147]

4.13.3.5.3. Neurological effects

Animal studies have shown that ketamine is directly neurotoxic. Abnormalities were also found in ketamine-dependent patients in bilateral frontal (including corpus callosum and anterior cingulate cortex) and left temporoparietal whiter matter. A recent human study of 41 ketamine-dependent users and 44 drug-free volunteers showed bilateral degeneration of frontal and left temporoparietal white matter in ketamine users.[148] The study also reported that fractional anisotropy* values negatively correlated with the total lifetime ketamine consumption.[148]

A case report has also demonstrated a reduction of frontal grey matter volume in ketamine-dependent patients. This reduction was correlated with duration of

* White matter integrity can be studied by examining the degree of fractional anisotropy; this is a measure that quantifies the restriction (anisotropy) of water diffusion by tissue microstructure in each image voxel.

ketamine use; reduction in the left superior frontal gyrus correlated with estimated total lifetime consumption.[149]

4.13.3.6. Social harms

A study of 100 recreational users of ketamine found that while one in five stated that they had ever experienced severe side-effects, more than a third (38%) reported having to deal with someone else who had suffered badly following ketamine use. The most common reported problems were in the areas of employment (20%), relationships (5%), financial (5%) and legal (1%).[28] The authors suggest that the problems were likely linked to the neurochemical consequences of ketamine use and the toxicity that might result.[28]

4.14. Management of harms related to chronic ketamine use

4.14.1. Numbers in specialist drug treatment for ketamine-related harms and dependence

Presentations among adults (18 years and over) in England for treatment for ketamine have risen year on year between 2005–06 and 2010–11 from 114 to 845 patients, falling to 751 in 2011–12. This rise followed by a reduction in presentation was also reported for young people under the age of 18, whereby numbers rose from 25 in 2005–05 to 405 in 2010–11 then falling to 387 in 2011–12.[150]

4.14.2. Identification and assessment

The first step for the identification of ketamine use and harms by specialist treatment services is to include questions relating to ketamine in routine care. The modification of existing national data collection tools is indicated, such as the Treatment Outcome Profile (TOP) forms. Assessment of ketamine use is similar to assessment for other drug use, with the addition of screening questions on urological and gastrointestinal symptoms and questions on the direct consequences of dissociation (e.g. cognitive impairment, sexual behaviours).

4.14.3. Psychosocial and pharmacological support

4.14.3.1. Psychological support

Information on psychosocial support is presented in Chapter 2 and is relevant for ketamine users.

A small number of ketamine-specific studies have also been conducted. Copeland et al. suggest that the harms that require further investigation are the association of ketamine use with unsafe sex and injecting behaviours and its neurotoxic effects. They also argue that effective brief and early interventions are needed for those who

are at risk of harm because of ketamine intoxication and/or excessive and regular consumption. Interventions should address ketamine use in situations where there is a heightened risk of accidental death because cognition is impaired.[7]

Critchlow described the treatment of a person with dependence on ketamine that involved three motivational interviewing sessions in the first instance.[73] Jansen and Maxwell suggest an abstinence-oriented approach be used for ketamine, similar to that used for psychostimulants.[151] They suggest following the model used for cocaine and amphetamine dependence, with abstinence from all drugs from day 1. This may require the therapist to avoid being confrontational to prevent treatment drop-out; relapse prevention is also indicated.[60]

4.14.3.2. Pharmacological interventions for dependence and withdrawal

Ketamine withdrawal is described in section 4.13.2. Only one case report is available and that describes medically assisted detoxification carried out in conjunction with three sessions of motivational interviewing. Detoxification was carried out using a reducing regimen of diazepam over three days. The regimen was successful and eliminated the majority of withdrawal symptoms.[73]

Others have also suggested that, in cases of sustained heavy use and where acute withdrawal syndrome is a possibility, a benzodiazepine detoxification regimen modified from alcohol detoxification regimens may lessen the symptoms arising from discontinuation.[152] It has been suggested that symptomatic management of withdrawal is indicated in some cases, with low-dose benzodiazepine as a starting point. There are no studies to support the use of other pharmaceutical agents, so any prescribing must be carried out based on clinical assessment.

4.14.3.3. Aftercare and support

Chapter 2 presents information on aftercare. A few ketamine-specific studies have been conducted, with some suggesting that ketamine users' ability and willingness to abstain from using the drug may be low, even when (and perhaps because) experiencing significant urological problems. Chu et al. showed that 9 out of 24 ketamine users with bladder problems were able to abstain from the drug and complete the Pelvic Pain and Urgency/Frequency questionnaire.[112] Another study found that only 3 out of 10 patients stayed ketamine free for more than one year.[109]

4.14.4. Management of urinary tract problems

It is recommended that patients with recurrent urological problems, or patients with unexplained urinary symptoms, are assessed by a urologist to exclude other causes and evaluate any damage. Any patients with unexplained symptoms should be screened for ketamine use.[64] Appropriate support to stop ketamine use must be available, as well as advice regarding appropriate medical pain relief.

The most effective treatment for ketamine-related urological problems is cessation of use and it is essential that use of ketamine is stopped upon recognition of symptoms. Strategies are limited when use continues.[153] If drug cessation is achieved, the syndrome may be partially or completely reversed, but if ketamine use persists, so do symptoms. In a few patients, however, symptoms persist despite stopping drug use.[63] Patients should also be referred to specialist drug services. [64] A survey of UK urologists suggested that approximately a third of urological problems resolved after drug cessation, a third remain static and a third progressed.[153]

Treatment for urinary tract symptoms is either symptomatic (analgesia, urinary diversion) or the treatment of complications (e.g. percutaneous nephrostomy insertion).[153] Early stages of the urological syndrome may present in casual or weekend users as episodes of cystitis, which can be treated empirically[64] (based on practical experience and observation). More frequent users may have irreversible damage and scarring. The most affected patients may require major surgery, in the form of cystectomy and bladder reconstruction.[64]

Where ketamine is identified as a factor, it has been recommended that renal function be assessed; a CT urogram can also be an important investigation to reveal the extent of the disease. A urine culture is mandatory. A routine evaluation of the upper tracts with a CT urogram can rule out ureteric stricture and cystoscopy can be used to assess bladder capacity.[64] In patients with normal renal function and with an ultrasound that shows no hydronephrosis, a CT scan may not be necessary.[154]

A strategy for the treatment of ketamine-related urological problems has been suggested by Wood et al.[64] Central to this is the requirement for patients to stop their ketamine use. However, this may be complicated by a need for pain control in those with ulcerative cystitis. This will require the treating team to develop an alternative pain management plan with the patient. There may also be a lack of motivation to abstain and non-compliance with urological investigation and treatment appointments.[64]

Winstock et al. recommended a multidisciplinary approach promoting harm reduction, cessation and early referral, to avoid progression to severe and irreversible urological pathologies.[63] Similarly, Wood et al. suggest a need for liaison between specialist drug services and local urology services.[63] Some drug agencies have developed proactive models.[64] However, this is not always possible, as patients can see urology departments outside their residential area. In this case, support is best organised by the general practitioner.[64]

4.15. Public health and public safety

4.15.1. Viral and bacterial infections

Studies have reported that ketamine injecting is associated with high-risk behaviours like the sharing of injecting equipment and paraphernalia,[155,156] poly-drug use[156,157] and multiple injections. Ketamine injecting puts the user at risk of viral and bacterial infections and hence the potential risk of their transmission to others.

4.15.2. Accidents and assaults

Ketamine impairs psychomotor functioning dose dependently and higher doses increase the risk of accidents.[158] Ketamine use has been associated with driving accidents in Hong Kong: 9% of fatal drug and alcohol-related single-car collisions during 1996–2000 involved ketamine.[159] New regulation (coming into force in March 2015) has identified ketamine as one of the specified controlled drugs for the purposes of section 5A of the Road Traffic Act 1988.[160]

Ketamine use can place the user at risk of sexual assault, although studies have suggested that ketamine is not implicated in drug-facilitated assault.[161,162]

4.16. Harm reduction

It has been recommended that all ketamine users are given the standard harm reduction advice, which includes not using the drug when alone, avoiding poly-use and co-ingestion of other substances, including alcohol, and information on a safe environment and safer injecting techniques.[7,59]

The following more specific harm reduction advice should be given to ketamine users:

- Users should be advised to measure dose carefully and start with a small test dose. They should also be advised to measure intervals between doses accurately.
- The use of ketamine with other drugs including alcohol should be avoided.[7]
- Users should minimise the risk of accidental injury by ensuring that intoxicated friends are always accompanied by others who are not.[82] The dissociative effects of ketamine puts users at risk: drowning in shallow waters, including a bath, and hypothermia from long walks have been highlighted as risks.
- Users should be made aware of the link to urological problems, and other ketamine-related harms.
- Users who develop tolerance and who find themselves needing to use increasingly higher doses, and who are using more frequently than intended, should be advised to monitor their intake. Diaries and electronic tools can be very useful.
- Advice should be given to users that those acutely intoxicated should not be left alone in case of accidents and should have with them someone who has not used the substance.[82]
- Users should be made aware of the potential neurological and cognitive changes following frequent use of ketamine, which can result in poor performance at school, college or work.[82]
- Ketamine users who feel depressed and anxious when stopping or reducing ketamine should be encouraged to seek professional help to manage their symptoms during a gradual reduction or detoxification.

- Users should be made aware that the anaesthetic topical effects of ketamine mean that they may not feel pain from tissue trauma and extra caution must be exercised with any sexual activity which risks tissue damage (e.g. 'fisting').
- Daily use of ketamine should be avoided, due to the urological risks.
- Ketamine users with urological problems should be strongly encouraged to cease using the drug.
- Advice should be given to users with urological problems not to deliberately dehydrate and to seek medical help and referral to a specialist to reduce the risk of permanent harm.

Corazza et al. in their analysis of internet sites found that users themselves suggested that dosages should increase only gradually. Users recommended that doses of 50 mg should not be exceeded on the first occasion of use, or when the drug was taken orally. The websites also advised users not to use methoxetamine with alcohol, tetrahydrocannabinol, selective serotonin reuptake inhibitors or monoamine oxidase inhibitors. Users were advised to try a test dose of a few milligrams and to wait 2 hours before re-dosing.

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