Ketamine

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Abstract

Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone), an anaesthetic derivative of phencyclidine (PCP) with analgesic, neuroprotective and psychedelic properties, is an unusual anaesthetic in its ability to produce a "dissociative" state. It is the action (antagonism) at NMDA (*N*-methyl aspartate) receptors that is thought to underlie ketamine's qualities. Whilst ketamine use in medicinal and veterinary settings is well documented and has a good safety record, the increase in its unregulated use outside of such controlled environments is a cause for concern. In non-medicinal use, the stereo-selective kinetics and the complex mechanism of action may lead to unpredictable effects. It is reported that the perceptual and mood changes observed in those who have consumed ketamine are highly sensitive to age, dose, route, previous experience and setting. At low doses stimulant effects predominate and environmental conditions are significant, but with higher doses psychedelic effects become the primary experience. When used recreationally in sub-therapeutic doses by inhalation (or insufflation) the alteration in perception of auditory, visual and painful stimuli result in a general "lack of responsive awareness" which puts the recreational user at risk of personal damage which can go unrecognized. The recreational use of this drug, the effects and potential risks associated with its unregulated use will be discussed.

Learning Objectives

- Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) is an anaesthetic derivative of phencyclidine developed by Parke Davis laboratories in 1962
- Ketamine is a dissociative anaesthetic with analgesic properties and has a wide range of clinical applications and a wide margin of safety in overdose
- Antagonism at NMDA (*N*-methyl aspartate) receptors underlies ketamine's analgesic, dissociative and neuroprotective qualities
- Complex in its pharmacology, the isomeric form of ketamine can exert a significant influence upon both monoaminergic and glutaminergic neurotransmission
- Ketamine, both acutely and chronically, may have specific and yet wide-ranging effects on memory systems
- Acute doses impair episodic memory (processes involved in retrieval and initial encoding of information)
- Ketamine has reinforcing properties when used chronically and sequential use may in susceptible individuals result in acute episodes of paranoia, panic and psychosis
- Recreational use of ketamine is now a global phenomenon

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Issues that Need to Be Addressed by Future Research

- Investigations to explore acute cardio respiratory problems especially when combined with other (stimulant) drugs are necessary for prevention and harm reduction initiatives with recreational users
- Investigating some of the relatively unique effects of ketamine, for example on semantic memory, may provide clues as to the neurochemical basis of memory
- As a research probe in the study of schizophrenia, ketamine has given increasing prominence to the role of glutamate in the aetiology of this illness. Further research should seek to unravel this role
- In relation to the cognitive effects of chronic ketamine use, future work should address the neuroanatomical and neurochemical correlates of such impairments
- Future research into the long term consequences of misuse might need to include investigation of social–psychological as well as physiological parameters
- Ketamine can be subjectively reinforcing to both healthy volunteers and drug users. The addiction potential of ketamine needs to be further explored
- Knowledge of the chronic use of ketamine is a priority as the drug has become a preferred choice for many
- Systematic research is required to investigate animal evidence that indicates ketamine, as a NMDA antagonist, may be a potent neurotoxin [1]

Medicinal Use

Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) developed by Parke Davis laboratories in 1962 (Figs. 15.1 and 15.2) is an anaesthetic derivative of phencyclidine (PCP).

Manufactured as a hydrochloride, ketamine has been utilized effectively in several areas of medicine including paediatrics, anaesthesia (pre-operative, emergency and high altitude) [2], dentistry, obstetrics, battle-zones [3] and in the management of neuropathic and cancer pain. It is one of those rare anaesthetic agents that does not cause hypotension and this benefit is used to best advantage in treating patients with serious trauma and hypovolemic shock [4]. Ketamine is also widely used in veterinary practice, particularly to sedate large uncooperative animals at a distance, for example in the case of free-ranging giraffes and gorillas [5, 6].

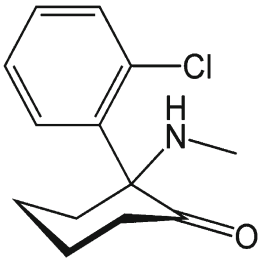

Fig. 15.1 Chemical structure of Ketamine (*RS*)-2-(2-chlorophenyl)-2-methylamino-cyclohexan-1-one)

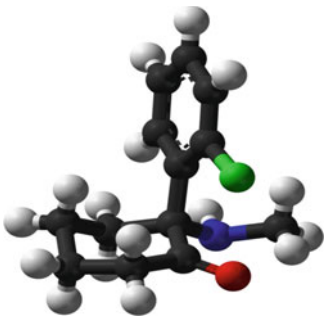

Fig. 15.2 Three dimentional structure of Ketamine (*RS*)-2-(2-chlorophenyl)-2-methylamino-cyclohexan-1-one); white balls-hydrogen atom; black balls-carbon atoms; red ball-oxygen atom; blue ball-nitrogen atom; green ball-chlorine atom

Clinical Disorders Research Use

The psychotogenic and cognitive effects of ketamine have led to the drug being used as a pharmacological model for studying transitory schizophrenic-thought disorder in normal subjects [7]. The state of dissociation achieved with ketamine are thought to mimic the phenomenology of schizophrenia [8] and reliably induce a psychosis like syndrome with cognitive, negative and positive features [9, 10] This has led to the so-called NMDA (*N*-methyl aspartate) hypothesis of schizophrenia [11] which has been the subject of debate for over 25 years [12]. Ketamine as with other drug models of clinical disorders only has partial validity, mimicking some but not other symptoms. For instance, acute ketamine administration is subjectively rewarding and produces euphoria, phenomena not often associated with the illness [13]. The similarity of the cognitive profile of an acute dose of ketamine with that observed in schizophrenia has been discussed in Fletcher and Honey's review [14]. According to the DSM-IV classification system a ketamine-induced psychosis would best fit the criteria for the disorganized or the undifferentiated subtype model of schizophrenia [15, 16].

Contemporary debate regarding the "ketamine (or NMDA-hypo function) model" of schizophrenia [17] has concerned itself with whether an acute dose of ketamine or chronic self-administration provides the better model of the cognitive deficits observed in schizophrenia in drug-naive volunteers.

There are evidence-based arguments for both models [18–20]. Although no work exists as yet to indicate whether NMDA-R up-regulation occurs in ketamine users, pre-clinical research seems to support this view [21] as do observations following repeated administration of the drug [22]. Meador-Woodruff and Healy [23] suggest that similar up-regulation occurs in schizophrenia. Thus, whilst not mimicking the aetiology or acute phases of the disorder, the ketamine-abusing population may still depict later functional changes.

Ketamine has been used as a probe to explore the potential clinical importance of NMDA receptor antagonism among the mechanisms underlying the subjective effects of ethanol in humans [24]. There is a growing body of research which indicates that alcohol acts in a similar way blocking glutamate effects at the NMDA receptor in a non-competitive and concentration dependent fashion at alcohol concentrations associated with alcohol intoxication (5–100 mmol/L) in man [25].

Ketamine has also been shown to attenuate the development of opioid tolerance and has been used as a research probe in studies of the modulation of opioid neurobiology [26]. Ketamine is thought to have a modulating effect on the analgesic (μ-opioid receptors) and dysphonic (kappa α-receptors) opioid receptors binding to these with one-tenth and one-fifth of its NMDA receptor affinity, respectively. The opioid antagonist Naloxone therefore has only a limited capacity to reverse the effects of ketamine and could not reverse key effects in vivo [27]. In animal models, ketamine and other NMDA antagonists such as methadone have been demonstrated to inhibit the development and acquisition of opioid dependence and tolerance [28], whilst small doses of ketamine have been shown to prevent tolerance developing acutely on repeated administration, of alfentanyl [29].

The use of ketamine as a research tool to study the pathophysiology of psychosis and as a screen to evaluate new drug action [29] has raised concerns in terms of the distress inflicted on patients. The potential for adverse events and the serious long-term effects that might be induced by the symptom-stimulating action of ketamine have led to the view that such use is unethical. Work to investigate the question of prolonged psychological effects as a result of the administration of ketamine in controlled experiments in the general population [30, 31] have however concluded that there was no evidence for long-lasting events nor increased distress [32, 33]. Safety aspects of the drug used in areas that do not permit these controls is, however, poorly researched.

Recreational Use

The recreational use of ketamine was first reported in 1971 in North America [34] linked by some to returning Vietnam veterans who may have been exposed to the drug on the battlefield [35, 36]. Intellectual hedonism popularized ketamine in the 1970s and 1980s, particularly in the United States and periodic reports of its misuse by healthcare professionals gradually appeared [37, 38]. This was followed by a growing number of reports of recreational use of the drug elsewhere, including in the United Kingdom [39, 40], Sweden [41] and Australia [42].

Ketamine use was linked to the gay dance scene during the early 1990s, with many users adhering to strict, carefully pre-planned, set and setting rituals [43, 44] emphasizing comfort and familiarity [45]. Its popularity as a recreational drug has continued to grow especially among UK dance and rave scene attendees. In a survey of club drug users in 1997, 32% reported having used ketamine [46]. A UK survey in 1999 reported a lifetime prevalence of use of 25% ($n=1{,}100$), half of which used in combination with ecstasy. Prevalence had increased to 35% in a similar population 1 year later [47] and to 43% in 2004 [48]. Other surveys in Australia reported an increase in "ever use" of ketamine from 6 to 15% between 1997 and 2001 [49, 50] and surveys of year-on-year trends have reported similar findings [51]. Knowledge of the drug has also grown: 31% of young people surveyed aged 11–14 and 50% of 15 year olds reported knowledge of ketamine [45] and 0.8% of 16–24 year olds responding to the British Crime Survey had used the drug [51].

Seizures of ketamine intended for non-medical use have increased over the last decade: in the US (Drug Enforcement Administration 2001) by more than 500% [52], whilst in Hong Kong in 2002, of all reported drug users under the age of 21, 59% were using ketamine (greater numbers than ecstasy) [53]. The use of ketamine as a street drug has been recognized by the authorities and in 2006 ketamine was registered as a scheduled drug in the UK. In North America, possession of ketamine without a prescription had become illegal in 1997, and was listed as a controlled drug (Schedule III) in 1999. Ketamine use has grown exponentially during the first decade of the new millennium [54] recreational use of the drug is now a global phenomenon.

Ketamine: Sought After Effects

Ketamine is most frequently misused for its psychedelic properties sometimes as a dance drug and sometimes to "explore the mind" [55]. Used for recreational purposes ketamine has been reported to be a collection of "paradoxes" and has many effects that are associated with other substances: "cannabis-like imagery", "alcohol-like intoxication", cocaine-like stimulation and opiate-like calming [56].

Ketamine Preparations/Route of Administration

Ketamine can be purchased for recreational use in a number of preparations but is used mainly in powdered or liquid form or crystalline powder for intranasal use (Fig. 15.3).

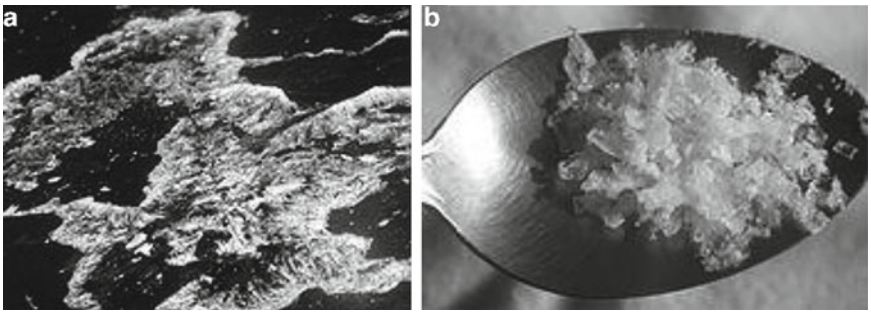

Fig. 15.3 Solution of ketamine from a 10 ml ampoule drying into crystals (**a**) and dried and scraped onto a spoon for intranasal use (**b**). Doses of 100–400 mg of the drug are usual [54]

Ketamine for non-medical use may be smuggled into a country from China and India where it is legally manufactured [57], purchased entirely from legitimate medical supplies [58], such as in Holland, Germany, France and Mexico [40] or diverted directly from hospitals and vetinary clinics. The illicit manufacture of ketamine is almost unknown because it is very difficult to synthesize. Although those selling the drug for non-medical use reportedly add various adulterants to make the drug go further. The particular brand of pharmaceutical ketamine may make a difference to drug effects beyond anecdotal reports. Ketalar contains a preservative (benzthonium chloride, an anticholinergic agent) that has a significant effect upon the brain and Astrapin's ketamine-500 contains the toxic organic preservative chlorobutanol, which has shown harmful effects in some animal experiments [59].

In powdered form (Fig. 15.4), ketamine's appearance is similar to that of cocaine and the drug can be insufflated, injected, or dissolved in beverages. It is an inexpensive drug and can be purchased in the UK for between £6.00 and £10.00 a gramme. It is also possible to smoke the drug in a joint or pipe, usually mixed with marijuana and tobacco [60]. The smoke has a distinctive bitter taste but the onset of effects sought after occurs much faster than when insufflated, ingested or injected intramuscularly.

Oral use usually requires more drug, but results in prolonged effects due to the production of the inactive metabolite nor-ketamine (see box below), which possesses sedating effects; this route of administration is unlikely to produce a dissociative state unless very high doses (>500 mg) are ingested [61]. Ketamine has also appeared as a constituent of tablets purporting to be ecstasy (special K), often in combination with drugs such as ephedrine.

The nasal route of administration of ketamine tends to be favoured with users, snorting or inhaling lines (50–400 mg) of a powdered formulation although ketamine has also been produced as an intranasal spray (Fig. 15.3). There are some reports of "freebasing" ketamine, produced by the removal of benzthonimum chloride and salts from Ketalar to achieve fewer unwanted side-effects.

Fig. 15.4 Ketamine hydrochloride (500 mg) powder [54]

There is wide variation in consumption patterns among users with tolerant and experienced consumers reporting use of 1 g or more of ketamine over the course of an evening/weekend. A standard street dose of ketamine in a Scottish study was found to be much lower typically around 125 mg (⅛g) [46], whilst recreational users with low tolerance will experience a mild "trippy" euphoria from a dose (a bump) of 10–30 mg.

Pharmacokinetics

Ketamine

- May be effectively administered medically by a number of routes (oral, intranasal, intravenous, intramuscular, intrathecal, intra-articular [62], transdermal [63], rectal [64] and subcutaneously) which all permit adequate absorption and excellent bioavailability [9].
- Intranasal use is common amongst recreational users, providing a rapid onset of action and an estimated duration of action of 2–3 h [65].
- Is rapidly distributed to highly perfused tissues (brain, heart and lungs).

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- Doses for intravenous analgesia are <1 mg/kg with oral doses being much higher (100–500 mg).
- Has a short half-life and elimination is variable depending upon the route of administration, but is generally of the order of 1–3 h [66].
- Ketamine is metabolized and eliminated from the body within 24 h.
- Effects following oral administration may be prolonged due to the presence of the active metabolite—nor-ketamine, with anaesthetic potency approaching one-third, that of the parent compound [67].
- Ketamine is mainly eliminated by hydroxylation as conjugated metabolites, with <4% appearing in urine as the parent compound or as nor-ketamine.

Optical Isomers of Ketamine

Ketamine is manufactured as a racemic mixture of two optical isomers (enantiomers), *S*(+)-ketamine and *R*(−)-ketamine [68], with *S*(+) ketamine being twice as potent an analgesic and a hypnotic as the racemic mixture (Fig. 15.5) [66].

The anaesthetic potency of *S*(+)-ketamine has been observed to be three times higher than *R*(−)-ketamine. Its higher anaesthetic potency and minor psychotomimetic side effects suggests *S*(+)-ketamine may have a better therapeutic efficacy when compared with the racemic form [68]. However, the likelihood of ketamine being formulated in its *S*(+) form is unlikely due to cost and difficulty of production.

Pharmacological differences exist between the enantiomers of ketamine against several targets (transporter proteins) of the drug [69]. In particular, it was found that *S*(+)-ketamine binds with a 4–5 times higher affinity to the phencyclidine (PCP) binding site of the NMDA receptor complex in the human brain than *R*(−)-ketamine [70]. It was also found that at sub-anaesthetic (recreational) doses, racemic ketamine has a weak affinity for the sigma receptor sites, whereas *S*(+)-ketamine binds only negligibly [71]. It has been speculated that the occurrence of psychotomimetic effects results from the higher affinity of *R*(−) ketamine to the sigma receptor site [72]. However, studies with *S*(+)-ketamine in healthy volunteers indicate that *S*(+)-ketamine is more likely to be associated with hallucinogenic effects than *R*(−)-Ketamine [73, 74]. This finding is conducive with the much higher affinity of *S*(+)-ketamine for the NMDA receptor.

Since psychotomimetic effects are generally considered to be caused by a relative excess of dopamine, it is possible to consider that stereo-selective inhibition of dopamine re-uptake might contribute to the ketamine-induced psychotomimetic effects. However, the inability of haloperidol to block these effects suggest other transmitters are involved [75] and would imply that nor-epinephrine and serotonergic systems are more strongly activated in those individuals who have greater *R*(−) ketamine activity. The over stimulation of nor-epinephrinergic and serotonergic pathways by *R*(−) ketamine may have a contributory role in the adverse effects observed in recreational users and in those who use the drug for non-medical purposes during ketamine-induced overdose. It has been postulated that the psychotomimetic and sympathomimetic effects of ketamine are thus mediated through this enhanced monoaminergic effect on the brain [25].

Neurochemical Effects

The activity of ketamine is complex with multiple actions at numerous receptor sites, particularly affecting glutaminergic and monoaminergic neurotransmission. The most significant pharmacological action of ketamine is the non-competitive antagonist binding at the cation channel of the NMDA receptor and consequent interference with excitatory amino acid transmitters—glutamate and aspartate [76, 77]. Not only thought to underlie its analgesic and dissociative effects, but action at the NMDA receptor is also thought to be important in its effects on memory. Antagonism at the NMDA receptor is thought to disrupt long-term potentiation and synaptic growth, which are crucial in the development of synaptic plasticity, learning and memory [78, 79]. Clinical studies also implicate glutamate in the mediation of the dissociative symptoms of ketamine with acute administration leading to a transient hyper-glutaminergic state [80]. Indeed the pre-administration of drugs that reduce glutamate release partly negate the perceptual disturbances seen with ketamine [81].

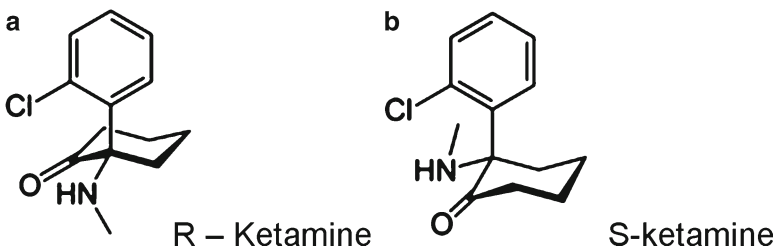

Fig. 15.5 Optical isomers of Ketamine [54] (**a**) *R*-Ketamine; (**b**) *S*-Ketamine

Research has begun to address the relationship between the modulation of other neurotransmitter systems by ketamine and its memory-impairing effects suggesting contributions of GABA-ergic and DA-ergic effects, in addition to the glutamatergic properties. Ketamine may then in part produce psychotomimetic effects through an increase in glutamate release that in turn acts on the AMPA subtype of glutamate receptor in the prefrontal cortex to induce a hyperdopaminergic state [82]. Ketamine can block excitotoxicity (brain damage due to low oxygen, low sugar, epilepsy, trauma, etc.) but it can also excite the brain at low doses by switching off the inhibitory system. Why this is not damaging in humans probably lies in the fact that ketamine binds to an increasingly wide range of different receptors: As the dose level rises some of these receptors act to shut down the excitement, by the time a potentially toxic dose is reached, the "excitement window" has been passed and the drug is starting to activate other systems that switch cells off again. Hence ketamine's promiscuity actually improves its safety [83].

Pharmacodynamics

Recreationally ketamine has been reported to have the advantage of being easy to administer: the clear dose response effect and relatively short half-life making the effects easier to titrate than LSD [36]. The spectrum of effects has been reported to be reflected in the different groups of users who choose ketamine for differing reasons. For instance, communal events where individual or small groups of users participate in sequential dosing over the evening are preferred by some and may well evoke different events to the over stimulation of a dance club venue [84].

Ketamine

- Produces anaesthesia at doses of 5–10 mg/kg (300–800 mg).
- With doses adequate to bring about anaesthesia, produces a *trance-like cataleptic state* with *amnesia*, without impairment of laryngeal and pharyngeal reflexes or depression of respiration or cardiac function [85].
- Is able to produce potent analgesia at sub-therapeutic concentrations.
- Produces dissociation at doses as low as 50–100 mg [2, 86] typically, eyes remain open with a disconnected stare: The recreational drug user may appear to be awake but is dissociated from the environment, *immobile* and *unresponsive to pain* [87].
- Use may cause *Nystagmus* but this is not universally experienced [54].
- Induces with doses >150 mg a dissociation commonly referred to as the "*K hole*"—described as detachment from one's physical body (depersonalization) [83], the external world (derealization) [88] and from one's immediate surroundings.
- Insufflated or injected may cause hallucinations lasting about 1 h and up to 2 h when ingested [89].
- Hallucinations following a low dose are only experienced with closed eyes and in a darkened room [90] but distortion of time and space is achieved with mild dissociative effects.
- Has a wide margin of safety in overdose [2, 44].
- Is somewhat unusual, almost acting as a partial antagonist with regard to brain reward enhancements; being stimulatory at low doses and inhibiting brain reward centres at higher doses.
- May produce problematic emergence phenomena and other unpleasant experiences. These appear maximal in early adolescence.

The characteristic most commonly associated with ketamine is the cerebral "dissociative" state following anaesthesia [86, 88]. It is the action at NMDA receptors that underlies these qualities inducing a functional and electrophysiological dissociation between the thalamoneocortical and limbic systems [75, 76]. This is potentially hazardous outside clinical settings with great risk of injuries being masked and the risk of accidents increased.

Low Dose Administration

Ketamine may initially be thought of as an odd choice of drug given its dissociating and immobilizing effects; however, the drug in fact produces a syndrome of effects in individuals who take sub-therapeutic doses in a recreational manner. Reactions to low sub-anaesthetic doses illustrated in a number of texts [91] describe disoriented perceptions and the total loss of an observer consciousness. However, immobility has been reported to be reduced by the concurrent use of amphetamine, or cocaine. The symptoms of low dose ketamine intoxication appear to be short-lived and in line with the pharmacokinetics of the drug. In a case series study of North American ketamine users, 18 of 20 patients were discharged from the Emergency Department within 5 h of presentation [69]. The commonest complaints in these were

symptoms of a stimulatory event (anxiety, chest pain and palpitations) with tachycardia being the most common finding following physical examination [92, 93].

The short duration of effect and rapid onset of action when taken by intranasal or intravenous routes often leads recreational users to administer repeated doses in order to maintain a desired psychoactive effect. The amnesic properties of the drug may make it difficult to remember the total number of doses consumed, increasing the likelihood of prolonged intoxication. Indeed the acute amnesic effects have been reported to be marked and subjects given ketamine under experimental conditions have struggled to describe their experience to researchers attempting to record the episode [94]. Johnston [95], who self-administered ketamine, reported "cycling into and out of awareness—a frightening experience".

In laboratory settings one-off sub-anaesthetic doses of ketamine have led to transient disruption of attentional performance, impaired performance on tests of vigilance, recognition memory, verbal fluency, working, and episodic memory. On tests of higher executive function such as the Wisconsin Card Sorting Test, ketamine use led to an increase in perseverative errors and preferentially disrupts delayed word recall, sparing immediate recall and post-distraction recall [10, 26, 96]. Dysfunction seen in episodic memory (personal life event) is of particular note, since this highly correlated with everyday memory difficulties [9, 97, 98].

Ketamine can leave the user in a confused state, since the principal physical dangers of most non-medical use are believed to arise mainly from the setting, or an interaction between the user and the setting [37, 40, 55]. This can result in falls (sometimes fatal), drowning, road traffic accidents and becoming a victim of crimes such as sexual assault [68, 99]. The likelihood of such incidences is enhanced when the drug is consumed unwittingly when it has been marketed under the guise of another drug such as ecstasy [100, 101] or as a spike in a beverage.

High Dose Administration

The perceptual and mood changes observed in those who have consumed ketamine are, as with other effects, highly sensitive to age, dose, route, previous experience (expectations, personality, motivation and mood) and setting (social, physical and emotional environment) [101–104]. The collective term for the myriad of experiences associated with the use of higher doses of ketamine is known as the "K hole" [105]. Users may feel as though their perceptions are located so deep inside the mind that the real world seems distant (hence the use of the word "hole" to describe the experience). Reported experiences are wide ranging and have included emergence and toxic effects such as out-of-body experiences, temporal and spatial distortion, a sense of floating, rebirthing and experiencing evolution, and sudden insights into the meaning of existence, as well as tactile and visual distortions and hallucinations [40, 55].

Sometimes the "K hole" can reproduce the features of a "near-death" experience, including buzzing/ringing/whistling sounds at the beginning, travel through a dark tunnel into light, at a high speed, with intense visions [106]. Users may experience worlds or dimensions that are ineffable, all the while being completely unaware of their individual identities or the external world [56, 87, 107]. Some users may not remember the "K-hole" experience after regaining consciousness, in the same way that a person may forget a dream. The "re-integration" process following intoxication is slow, and the user gradually becomes aware of surroundings. At first, users may not remember their own names, or even know that they are human, or what that means. Movement is extremely difficult, and a user may not be aware that he or she has a body at all.

Ketamine Dependence

Ketamine demonstrates reinforcing efficacy in animal self-administration models and is found to be a discriminative stimuli in operant tasks [108, 109], with the ability to release dopamine within the reward pathway [110]. Heavy habitual use has been described [111], and cases of dependence have been reported among anaesthetic staff [112, 113]. Heavy users report a rapid increase in tolerance with extended use and "a line" (when snorted) which might leave a naive user passed out may have no effect on a more experienced user. It is not known how long it takes to become dependent, or the risk factors that influence this eventuality.

Historical data on the long-term consequences of ketamine use has been difficult to collect due to limited access to those using ketamine as a drug of choice. Early reports in social users of ketamine record prolonged "psychic" phenomena occurring for periods of up to 1 year [1, 114] including "flashbacks", attentional dysfunction, anxiety, and decreased sociability following nasal, intravenous or intramuscular use of the drug [115]. However, flashbacks reported following repetitive use [65], may only be "a graininess of vision" under anxiety provoking circumstances [116]. Long-term users also reportedly experience stimulant-like weight loss and loss of appetite during periods of heavy use.

Chronic intravenous use by the American psychiatrist Lilly [117] led to several admissions for paranoid psychosis; self-reported attentional difficulties and social withdrawal. Employment problems have also been reported in survey respondents, linked to vagueness affecting work performance [48, 49]. Conversely, however, some report positive long-term effects such as chronic elevation in mood, and deeper

insights into one self and others [65]. Long-term users report "K-Pains" or "Ketamine cramps" the exact cause of these are unknown but seem to relate to extreme pain in the lower abdomen. Symptoms include an increased need to urinate, passing blood in urine, leakage of urine and pain on urination [118]. In a case study, Colebunders [119] found cystitis following recreational use of ketamine, and more recently abdominal pain and lower urinary tract symptoms were reported as common in ketamine users presenting at emergency departments in Hong Kong [120].

Overdose

The most frequent complications reported following ketamine overdose were severe agitation and rhabdomyolysis. In an Australian study, which surveyed 100 lifetime ketamine users, many reported regularly experiencing an inability to speak, blurred vision, lack of co-ordination and increased body temperature [48, 49]. It is reported that sequential dosing, variations in purity, intravenous route, tolerance and the amnesic effects of the drug (which may impair recall of total dose consumed) could result in acute episodes of paranoia, panic and psychosis [121]. A study of ketamine anaesthesia in over 300 subjects identified premorbid anosognosia and paranoia (as assessed with MMPI) as risk factors for experiencing psychotic disorders after ketamine administration [122].

Summary

Ketamine is a dissociative anaesthetic with a wide range of clinical applications and a wide margin of safety in overdose. The marked perceptual and cognitive psychedelic effects of ketamine have led to a global rise in prominence in the recreational drug scene. Somewhat complex in its pharmacology, ketamine effects are dose dependent and somewhat unusual, almost acting as a partial antagonist with regard to brain reward enhancements; being stimulatory at low doses and inhibiting brain reward centres at higher doses [1]. Acutely there is significant disturbance in semantic and episodic memory as well as in attention and higher executive functioning. Acute adverse psychological reactions may also occur and many regular users report "grainy" flashbacks following consumption of ketamine. Chronic use has been associated with acute cardio respiratory problems especially when combined with other (stimulant) drugs and may lead to accidental injury. Numbers involved in habitual use have grown significantly during recent years. Its future as a novel clinical and research tool is matched; it would appear, by its abuse potential outside medical settings.

References

1. Gardner EL. Brain reward mechanisms. In: Lowinson H, Ruiz P, Millman RB, Langrod JG, editors. Substance abuse: a comprehensive textbook. 3rd ed. Baltimore: Williams and Wilkins; 1996. p. 51–85.
2. Bishop RA, Litch JA, Stanton JM. Ketamine anesthesia at high altitude. High Alt Med Biol. 2000;1(2):111–4.
3. Cottingham R, Thomson K. Use of ketamine in prolonged entrapment. J Accid Emerg Med. 1994;11(3):189–91.
4. White PF, Way WL, Trevor AJ. Ketamine: its pharmacology and therapeutic uses. Anaesthesiology. 1982;56:1.
5. Bush M, Grobler DG, Raath JP, Phillips Jr LG, Stamper MA, Lance WR. Use of medetomidine and ketamine for immobilization of free-ranging giraffes. J Am Vet Med Assoc. 2001;218(2):245–9.
6. Vercruysse Jr J, Mortelmans J. The chemical restraint of apes and monkeys by means of phencyclidine or ketamine. Acta Zool Pathol Antverpiensia. 1978;70:211–20.
7. Hetem LA, Danion JM, Diemunsch P, Brandt C. Effect of a subanesthetic dose of ketamine on memory and conscious awareness in healthy volunteers. Psychopharmacology. 2001;22:59–72.
8. Giannini AJ. Drugs of abuse. 2nd ed. Los Angeles: Practice Management Information Company; 1997. ISBN 1-57066-053-0.
9. Newcomber JW, Farber NB, Jevtovic-Todorovic V, Selke G, Melson AK, Hershey T, Craft S, Olney JW. Ketamine induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neuropsychopharmacology. 1999;20:106–18.
10. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB, Charney DS. Subanaesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry. 1994;51(3):199–214.
11. Abi-Saab WM, D'Souza DC, Moghaddam B, Krystal JH. The NMDA antagonist model for schizophrenia: promise and pitfalls. Pharmacopsychiatry. 1998;31:104–9.
12. Carpenter WT. The schizophrenia ketamine challenge study debate. Biol Psychiatry. 1999;46(8):1081–91.
13. Morgan CAJ, Curran HJ. Acute and chronic effects of ketamine upon human memory: a review. Psychopharmacology. 2006;188:408–24.
14. Fletcher PC, Honey GD. Schizophrenia, ketamine and cannabis: evidence of overlapping memory deficits. Trends Cogn Sci. 2006;10:167–74.
15. Green MF. What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry. 1996;153:321–30.
16. Malhotra AK, Pinals DA, Caleb MA, Elman I, Clifton A, Pickar D, Breier A. Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. Neuropsychopharmacology. 1997;17:141–50.
17. Olney J, Labruyere J, Wang G, Wozniak D, Price MT, Sesma M. NMDA antagonist neurotoxicity: mechanism and prevention. Science. 1991;254:1515–8.
18. Harvey PD, Green MF, McGurk SR, Meltzer HY. Changes in cognitive functioning with risperidone and olanzapine treatment: a large-scale, double-blind, randomized study. Psychopharmacology. 2003;169:404–11.
19. Tamlyn D, McKenna PJ, Mortimer AM, Lund CE, Hammond S, Baddeley AD. Memory impairment in schizophrenia: its extent, affiliations and neuropsychological character. Psychol Med. 1992;22:101–15.

20. Saykin AJ, Gur RC, Gur RE, Mozeley PD, Mozeley LH, Resnick SM, Kester DB, Stafiniak P. Neuropsychological function in schizophrenia: selective impairment in memory and learning. Arch Gen Psychiatry. 1991;48:618–24.
21. Keilhoff G, Bernstein HG, Becker A, Grecksch G, Wolf G. Increased neurogenesis in a rat ketamine model of schizophrenia. Biol Psychiatry. 2004;56:317–22.
22. Feldman RS, Meyer JS, Quenzer LF. Principles of neuropsychopharmacology. Sunderland, MA: Sinauer; 1997.
23. Meador-Woodruff JH, Healy DJ. Glutamate receptor expression in schizophrenic brain. Brain Res Rev. 2000;31:288–94.
24. Rothman SM, Thurston JB, Hauhart RE, Clark GD, Soloman JS. Ketamine protects hippocampal neurons from anoxia in vitro. Neuroscience. 1987;21:673–8.
25. Meldrum B. Possible therapeutic applications for antagonists of excitatory amino acid neurotransmitters. Clin Sci. 1985;68: 113–22.
26. Sonsalla PK, Nicklas WJ, Heikkila RE. Role for excitatory amino acids in methamphetamine-induced nigrostriatal dopaminergic toxicity. Science. 1989;243(4889):398–400.
27. Krystal JH, Petrakis IL, Webb E, Cooney NL, Karper LP, Namanworth S, Stetson P, Trevisan LA, Charney DS. Dose-related ethanol-like effects of the NMDA antagonist, ketamine, in recently detoxified alcoholics. Arch Gen Psychiatry. 1998;55(4): 354–60.
28. Trujillo KA. The effects of non-competitive N-methyl-D-aspartate receptor antagonists on opiate tolerance and physical dependence. Neuropsychopharmacology. 1995;13(4):301–7.
29. Byrd LD, Standish LJ, Howell LL. Behavioral effects of phencyclidine and ketamine alone and in combination with other drugs. Eur J Pharmacol. 1987;144(3):331–41.
30. Kissin I, Bright CA, Bradley Jr EL. The effect of ketamine on opioid-induced acute tolerance: can it explain reduction of opioid consumption with ketamine-opioid analgesic combinations? Anaesth Analg. 2000;91(6):1483–8.
31. Lahti AC, Warfel D, Michaelidis T, Weiler MA, Frey K, Tamminga CA. Long-term outcome of patients who receive ketamine during research. Biol Psychiatry. 2001;49:869–75.
32. Hersack RA. Ketamine's psychological effects do not contraindicate its use based on a patient's occupation. Aviat Space Environ Med. 1994;65:1041–6.
33. Ishihara H, Kudo H, Murakawa T, Kudo A, Takahashi S, Matsuki A. Uneventful total intravenous anaesthesia with ketamine for schizophrenic surgical patients. Eur J Anaesthesiol. 1997;14: 47–51.
34. Carpenter WT. The schizophrenia ketamine challenge study debate. Biol Psychiatry. 1999;46:1081–91.
35. Lahti AC, Warfel D, Michaelidis T, Weiler MA, Frey K, Tamminga CA. Outcome of patients who receive ketamine. Biol Psychiatry. 2001;49:869–75.
36. Gboniem MM, Hinricks JV, Mewaldt SP, Peterson RC. Ketamine: behavioural effects of subanaesthetic doses. J Clin Psychopharmacol. 1985;5:70–7.
37. Dillon P, Copeland J, Jansen K. Patterns of use and harms associated with non-medical ketamine use. Drug Alcohol Depend. 2003;69:23–8.
38. Dotson JW, Ackerman DL, West LJ. Ketamine abuse. J Drug Issues. 1995;25:751–7.
39. Zinberg NE. The basis for controlled intoxicant use. New Haven: Yale University Press; 1984.
40. Jansen KL. Non medical use of ketamine. BMJ. 1993;306(6878): 601–2.
41. Jansen KLR. Ketamine: dreams and realities. Santa Cruz: Multi disciplinary Association for Psychedelic Studies; 2000.
42. Release. Release drugs and dance survey: an insight into the culture. London: Release; 1997 (Contact: Release, 388 Old Street, London EC1V 9LT, UK).
43. Skovmand K. Swedes alarmed at ketamine misuse. Lancet. 1996;348(9020):122.
44. White JM, Ryan CF. Pharmacological properties of ketamine. Drug Alcohol Rev. 1996;15(2):145–55.
45. Shapiro H. Ketamine fact sheet. London: Institute for the Study of Drug Dependence (ISDD); 1991.
46. Winstock AR, Griffiths P, Stewart D. Drugs and the dance music scene: a survey of current drug use patterns among a sample of dance music enthusiasts in the UK. Drug Alcohol Depend. 2001;64(1):9–17.
47. Mixmag. The Mixmag drug survey 2004: the world's biggest drug survey. London: Emap; 2004. p. 30–51.
48. Topp L, Hando J, Degenhardt L, Dillon P, Roche A, Solowiji N. Ecstasy use in Australia, Monograph Number 39. Sydney: National Drug and Alcohol Research Centre; 1998.
49. Topp L, Breen C, Kaye S, Darke S, NSW Party Drug Trends. Findings from the Illicit Drug Reporting System (IDRS), Technical Report Number 136. Sydney: National Drug and Alcohol Research Centre; 2001.
50. McCambridge J, Winstock A, Hunt N, Mitcheson L. 5-Year trends in use of hallucinogens and other adjunct drugs among UK dance drug users. Eur Addict Res. 2007;13(1):57–64.
51. Murphy R, Roe S. Drug misuse declared: findings from the 2006/2007 British Crime Survey. 2007. ISBN: 978-1-84726-541-8. http://www.homeoffice.gov.uk/rds/pdfs07/hosb1807.pdf.
52. Drug Enforcement Agency, Ketamine abuse increasing, February 4, 1997.
53. Gough N. Ketamine: China's other white powder. Time Asia. com. 2003. http://www.time.com/time/asia/covers/1101020520/ketamine.html.
54. Hansen G, Jenson SB, Chandresh L, Hilden T. The psychotropic effect of ketamine. J Psychoactive Drugs. 1988;20(4):419–25.
55. Jansen KL. A review of the nonmedical use of ketamine: use, users and consequences. Psychoactive Drugs. 2000; 32(4):419–33.
56. Tori SP. Ketamine abuse "Special K". Pennsylvania: Middle Atlantic-Great Lakes Organized Crime Law Enforcement Network (MAGLO-CLEN); 1996.
57. Winstock AR, Wolff K, Ramsey J. Ecstasy pill testing: harm minimisation gone too far? Addiction. 2001;96(8):1139–48.
58. Bohr N. On atoms and human knowledge. Daedalus. 1958;87(2): 53–61.
59. Muetzelfeldt L, Kamboj SK, Rees H, Taylor J, Morgan CJA, Curran HV. Journey through the K-hole: phenomenological aspects of ketamine use. Drug Alcohol Depend. 2008;95:219–29.
60. http://en.wikipedia.org/wiki/Ketamine. Wikipedia, the free encyclopedia. Accessed 23 April 2009.
61. Dalgarno PJ, Shewan D. Illicit use of ketamine in Scotland. J Psychoactive Drugs. 1996;28(2):191–9.
62. Huang GS, Yeh CC, Kong SS, Lin TC, Ho ST. Wong Intra-articular ketamine for pain control following arthroscopic knee surgery. Acta Anaesthesiol. 2000;152(3):283–8.
63. Azevedo VM, Lauretti GR, Pereira NL, Reiss MP. Transdermal ketamine as an adjuvant for post operative analgesia after abdominal gynecological surgery using lidocaine epidural blockade. Anesth Analg. 2000;91(6):1479–82.
64. Marhofer P, Freitag H, Hochtl A, Greher M, Erlacher W, Semsroth M. S(+)-Ketamine for rectal premedication in children. Anesth Analg. 2001;92(1):62–5.
65. Siegel RK. Phencyclidine and ketamine intoxication: a study of four populations of recreational users. In: Peterson RC, Stillman RC, editors. Phencyclidine abuse: an appraisal. Rockville: National Institute on Drug Abuse; 1978.
66. Kienbaum P, Heuter T, Pavlakovic G, Michel MC, Peters J. S(+)-ketamine increases muscle sympathetic activity and maintains the neural response to hypotensive challenges in humans. Anesthesiology. 2001;94(2):252–8.

67. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of MI and oral ketamine. Br J Anaesth. 1981;53: 805–10.
68. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. Can J Anesth. 1989;36(2):186–97.
69. Weiner AL, Vieria L, McKay CA, Bayer MJ. Ketamine abusers presenting to the Emergency Department: a case series. J Emerg Med. 2000;18(4):447–51.
70. Doenicke A, Kugler J, Mayer M, Angster R, Hoffman P. Influence of racemic ketamine and S-(+) – ketamine on vigilance, performance and wellbeing. Anaesthestist. 1992;41:610–8.
71. Oye I, Paulsen O, Maurset A. Effects of ketamine on sensory perception: evidence for a role of N-methyl-D-aspartate receptors. J Pharmacol Exp Ther. 1992;260(3):1209–13.
72. Zeilhofer HU, Swandulla D, Geisslinger G, Brune K. Differential effects of ketamine enantiomers on NMDA receptor currents in cultured neurons. Eur J Pharmacol. 1992;213:155–8.
73. Engelhardt W. Recovery and psychic emergence reactions after S-(+)-ketamine. Anaesthesist. 1997(Suppl 1);46:538–42.
74. Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J. Differential psychopathology and patterns of cerebral glucose utilization produced by (s)- and (R) – ketamine in healthy volunteers using positron emission tomography (PET). Eur Neuropsychopharmacol. 1997;7:25–38.
75. Øye I, Hustveit O, Maurset A, Ratti Moberg E, Paulsen O, Skoglund LA. Thc chiral forms of ketamine as probes for NMDA-receptor function in humans. In: Kameyama T, Nabeshima T, Domino EF, editors. NMDA receptor related agents: biochemistry, pharmacology and behavior. Ann Arbor: NPP Books; 1991. p. 381–9.
76. Fagg GE. Phencyclidine and related drugs bind to the activated NMDA receptor channel complex in rat brain membranes. Neurosci Lett. 1987;76:221–9.
77. Anis NA, Berry SC, Burton NR, Lodge D. The dissociative anaesthetics ketamine and phencyclidine selectively reduce excitation of central mammalian neurons by N-methyl-D-Aspartate. Br J Pharmacol. 1983;79:565–75.
78. Morris RGM, Anderson E, Lynch GS, Baudry M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist. AP5. Nature. 1986;319:774–6.
79. Lynch G, Baudry M. The biochemistry of memory: a new and specific hypothesis. Science. 1984;224:1057–63.
80. Cotman CW, Monaghan DT. Excitatory amino acid neurotransmission: NMDA receptors and Hebb-type synaptic plasticity. Annu Rev Neurosci. 1988;11:60–80.
81. Chambers RA, Bremner JD, Moghaddam B, Southwick SM, Charney DS, Krystal JH. Glutamate and post-traumatic stress disorder: toward a psychobiology of dissociation. Semin Clin Neuropsychiatry. 1999;4(4):274–81.
82. Anand A, Charney DS, Oren DA, Berman RM, Hu XS, Cappiello A, Krystal JH. Attenuation of the neuropsychiatric effects of ketamine with lamotrigine: support for hyperglutamatergic effects of N-methyl-D- aspartate receptor antagonists. Arch Gen Psychiatry. 2000;57(3):270–6.
83. Moghaddam B, Adams B, Verma A, Daly A. Activation of glutaminergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to doperminergic and cognitive disruptions associations with the prefrontal cortex. J Neurosci. 1997;17:2921–7.
84. Stone JM, Erlandsson K, Arstad E, Bressan RA, Squassante L, Teneggi V, Ell PJ, Pilowsky LS. Ketamine displaces the novel NMDA receptor SPET probe [(123)I]CNS-1261 in humans in vivo. Nucl Med Biol. 2006;33:239–43.
85. Wolff K, Winstock. Ketamine: from medicine to misuse. Rev CNS Drugs. 2006;20:199–218.
86. Dillon P, Copeland J, Jansen K. Patterns of use and harms associated with non-medical ketamine use. Drug Alcohol Depend. 2003;69:23–8.
87. Leary T, Sirius RU. Design for dying. London: Thorsons/Harper Collins; 1997.
88. Adams HA, Thiel A, Jung A, Fengler G, Hempelman G. Effects of S-(=)-ketamine on the endocrine and cardiovascular parameters. Recovery and psychomimetic reactions in volunteers. Anaesthesist. 1992;41:558–96.
89. Jevtovic-Todorovic V, Todorovic SM, Mennerick S, Powell S, Dikranian K, Benshoff N, Zorumsk CF, Olney JW. Nitrous Oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nat Med. 1998;4:460–3.
90. Grinspoon L, Bakalar JB. The major psychedelic drugs: sources and effects. Chap 2. New York: Basic Books; 1981. p. 32–6.
91. Giannini AJ, Loiselle RH, Giannini MC, Price WA. Phencyclidine and the dissociatives. Med Psychiatry. 1987;3(3):197–204.
92. Stafford P. Contrasting profiles. In: Stafford P, editor. Psychedelics encyclopedia. 3rd ed. Berkeley, CA: Ronin; 1991. p. 392–5.
93. Gill JR, Stajic M. Ketamine in non-hospital and hospital deaths in New York City. J Forensic Sci. 2000;45(3):655–8.
94. Baer G, Parkas P. Ketamine-induced psychopathological changes in normal volunteers during conditions used for experimental psychoses (author's transl). Anaesthesist. 1981;30(5):251–6.
95. Johnston REA. Ketamine trip. Anaesthesiology. 1973;39:460–1 (Clinical workshop, Letter to Editor).
96. Malhotra AK, Pinals DA, Weingartner H, Sirocco K, Missar CD, Pickar D, Breier A. NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. Neuropsychopharmacology. 1996;16:120–25.
97. Green SM, Johnson NE. Ketamine sedation for pediatric procedures: part 2, review and implications. Ann Emerg Med. 1990;19:1033–46.
98. Ghonheim MM, Hinrichs JV, Mewaldt SP, Peterson RC. Ketamine: behavioural effects of subanaesthetic doses. J Clin Psychopharmacol. 1985;5:70–7.
99. Merle R. "Special-K" is latest US drug fad. The Seattle Times, 1997, June 20.
100. Hansen G, Jenson SB, Chandresh L, Hilden T. The psychotropic effect of ketamine. J Psychoactive Drugs. 1988;20(4):419–25.
101. Wolff K, Hay AWM, Sherlock K, Conner M. Contents of Ecstasy. Lancet. 1996;346:1100–1.
102. Ahmed SN, Petchkovsky L. Abuse of ketamine. Br J Psychiatry. 1980;137:303.
103. Curran HV, Morgan C. Cognitive dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. Addiction. 2000;95(4):575–90.
104. Curran HV, Monaghan L. In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. Addiction. 2001;96(5):749–60.
105. Smith GS, Schloesser R, Brodie JD, Dewey SL, Logan J, Vitkuns SA, Simkovitz P, Hurley A, Cooper T, Volkow ND, Cancro R. Glutamate modulation of dopamine measured in vivo with positron emission tomography (PET) and 11-raclopride in normal human subjects. Neuropsychopharmacology. 1998;18:18–25.
106. Klein M, Calderon S, Hayes B. Abuse liability assessment of neuro-protectants. Ann NY Acad Sci. 1999;890:515–2.
107. Beardsley PM, Balster RL. Behavioral dependence upon phencyclidine and ketamine in the rat. J Pharmacol Exp Ther. 1987;242(1):203–112.
108. Jansen KL. Ketamine–can chronic use impair memory? Int J Addict. 1990;25(2):133–9.
109. Kamaya H, Krishna PR. Ketamine addiction. Anesthesiology. 1987;67(5):861–2.
110. Hurt PH, Ritchie EC. A case of ketamine dependence. Am J Psychiatry. 1994;151(5):779.

111. Moore NN, Bostwick JM. Ketamine dependence in anesthesia providers. Psychosomatics. 1999;40(4):356–9.
112. Steen PA, Michenfelder JD. Neurotoxicity of anesthetics. Anesthesiology. 1997;50:437.
113. Schorn TOF, Whitwam JG. Are there long term effects of ketamine on the central nervous system? Br J Anaesth. 1980;52:967–8.
114. Siegal RK. Phenocyclidine and ketamine intoxication a study of 4 populations of recreational users. Natl Inst Drug Abuse Res Monogr Ser. 1978;21:110–9.
115. Lilly JC. The scientist: a novel autobiography. New York: J.B. Lippincott; 1978.
116. Adler CM, Goldbert TE, Malhotra AU, Pickar D, Breir A. Effects of ketamine on thought disorder, working memory and semantic memory in healthy volunteers. Biol Psychiatry. 1998;43:811–6.
117. Albin M, Dresner J, Paolin A, Sweet R, Virtue R, Miller G. Long-term personality evaluation in patients subjected to ketamine hydrochloride and other anaesthetic agents. Pharmacology: Abstracts of Scientific Papers. American Society of Anesthesiologists Annual Meeting, 1970. p. 166.
118. Cottrell AM, Athreeres R, Weinstock P, Warren K, Gillatt D. An emerging problem: urinary tract disease associated with chronic ketamine use. BMJ. 2008;336(7651):973. doi:10.1136/bmj.39562.711713.80.
119. Colebunders B, Van Erps P. Cystitis due to the use of ketamine as a recreational drug: a case report. J Med Case Rep. 2008;2:219. doi:10.1186/1752-1947-2-219.
120. Ng SH, Tse ML, Ng HW, Lau FL. Emergency department presentation of ketamine abusers in Honmg Kong: a review of 233 cases. Hong Kong Med J. 2010;16:6–11.
121. Lily JC. The scientist: a novel autobiography. New York: J.B Lippincott; 1978.
122. Melkonian DL, Meschcheriakov AV. Possibility of predicting and preventing psychotic disorders during ketamine anesthesia. Anesteziol Reanimatol. 1989;3:15–8.