Review

A REVIEW OF KETAMINE ABUSE AND DIVERSION

Sean Sassano-Higgins, M.D.,[1,2]* Dave Baron, D.O.,[1,2] Grace Juarez, M.D.,[1,2] Neevon Esmaili, M.D.,[2] and Mark Gold, M.D.[3]

Ketamine was discovered in the 1960s and released for public use in 1970. Originally developed as a safer alternative to phencyclidine, ketamine is primarily used in clinical settings for analgesia and sedation. In recent years, other uses have been developed, including pain management and treatment of asthma and depression. Clinical use of ketamine causes dissociation and emergence delirium. These effects have led to recreational abuse. Although death from direct pharmacologic effects appears rare, the disinhibition and altered sensory perceptions caused by ketamine puts users at risk of environmental harm. Ketamine has also been implicated in nonconsensual sexual intercourse. Data continue to build that chronic ketamine use may lead to morbidity. Impairment of memory and persistent dissociative, depressive, and delusional thinking has also been reported with long-term use. Lower urinary tract symptoms, including cystitis have been described. Gastric and hepatic pathology have also been noted, including abnormal liver function tests, choledochal cysts and dilations of the common bile duct. S-ketamine, an enantiomer in racemic ketamine, has been shown to be hepatotoxic in vitro. Abstinence from ketamine may reduce the adverse effects of chronic use and is considered the mainstay of treatment. Specialized urine drug testing may be required to detect use, as not all point of care urine drug screens include ketamine. Depression and Anxiety 33:718–727, 2016.

Key words: ***ketamine; delirium; depression; phencyclidine; substance-related disorders; dissociative disorders***

INTRODUCTION

Ketamine, an arylcycloalkylamine with the chemical formula of 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone, was originally developed as an anesthetic agent in 1962 and was released for public use in 1970.[1] Ketamine is a derivative of phencyclidine (PCP), and due to potential for abuse, became a Schedule III controlled substance in 1999. Low dosage use produces changes in mood, body image, and hallucination. The purpose of this paper is to review the pharmacology, therapeutic use, adverse effects, and recreational abuse of ketamine.

Ketamine is a dissociative anesthetic. The term dissociation was originally used in reference to the drug's effective disconnection of the thalamo-neocortical and limbic systems.[2,3] However, dissociation has now become a term used to describe the feeling of disconnect of the mind from the body in those administered the drug.[4,5]

Ketamine is approved by the United States Food and Drug Administration for the induction and maintenance of anesthesia. Ketamine induces analgesia, sedation, and amnesia, but has minimal impact on the cardiovascular or pulmonary system.[6] In clinical settings, ketamine is usually administered by intravenous or intramuscular injection, and is a useful medication in surgical procedures

[1]Department of Psychiatry, University of Southern California, Los Angeles, California
[2]Rivermend Health, Atlanta, Georgia
[3]Rivermend Health Scientific Advisory Board, Atlanta, Georgia

*Correspondence to: Sean Sassano-Higgins, Department of Psychiatry, University of Southern California, 1520 San Pablo St., Suite 1652, Los Angeles, CA 90033.
E-mail: Sean.sassano-higgins@med.usc.edu
Received for publication 16 October 2015; Revised 16 May 2016; Accepted 20 May 2016

DOI 10.1002/da.22536
Published online 22 June 2016 in Wiley Online Library (wileyonlinelibrary.com).

or for analgesia when cardiovascular or pulmonary concerns are present.[2,3,7] Ketamine has also been used as a preoperative agent for anxiety reduction and to facilitate induction of general anesthesia in various procedures.[8,9] Unlike other medications used for pain and sedation (e.g., opiates or benzodiazepines), once the dissociative threshold is reached, administration of additional ketamine typically does not lead to further sedation,[10,11] although death has been known to occur at very high doses.[12] Dissociation from ketamine typically appears in adults at single doses of 1–1.5 mg/kg intravenously or 4–5 mg/kg intramuscularly.[13]

One of the main factors limiting clinical use of ketamine is an emergence delirium, consisting of hallucinations and an altered sensory state.[14] This symptom constellation was reported during the first human volunteer trial,[15] and the incidence of emergence delirium may be as high as 30%.[13] Use of benzodiazepines has been shown to reduce the emergence reaction.[16] Transient diplopia secondary to rotary nystagmus, as well as transient blindness, have also been reported as adverse effects of clinical use of ketamine.[17]

Recreational misuse of ketamine began in approximately 1971,[18] with increased reports in the 1990s.[19,20] Recreational use started in the United States and then spread to international locations, largely following the "rave" culture.[1,5,21] Ketamine abuse rose to prominence in the 1980s as a "club drug" and also due to use in drug-facilitated sexual assault.[22] Street names for ketamine include, among others, special K, jet, cat valium, vitamin K, K-hole, Kit Kat, and liquid E.

The emergence delirium that limits the clinical use of ketamine is the same effect that has led to recreational misuse. In subanesthetic doses, ketamine causes an altered "psychedelic" state of mind, resembling schizophrenic psychosis.[23,24] Psychoactive effects of ketamine include hallucinations, synesthesia, pronounced derealization and depersonalization, alterations in bodily perceptions, impairments in proprioception, and preoccupation with unimportant sounds.[25] At higher doses, users may become "lost in the K-hole," a term used to label the pronounced depersonalization "out of body" experience, involving a loss of sense of space and time. The recreational user may experience the undesirable effects of anxiety, impaired memory, poor attention, impaired verbal fluency and perseveration, emotional withdrawal, disorganized speech, slurred speech, blunted affect, paranoia, ideas of reference, and unusual thought content.[26–29] Chest pain, palpitations, tachycardia, temporary paralysis, and blurred vision have also been known to occur with recreational use.[30,31]

Ketamine was initially only obtainable in the commercially available aqueous (injectable) form, but is now available illicitly in capsules, powder, crystals, and tablets.[21] Tablets have been found to contain several adulterants: pseudoephedrine, caffeine, amphetamine/methamphetamine, and 3,4-Methylenedioxymethamphetamine (MDMA).[32] Ketamine is also an occasional adulterant of MDMA.[33] Recreational ketamine use is commonly part of polysubstance use, and ketamine is often taken together with other club drugs, alcohol, and/or stimulants.[34]

According to the Drug Enforcement Agency (DEA), ketamine powder is usually snorted, smoked, or added to a beverage, while liquid ketamine is injected, applied to a smokeable material or consumed in drinks. The most popular method of recreational ketamine use is insufflation of the powder form,[35] which is produced by dehydrating ketamine solution. The prevalence of recreational use of ketamine worldwide is unknown, but studies suggest a lifetime incidence ranging from 0.1% in the United States to 4% in the United Kingdom.[36–39]

KETAMINE PHARMACOKINETICS AND ROUTES OF ADMINISTRATION

The intravenous, intramuscular, nasal, and oral route of ketamine administration all lead to fairly rapid absorption.[3,40] Intravenous administration of ketamine results in an onset of action within 30 s. Intramuscular administration of ketamine results in a similar onset of action, and has a bioavailability that may be as high as 90%.[41] Intranasal use of ketamine is common among recreational users, and this route is associated with a rapid onset of action.[18] Nasal administration bioavailability is approximately 50%.[42]

Onset of effect is much slower with oral administration, with plasma concentrations becoming detectable approximately 30 min after administration.[43] Peak plasma concentration is estimated to be 20% of that observed with equivalent doses administered intramuscularly.[26] Bioavailability is low with oral administration (20%), primarily due to extensive first pass metabolism.[43,44] There is individual variability in the oral absorption of ketamine, which can lead to poor anesthesia when used therapeutically and adverse effects when used recreationally.[45]

Ketamine is predominantly eliminated by liver metabolism and elimination half-life is approximately 2.5 hr.[46] Ketamine is highly lipid soluble, and has a short distribution half-life of 10 min,[46] as it is quickly distributed to areas with high blood perfusion, such as the brain.[3] Ketamine is metabolized by cytochrome P450 CYP2B6 and the majority is eliminated from the body within 24 hr. However, active metabolites exist and may cause prolonged effects.[47,48]

KETAMINE PHARMACODYNAMICS

Ketamine is a noncompetitive antagonist of the NMDA glutamate receptor. The NMDA receptor mediates sensory input at the spinal, thalamic, and cortical levels, and moderates emotional responses, learning, and memory.[7] Dopamine, norepinephrine and serotonin levels may also be increased by ketamine.[49,50] The analgesic effects of ketamine appear to be, at least in part,

mediated through opioid receptor agonism,[51] and a state of cross-tolerance to morphine in an animal model has been demonstrated.[52] Norketamine, the main metabolite of ketamine, may play a large role in analgesia and the antagonism of the NMDA receptor.[53]

Effects of recreational ketamine use appear to be influenced by age, route of administration, setting, and previous experiences with ketamine.[54–56] Stimulant effects are present at low doses, with psychedelic effects occurring as the dose escalates.[57]

Ketamine is a mild respiratory depressant. However, at recreational doses, it is unusual for respiratory effects to occur. Although effects on the cardiovascular system are minimal with clinical doses, at doses used by recreational users, ketamine may increase heart rate, cardiac output, and blood pressure.[3] Tachycardia is the most common presenting sign in ER visits by recreational users,[30] and the stimulatory effects on the cardiovascular system may have implications for recreational users with cardiac issues or hypertension.

The risk of death from ketamine overdose is low, as ketamine has a wide therapeutic range. The median lethal dose (LD50) in animals is 100 times the average therapeutic intravenous dose.[58] The main concern with acute ketamine use is the reduction of the user's awareness and monitoring of their physical environment.[19] Ketamine causes perseverative errors and word recall, indicating disruptions in executive functioning.[23,27] Worsening the risk of accidental harm is the lack of coordination, temporary paralysis, and blurred vision associated with recreational ketamine use.[59] Traffic accidents, drowning, and hypothermia through prolonged environmental exposure are noted as potential causes of harm to users.[5]

KETAMINE FOR DEPRESSION IN COMPARISON TO ABUSE

For the treatment of depression, the intranasal, intravenous, intramuscular, and oral routes of ketamine administration have been utilized.[60–75] Administration via these routes has been shown to be safe and well tolerated in clinical settings. Repeated ketamine infusions have also been used safely for the treatment of depression in clinical settings,[64–69] however, the safety of chronic therapeutic use remains somewhat unclear. A review of the typical dose of ketamine for the treatment of depression is presented below to provide a comparison with the doses used in abuse.

Most studies have focused on a single 0.5 mg/kg infusion of ketamine (e.g.,[70]). These studies have found a rapid, although transient, antidepressant response. Use of multiple infusions of ketamine has been examined as a potential strategy to sustain the antidepressant response. The most common schedule of multiple intravenous administrations involves 0.5 mg/kg of ketamine infused over 40 min, three times per week (Monday, Wednesday, and Friday), for a total of six administrations. This strategy has demonstrated rapid reduction of depressive symptoms (e.g.,[65]). However, the antidepressant effect appears to diminish shortly after discontinuation of infusions.

Case reports found two intramuscular doses of 0.5 mg/kg of ketamine, administered 3 days apart, resulted in rapid improvement of depression, although it is unclear how long these effects were maintained.[71]

A case report of intranasal administration involved 4 months of twice-weekly administration of ketamine 50 mg.[73] Depressive symptoms were reported to improve by day 3, and were sustained during the course of treatment.

A 14-day trial of oral S-ketamine 1.25 mg/kg as an augmenting strategy for concurrent antidepressant therapy showed potential benefit in a case series of four patients.[75]

When used for the treatment of depression, adverse effects appear minimal, but generally include dizziness, blurred vision, headache, nausea vomiting, dry mouth, poor coordination, poor concentration, restlessness, and dissociation.[70] More serious adverse effects of hypertension, tachycardia, and asymptomatic premature ventricular contractions,[70,74] as well as bradycardia and hypotension[74] have been reported.

The mechanism of antidepressant response with ketamine does not appear to be solely due to its sedative effect, as ketamine was found to outperform midazolam for treatment-resistant depression.[70] It has been suggested the dissociative effects of ketamine may mediate antidepressant response. Higher levels of dissociation during ketamine administration have been associated with improvement in depressive symptoms.[76] The "mystical" effects of ketamine may also mediate ketamine efficacy for cessation of cocaine use.[77] It has also been hypothesized that restoration of neural networks may be responsible for the efficacy of ketamine for treatment of cocaine dependence.[78]

When ketamine is used recreationally, intranasal insufflation appears to be the most common route, but the intravenous, subcutaneous, intramuscular, and oral route (often in combination with other substances such as LSD or methamphetamine) are also frequently used.[30,59] Doses of ketamine administered in abuse are significantly higher than those used in depression. When abused, ketamine doses appear to typically range from 100 to 200 mg per dose, with abusers often using multiple doses in a single day to extend intoxication.[30,56,59] It is important to note that oral and intramuscular use of ketamine results in unpredictable serum levels,[61] which has possible implications for overdose in recreational use.

OTHER THERAPEUTIC USES OF KETAMINE

PAIN

As stated earlier, ketamine has use as a dissociative anesthetic, with a major advantage being lack of

respiratory suppression. Ketamine administration may reduce the need for opioids in patients with musculoskeletal trauma and improve chronic pain symptoms.[79] However, the long-term tolerability and efficacy of ketamine is not well known.[80] Dose-dependent adverse effects of ketamine in short-term use for pain include hallucinations, nightmares, and visual disturbances.[79] Ketamine may be particularly useful in cases of comorbid depression and pain.[81]

PERIOPERATIVE SEDATION

Ketamine is often used for procedural sedation in children and adults. Nausea, hypertension, and tachycardia are the most common side effects.[82,83] Ketamine administered preoperatively has analgesic effects that outlast the duration of procedural sedation, which is associated with reduced postsurgical pain.[79] Perioperative use of ketamine is associated with less pain postsurgery, but is not routinely recommended.[79,84] Case reports of ketamine abuse in anesthesiologists exist, although the actual incidence of abuse in this group is unknown.[85,86]

ASTHMA

Ketamine has bronchodilator properties and may have applications for use in asthma. The use of ketamine in asthma remains controversial due to the lack of studies supporting its use, but may have utility in status asthmaticus cases unresponsive to conventional first-line agents.[87] Ketamine has been safely used as an anesthetic agent intraoperatively and postoperatively for analgesia and sedation in asthma patients.[87]

LONG-TERM EFFECTS OF KETAMINE USE

COGNITIVE DEFICITS

The sequelae of long-term ketamine use are unclear, but appear to include schizophrenia-like symptoms of cognitive impairment in working memory and long- and short-term memory.[88,89] Persistent dissociative, depressive, and delusional thinking have also been reported with long-term use.[88,89]

TOXICITY TO THE URINARY SYSTEM

Studies have reported lower urinary tract symptoms in approximately a third of chronic ketamine users.[90–94] Specific symptoms include dysuria, suprapubic pain, and painful hematuria. The first report of these symptoms was described in a 2007 case series of nine ketamine-dependent patients who exhibited urinary frequency and urgency, dysuria, hematuria, and urge incontinence.[95] Computed tomography imaging of the bladder was performed on one patient in this case series, with the finding of severe bladder inflammation. Cystoscopy of all nine patients showed severe ulcerative cystitis. Seven patients were administered pentosan polysulfate, a medication to supplement the gylcosamnioglycan layer of the bladder, which was associated with improvement of symptoms. Abstinence from ketamine was also associated with improvement of symptoms.

The exact mechanism as to how ketamine causes bladder injury is unknown. These symptoms are possibly explained by ulcerative cystitis[95] and/or obstructive nephropathy.[96] It is possible that the pathophysiology of ketamine cystitis is more complex and may involve several pathways, including direct toxic damage to the cells of the bladder, bladder wall barrier dysfunction, neurogenic inflammation, IgE-mediated inflammation and hypersensitivity, carcinogenesis, cell apoptosis, and nitric oxide synthase-cyclooxygenase mediated inflammation.[97] Adulterants of recreational ketamine have also been hypothesized as causes of cystitis.[95]

Despite increasing knowledge regarding ketamine's effect on the urinary tract, the treatment of ketamine cystitis largely focuses on symptom management. The consensus is the treatment most effective is cessation of ketamine use, which is recommended as the first-line strategy.[97–99] However, some damage appears irreversible with abstinence alone, including collagen accumulation, contraction in the bladder, thickened bladder walls, and hydronephrosis.[100] Treatment with anticholinergics, urothelium protective agents, non-steroidal anti-inflammatory drugs, steroids, and botulinum injections could be helpful in preventing further disease progression for these patients.[98] Surgical interventions for more advanced cases are indicated, particularly cases involving damage to the ureters and kidneys.[100]

TOXICITY TO THE GASTROINTESTINAL SYSTEM

Regular ketamine use is associated a phenomenon known as "K cramps," consisting of symptoms ranging from vague abdominal pain[5] to intense, colicky abdominal pain.[98,101] The etiology is unknown, but gastric and hepatic pathology have been noted, along with abnormal liver function tests, choledochal cysts, and dilations of the common bile duct.[96,102–105] Heavy ketamine users may perpetuate symptoms by ingestion of additional ketamine to alleviate abdominal pain. S-ketamine, an enantiomer in racemic ketamine, has been shown to be hepatotoxic in vitro.[102]

In a large study of emergency department presentation of ketamine users in Hong Kong, 21% of users reported abdominal pain as one of their symptoms, with 16% exhibiting abnormal liver function laboratory results.[101] In another study, ketamine-related fusiform dilation of the common bile duct was found on imaging in 18 out of 26 patients (69%). The degree of dilation of the common bile duct was positively correlated with duration of ketamine abuse.[106] Ketamine may adversely affect the liver by direct toxicity to parenchymal cells, resulting in bile duct damage.[107] Impairment of the smooth muscle

of the sphincter of Oddi may also be responsible for bile duct dilation.[107] Cessation of ketamine use potentially reverses the bile duct and liver injury in these patients.[98]

NEUROBIOLOGY OF KETAMINE REINFORCING EFFECTS

It is unclear why dissociative substances are addictive. Animals will self-administer ketamine,[108] as well as other NMDA antagonists, such as PCP[109] and dextromethorphan.[110] The pleasant sensations resulting from the dissociative effects of ketamine may be the primary mechanism through which ketamine reinforces use. It is also plausible that, in those with negative emotional states, ketamine may be reinforcing by providing a temporary relief.[7]

Dopamine activity is increased with ketamine administration.[111–113] The exact mechanism of dopaminergic effects of ketamine is unknown, but may be due to release of dopamine from storage sites.[114] This dopaminergic effect may be responsible, at least in part, for the euphoric and addictive potential of ketamine.

Several studies indicate that opioid receptors are also involved in the pharmacological effects of ketamine.[115] As discussed earlier, the analgesic effect of ketamine may largely be attributed to agonism of mu opioid receptors,[51] which is also the receptor believed to be responsible for the reinforcing effects of opiates. The NMDA system has been found to have strong interactions with the opioid system in animal models,[116] and potentially has a role in preventing opiate withdrawal. This suggests ketamine users may continue administration to prevent symptoms of withdrawal.[117]

KETAMINE TOLERANCE AND DEPENDENCE

Ketamine tolerance has been demonstrated in animals[118,119] and humans,[120] and is evidenced by the need to administer increasing amounts to achieve the same effect.[121,122] Ketamine tolerance may be due to induction of liver enzymes[89] and neuronal adaptations resulting in decreases in sensitivity.[98]

WITHDRAWAL

There is limited evidence for a specific physiological withdrawal syndrome after cessation of ketamine use, and to date, there is no specific ketamine withdrawal syndrome that has been described. A case report of a patient whose daily dose of ketamine reached up to 4 gm described withdrawal symptoms including irritability, tremulousness, intense sweating, restlessness, fragmentary sleep, frightening dreams, and intense cravings following 2 hr of abstinence from ketamine.[123] However, another case report of an individual with a 5-year history of up to 3 gm of ketamine use per day reported a complete lack of withdrawal symptoms after cessation of use.[124] A large Taiwanese study (n = 1,614), reported gender differences in discontinuation symptoms, with female users presenting with more discontinuation symptoms than males. Specific discontinuation symptoms included anxiety, dysphoria, and tremors.[125]

GLOBAL USE PATTERNS

There have been apparent increases in recent years in the illicit use of ketamine as a drug of abuse (party drug) globally. Although most of the extant literature is based in the United States, reports for abuse have been published in Australia, Italy, United Kingdom, China, Southeast Asia, and Eastern Europe.[20,126–130] The clinical pattern of use, and demographics of abusers, is similar to those described in the United States. Ketamine use is not as widespread as other abused drugs, such as cocaine and heroin, but is a drug of choice in party settings. Its shorter duration than PCP, and more rapid metabolism, has resulted in a use pattern more commonly seen in specific settings (parties) than in daily abuse. In reviewing the global literature, it appears as though ketamine addiction is low overall, but episodic use may be increasing. Accurate reporting of use is challenging, and is often related to sexual assaults which take place when someone is under the influence and acutely intoxicated. More coordinated research is needed internationally to better understand the current state of the problem, and develop prevention strategies focused on at risk populations.

KETAMINE DIVERSION

The age of ketamine users in the population ranges from adolescent to adult. Although it is often difficult to obtain accurate numbers on illicit drug use in the general population, studies have been conducted to try to determine the prevalence of illicitly used ketamine. The United States DEA, using the 2011 Monitoring the Future study, reported the annual use of ketamine among 8th, 10th, and 12th graders to be 0.8, 1.2, and 1.7%, respectively. At follow-up 1 year later, 12th graders use of ketamine decreased to 1.5% (no data were provided for 8th and 10th graders).[131] Bokor and Anderson[35] reported the prevalence of ketamine use in college students was 0.4% in 2012, decreased from 1.3% in 2002. In young adults, they noted the prevalence in 2012 to be 0.8%, lower than the previously reported 1.2% in 2002. The American Association of Poison Control Centers reported 220 exposures to ketamine in 2011, of which 121 were solely due to ketamine, but none of which resulted in fatality.[132] However, the Florida Department of Law Enforcement did report five deaths in 2011 attributed, in part, to ketamine.[133] The number of deaths due to ketamine increased the following year to eight (data are from January 2012 to June 2012).[134] In 2010, ketamine exposure was considered a factor in 915 emergency department visits. In 2011, this figure rose to 1,550 visits.[135]

Ketamine abuse is not limited to North America. A 2010 study[101] reviewed 233 emergency department cases in Hong Kong, finding ketamine was the most

commonly abused drug by persons under the age of 21 in 2005. In 2008, 85% of all drug abuse emergency department visits had ketamine as at least a component, up from 65% in 2005. Of all cases of drug abuse entering the emergency department, ketamine abuse represented 16% from July 2005 to December 2005, rising to 40% from January 2008 to June 2008.

Li et al.[136] report the prevalence of ketamine abuse in Indonesia to be 1.8% of high school students and 1.1% of workers/laborers. In Taiwan, among people between the ages of 12–64 years old who had reported using drugs recreationally, ketamine abusers ranked third (22%) behind amphetamines and MDMA. These data demonstrate that ketamine abuse is a global problem.

The distribution of illicit compounds is often very difficult to track, as multiple sources usually exist. According to the DEA, Mexico is a major global supplier of illicit ketamine.[137] In September of 2002, the DEA and Mexican law enforcement succeeded in dismantling the major drug ring supplying illicit ketamine to the United States. Another major bust, in November 2005, involved a widespread illegal drug distribution organization operating throughout Los Angeles, Riverside, and Orange counties of California. International distribution and sales are not limited to Mexico and the United States. In April 2005, an international illegal drug distribution organization was found to be smuggling ketamine from India into the United States. The drug bust resulted in seizing 108 kg of ketamine, with a street value of $1.62 million.

Despite its classification as a Schedule III nonnarcotic substance in 1999 by the FDA, the current rise of ketamine abuse has highlighted the concern of its overall safety. Although deaths from ketamine abuse are low, they do exist, particularly when used in combination with other illicit drugs. Limited research has been conducted examining drug–drug interactions with ketamine and other drugs of abuse. Ketamine has potential promise for the use as an antidepressant. However, it is important to recognize its potential for diversion, particularly in high-risk populations.

OTHER NMDA ANTAGONISTS OF ABUSE

Most newer synthetic drugs of abuse can be classified according to their chemical structure and/or based on their clinical effects as either primary stimulant, entactogenic, or hallucinogenic, although most drugs have a combination of such effects.[138] Designed dissociative anesthetic substances such as diphenidine and methoxphenidine have similar activity as PCP, ketamine, methoxetamine, and dextromethorphan.[139] They act as antagonists of the NMDA receptor and have emerged on the recreational drug market for their mind-altering effects.[140] The emergence of these new designer drugs poses a threat to the society. Although they are derivatives from previously known compounds, often their metabolism and clinical effects are not entirely similar to the parent compound.[141] It has also been documented that recreational drug users often combine different types of drugs, which further complicates acute management, clinical symptoms, and toxicity.[142]

CONCLUSION

Ketamine was introduced as an anesthetic many years ago, but has found a place in clinical use beyond sedation and pain management. Ketamine also shows promise for the treatment of depression that has been resistant to typical treatment strategies. The short-lived effects of a single ketamine administration leave the question of how to maintain antidepressant response. Although rare, clinical use can result in serious adverse consequences, including death. Unfortunately, ketamine has also been discovered by substance users. Clinicians need to be aware of the potential for harm when ketamine is abused recreationally and counsel those at risk about potential harm. Signs of recreational ketamine abuse may include cognitive, genitourinary, and gastrointestinal dysfunction. Ketamine is not included in the standard point of care urine toxicology screen, but is offered in expanded point of care urine toxicology and confirmatory urine drug screens. If use is suspected, clinicians should provide counseling on these risks and offer the same substance abuse treatment recommended for those with other substance use disorders.

REFERENCES

1. FDA. Ketamine abuse. FDA Drug Bull 1979;9:24.
2. Reich DL, Silvay G. Ketamine: an update on the first twenty-five years of clinical experience. Can J Anaesth 1989;36:186–197.
3. Haas DA, Harper DG. Ketamine: a review of its pharmacological properties and use in ambulatory anesthesia. Anesth Prog 1992:39:61–68.
4. Ketamine Jansen KL. Can chronic use impair memory? Int J Addict 1990;25:133–139.
5. Jansen KL. A review of the nonmedical use of ketamine: use, users and consequences. J Psychoactive Drugs 2000;32:419–433.
6. Mazzeffi M, Johnson K, Paciullo C. Ketamine in adult cardiac surgery and the cardiac surgery intensive care unit: an evidence based clinical review. Ann Card Anaesth 2015;18:202–209.
7. Ketamine Bergman SA. Review of its pharmacology and its use in pediatric anesthesia. Anesth Prog 1999;46:10–20.
8. Stewart KG, Rowbottom SJ, Aitken AW, et al. Oral ketamine premedication for pediatric cardiac surgery-a comparison with intramuscular morphine (both after oral trimeprazine). Anaesth Intensive Care 1990;18:11–14.
9. Wang HS, Cinelli AB, Pugh GB, Rock CK. Ketamine anesthesia in pediatric ophthalmic office procedures. Ann Ophthalmol 1990;22:26–29.
10. Green SM, Johnson NE. Ketamine sedation for pediatric procedures: part 2, review and implications. Ann Emerg Med 1990;19:1033–1046.
11. Green SM, Krauss B. The semantics of ketamine [editorial]. Ann Emerg Med 2000;36:480–482.
12. Dobbs T. Report: after patient death, UVM medical center waited weeks to fix flawed systems. VPR, July 7, 2015.

13. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med 2011;57:449–461.
14. White PF, Ham J, Way WL. Pharmacology of ketamine isomers in surgical patients. Anesthesiology 1980;52:231–239.
15. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of Ci-581, a new dissociative anesthetic, in man. Clin Pharmacol Ther 1965;6:279–291.
16. Sener S, Eken C, Schultz CH, et al. Ketamine with and without midazolam for emergency department sedation in adults: a randomized controlled trial. Ann Emerg Med 2011;57:109–114.
17. Fine J, Weissman J, Finestone SC. Side effects after ketamine anesthesia: transient blindness. Anesth Analg 1974;53:72–74.
18. Siegel RK. Phencyclidine and ketamine intoxication: a study of four populations of recreational users. NIDA Res Monogr 1978;21:119–147.
19. Jansen KL. Non-medical use of ketamine. BMJ 1993;306:601–602.
20. Dalgarno PJ, Shewan D. Illicit use of ketamine in Scotland. J Psychoactive Drugs 1996;28:191–199.
21. Dotson JW, Ackerman DL, West LJ. Ketamine abuse. J Drug Issues 1995;25:751–757.
22. Smith KM. Drugs used in acquaintance rape. J Am Pharm Assoc 1999;39:519–525.
23. Krystal JH, Karper LP, Seibyl JP, et al. Subanaesthetic effects of the noncompetitive NMDA anatgonist, ketamine, in humans. Arch Gen Psychiatry 1994;51:199–214.
24. Oranje B, van Berckel BN, Kemner C, et al. The effects of a sub-anaesthetic dose of ketamine on human selective attention. Neuropsychopharmacology 2000;22:293–302.
25. Hartvig P, Valtysson J, Lindner KJ, et al. Central nervous system effects of subdissociative doses of (S)-ketamine are related to plasma and brain concentrations measured with positron emission tomography in healthy volunteers. Clin Pharmacol Ther 1995;58:165–173.
26. White PF, Way WL, Trevor AJ. Ketamine: its pharmacology and therapeutic uses. Anaesthesiology 1982;56:119–136.
27. Malhotra AK, Pinals DA, Weingariner H, et al. NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. Neuropsychopharmacology 1996;16:120–125.
28. Newcomber JW, Farber NB, Jevtovic-Todorovic V, et al. Ketamine induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neuropsychopharmacology 1999;20:106–118.
29. Hetem LA, Danion JM, Diemunsch P, et al. Effect of a subanesthetic dose of ketamine on memory and conscious awareness in healthy volunteers. Psychopharmacology 2001;22:59–72.
30. Weiner AL, Vieira L, McKay CA, Bayer MJ. Ketamine abusers presenting to the emergency department: a case series. J Emerg Med 2000;18:447–451.
31. Bowdle TA, Radant AD, Cowley DS, et al. Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. Anaesthesiology 1998;88:82–88.
32. EMCDDA. Report on the risk assessment of ketamine in the framework of the joint action on new synthetic drugs. Luxembourg: Office for Official Publications of the European Communities; 2002.
33. Graeme KA. New drugs of abuse. Pharmacol Adv Emerg Med 2000;18:625–636.
34. Barrett SP, Gross SR, Garand I, Pihl RO. Patterns of simultaneous polysubstance use in Canadian rave attendees. Subst Use Misuse 2005;40:1525–1537.
35. Bokor G, Anderson PD. Ketamine: an update on its abuse. J Pharm Practice 2014;27:582–586.
36. AIHW (Australian Institute of Health and Welfare). 2007 National Drug Survey Household Survey: Detailed Findings. Canberra: Author; 2008.
37. SAMSHA (Substance Abuse and Mental Health Services Administration). The NSDUH Report: Use of Specific Hallucinogens 2006. Rockville, MD: Author; 2008.
38. Paglia-Boak A, Mann RE, Adlaf EM, Rehm J. Drug Use among Ontario Students, 1977-2009: Detailed OSDUHS Findings. Toronto, Ontario: Centre for Addiction and Mental Health; 2009.
39. Hoare J, Moon D, editor. Drug misuse declared: findings from the 2009/10 British Crime Survey England and Wales. In: Home Office Statistical Bulletin. London: Home Office; 2010: 1–109.
40. Kubota R, Komiyama T, Miwa Y, et al. Pharmacokinetics of ketamine and norketamine after oral administration of a liquid formulation of ketamine. J Curr Surg 2013;3:82–86.
41. Jantzen JP, Erdmann K, Hilley D, et al. Comparative study of analgesia and plasma level following rectal, intramuscular and intravenous administration of ketamine. Anaesthesist 1985;34:346–351.
42. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Therapeut 2013;19:370–380.
43. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of i.m. and oral ketamine. Br J Anaesth 1981;53:805–809.
44. Domino EF, Domino SE, Smith RE. Ketamine kinetics in unpremedicated and diazepam premedicated subjects. Clin Pharmacol Ther 1984;36:645–653.
45. Amiot JF, Roessler JG, Amadea B, et al. Anaesthesia with oral ketamine. Cah Anaesthesiol 1987;35:203–205.
46. Wieber J, Gugler R, Hengstmann JG, Dengler HJ. Pharmacokinetics of ketamine in man. Anaesthesist 1975;24:260–263.
47. Hijazi Y, Boulieu R. Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes. Drug Metab Dispos 2002;7:853–867.
48. Yanagihara Y, Kariya S, Ohtani M, et al. Involvement of CYP2B6 in N-demethylation of ketamine in human liver microsomes. Drug Metab Dispos 2001;6:887–890.
49. Lindefors N, Barati S, O'Connor WT. Differential effects of single and repeated ketamine administration on dopamine, serotonin and GABA transmission in rat medial prefrontal cortex. Brain Res 1997;759:205–212.
50. Nishimura N, Sato K, Okada T, et al. Ketamine inhibits monoamine transporters expressed in human embryonic kidney 293 cells. Anesthesiology 1998;88:768–774.
51. Crisp T, Perrotti JM, Smith DL, et al. The local monoaminergic dependency of spinal ketamine. Eur J Pharmacol 1991;194:167–172.
52. Finck AD, Samaniego E, Ngai H. Morphine tolerance decreases the analgesic effects of ketamine in mice. Anesthesiology 1988;68:397–400.
53. Shimoyama M, Shimoyama N, Gorman AL, et al. Oral ketamine is antinociceptive in the rat formalin test: role of the metabolite, norketamine. Pain 1999;81:85–93.
54. Hansen G, Jenson SB, Chandresh L, et al. The psychotropic effect of ketamine. J Psychoactive Drugs 1988;20:419–425.
55. 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;95:575–590.
56. 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;96:749–760.

57. Oye I, Paulsen O, Maurset A. Effects of ketamine on sensory perception: evidence for a role on N-methyl-D-aspartate receptors. J Pharmacol Exp Ther 1992;260:1209–1213.
58. Sinner B, Graf BM. Ketamine. Handb Exp Pharmacol 2008; 182:313–333.
59. Dillon P, Copeland J, Jansen K. Patterns of use and harms associated with non-medical ketamine use. Drug Alcohol Depend 2003;69:23–28.
60. Larkin GL, Beautrais AL. A preliminary naturalistic study of low-dose ketamine for depression and suicide ideation in the emergency department. Int J Neuropsychopharmacol 2011;14:1127–1131.
61. aan het Rot M, Zarate CA, Charney DS, Mathew SJ. Ketamine for depression: where do we go from here? Biol Psychiatry 2012;72:537–547.
62. Lapidus, KA, Levitch CF, Perez AM, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry 2014;76:970–976.
63. Chilukuri H, Reddy NP, Pathapati RM, et al. Acute antidepressant effects of intramuscular versus intravenous ketamine. Ind J Psychol Med 2014;36:71–76.
64. Blier, P, Zigman D, Blier J. On the safety and benefits of repeated intravenous injections of ketamine for depression. Biol. Psychiatry 2012;72:e11–e12.
65. Murrough, JW, Perez AM, Pillemer S, et al. Rapid and longer-term antidepressant effects of repeated ketamine infusions in treatment resistant major depression. Biol Psychiatry 2013;74:250–256.
66. Szymkowicz SM, Finnegan N, Dale RM. A 12-month naturalistic observation of three patients receiving repeat intravenous ketamine infusions for their treatment resistant depression. J Affect Disord 2013;147:416–420.
67. Diamond PR, Farmery AD, Atkinson S, et al. Ketamine infusions for treatment resistant depression: a series of 28 patients treated weekly or twice weekly in an ECT clinic. J Psychopharmacol 2014;28:536–544.
68. Segmiller, F, Ruther T, Linhardt A, et al. Repeated S-ketamine infusions in therapy resistant depression: a case series. J Clin Pharmacol 2013;53:996–998.
69. Shiroma PR, Johns B, Kuskowsko M, et al. Augmentation of response and remission to serial intravenous subanesthetic ketamine in treatment resistant depression. J Affect Disord 2014;155:123–129.
70. Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant depression: a two-site randomized controlled trial. Am J Psychiatry 2013;170:1134–1142.
71. Harihar C, Dasari P, Srinivas JS. Intramuscular ketamine in acute depression: a report on two cases. Indian J Psychiatry 2013;55:186–188.
72. Lara DR, Bisol LW, Munari LR. Antidepressant, mood stabilizing and procognitive effects of very low dose sublingual ketamine in refractory unipolar and bipolar depression. Int J Neuropsychopharmacol 2013;16:2111–2117.
73. Clark P. Treatment-refractory depression: a case of successful treatment with intranasal ketamine 10%. Ann Clin Psychiatry 2014;26:145.
74. aan het Rot, Collins KA, Murrough JW, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. Biol Psychiatry 2010;67:139–145.
75. Paslakis G, Gilles M, Meyer-Lindenberg AM, Deuschle M. Oral administration of the NMDA receptor antagonist S-Ketamine as add-on therapy of depression: a case series. Pharmacopsychiatry 2009;43:33–35.
76. Luckenbaugh DA, Niciu MJ, Ionescu DF, et al. Do the dissociative side effects of ketamine mediate its antidepressant effects? J Affect Disord 2014;159:56–61.
77. Dakwar E, AnerellaC, Hart CL, et al. Therapeutic infusions of ketamine: do the psychoactive effects matter? Drug Alcohol Depend 2014;136:153–157.
78. Dakwar E, Hart CL, Levin FR, et al. Cocaine self-administration disrupted by the N-methyl-D-aspartate receptor antagonist ketamine: a randomized, crossover trial. Mol Psychiatry 2016. doi: 10.1038/mp.2016.39. [Epub ahead of print].
79. Visser E, Schuga SA. The role of ketamine in pain management. Biomed Pharmacother 2006;60:341–348.
80. Persson J. Ketamine in pain management. CNS Neurosci Ther 2013;19:296–402.
81. Zanicotti CG, Perez D, Glue P. Mood and pain responses to repeat dose intramuscular ketamine in a depressed patient with advanced cancer. J Palliat Med 2012;15:400–403.
82. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. Am J Emerg Med 2008;26:985–1028.
83. Roback MG, Wathen JE, Bajaj L, Bothner JP. Adverse events associated with procedural sedation and analgesia in a pediatric emergency department: a comparison of common parenteral drugs. Acad Emerg Med 2005;12:508–513.
84. Lee SK. The use of ketamine for perioperative pain management. Korean J Anesthesiol 2012;63:1–2.
85. Moore NN, Bostwick JM. Ketamine dependence in anesthesia providers. Psychosomatics 1999;40:356–359.
86. Goyal S, Ambekar A, Ray R. Ketamine dependence in an anesthesiologist: an occupational hazard? Indian J Psychol Med 2014;36:335–337.
87. Goyal S, Agrawal A. Ketamine in status asthmaticus: a review. Indian J Crit Care Med 2013;17:154–161.
88. Morgan CJ, Muetzelfeldt L, Curran HV. Ketamine use, cognition and psychological wellbeing: a comparison of frequent, infrequent and ex-users with polydrug and non-using controls. Addiction 2009;104:77–87.
89. Morgan CJ, Muetzelfeldt L, Curran HV. Consequences of chronic ketamine self-administration upon neurocognitive function and psychological wellbeing: a 1-year longitudinal study. Addiction 2010;105:121–133.
90. Chan WH, Sun WZ, Ueng TH. Induction of rat hepatic cytochrome P-450 by ketamine and its toxicological implications. J Toxicol Environ Health 2005;68:1581–1597.
91. Chu PS, Ma WK, Wong SC, et al. The destruction of the lower urinary tract by ketamine abuse: a new syndrome? BJU Int 2008;102:1616–1622.
92. Cottrell A, Warren K, Ayres R, et al. The destruction of the lower urinary tract by ketamine abuse: a new syndrome? BJU Int 2008;102:1178–1179.
93. Muetzelfeldt L, Kamboj SK, Rees H, et al. Journey through the K-hole: phenomenological aspects of ketamine use. Drug Alcohol Depend 2008;95:219–229.
94. Tsai TH, Cha TL, Lin CM, et al. Ketamine-associated bladder dysfunction. Int J Urol 2009;16:826–829.
95. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine associated ulcerative cystitis: a new clinical entity. Urology 2007;69:810–812.
96. Selby NM, Anderson J, Bungay P, et al. Obstructive nephropathy and kidney injury associated with ketamine abuse [case report]. NDT Plus 2008;1:310–312.
97. Jhang JF, Hsu YH, Kuo HC. Possible pathophysiology of ketamine-related cystitis and associated treatment strategies. Int J Urol 2015;22:816–825.

98. Morgan CJ, Curran HV. Ketamine use: a review. Addiction 2011;107:27–38.
99. Winstock AR, Mitcheson L, Gillatt DA, Cottrell AM. The prevalence and natural history of urinary symptoms among recreational ketamine users. BJU Int 2012;110:1762–1766.
100. Chung SD, Wang CC, Kuo HC. Augmentation enterocystoplasty is effective in relieving refractory ketamine-related bladder. Neurourol Urodyn 2014;33:1207–1211.
101. Ng SH, Tse ML, Ng HW, Lau FL. Emergency department presentation of ketamine abusers in Hong Kong: a review of 233 cases. Hong Kong Med J 2010;16:6–11.
102. Lee ST, Wu TT, Yu PY, Chen RM. Apoptotic insults to human HepG2 cells induced by S-ketamine occurs through activation of a Bax-mitochondria-caspase protease pathway. Br J Anaesth 2009;102:80–89.
103. Ng SH, Lee HK, Chan YC, Lau FL. Dilated common bile ducts in ketamine abusers. Hong Kong Med J 2009;15:157.
104. Wong SW, Lee KF, Wong J, et al. Dilated common bile ducts mimicking choledochal cysts in ketamine abusers. Hong Kong Med J 2009;15:53–56.
105. Poon TL, Wong KF, Chan MY, et al. Upper gastrointestinal problems in inhalational ketamine abusers. J Dig Dis 2010;11:106–110.
106. Yu WL, Cho CC, Lung PF, et al. Ketamine-related cholangiopathy: a retrospective study on clinical and imaging findings. Abdom Imaging 2014;39:1241–1246.
107. Wong GL, Tam YH, Ng CF, et al. Liver injury is common among chronic abuses of ketamine. Clin Gastroenterol Hepatol 2014;12:1759–1762.
108. Moreton JE, Meisch RA, Stark L, Thompson T. Ketamine self-administration by the rhesus monkey. J Pharmacol Exp Ther 1977;203:303–309.
109. Newman JL, Perry J, Carroll ME. Social stimuli enhance phencyclidine (PCP) self-administration in rhesus monkeys. Pharmacol Biochem Behav 2007;87:280–288.
110. Nicholson KL, Hayes BA, Balster RL. Evaluation of the reinforcing properties and phencyclidine-like discriminative stimulus effects of dextromethorphan and dextrorphan in rats and rhesus monkeys. Psychopharmacology (Berl) 1999;146:49–59.
111. White JM, Ryan CF. Pharmacological properties of ketamine. Drug Alc Review 1996;15:145–155.
112. Vollenweider FX, Vontobel P, Øye I, et al. Effects of (S)-ketamine on striatal dopamine: a [^{11}C]raclopride PET study of a model psychosis in humans. J Psychiatr Res 2000;34:35–43.
113. Smith GS, Schloesser R, Brodie JD, et al. Glutamate modulation of dopamine measured in vivo with positron emission tomography (PET) and 11C-raclopride in normal human subjects. Neuropsychopharmacology 1998;18:18–25.
114. Hancock PJ, Stamford JA. Stereospecific effects of ketamine on dopamine efflux and uptake in the rat nucleus accumbens. Br J Anaesth 1999;82:603–608.
115. Freo U, Ori C. Opioid pharmacology of ketamine. Acta Anaesthesiol Ital 2002;53:149–163.
116. Brent PJ, Chahl LA. Enhancement of the opiate withdrawal response by antipsychotic drugs in guinea-pigs is not mediated by sigma binding sites. Eur Neuropsychopharmacol 1993;3:23–32.
117. Ji D, Sui ZY, Ma YY, et al. NMDA receptor in nucleus accumbens is implicated in morphine withdrawal in rats. Neurochem Res 2004;29:2113–2120.
118. Bree MM, Feller L, Corssen G. Safety and tolerance of repeated anesthesia with CI 581 (ketamine) in monkeys. Anesth Analg 1967;46:596–600.
119. Cumming JF. The development of an acute tolerance to ketamine. Anesth Analg 1976;55:788–791.
120. Byer DE, Gould AB Jr. Development of tolerance of ketamine in an infant undergoing repeated anesthesia. Anesthesiology 1981;54:255–256.
121. Khan MS, Bhatti AH. Ketamine tolerance. Postgrad Med J 1988;64:833–834.
122. Kalsi SS, Wood DM, Dargan Pl. The epidemiology and patterns associated with recreational ketamine use. Emerg Health Threats J 2011;4:7107.
123. Garg A, Sinha P, Kumar P, Prakash O. Use of naltrexone in ketamine dependence. Addict Behav 2014;39:1215–1216.
124. Liu JX, Zerbo E, Ross S. Intensive ketamine use for multiple years: a case report. Am J Addict 2015;24:7.
125. Cheng WC, Ng KM, Chan KK, et al. Roadside detection of impairment under the influence of ketamine—evaluation of ketamine impairment symptoms with reference to its concentration in oral fluid and urine. Forensic Sci Int 2007;170:51–58.
126. Degenhardt L, Dunn M. The epidemiology of GHB and ketamine use in an Australian household survey. Int J Drug Policy 2007;19:311–316.
127. De Luca MT, Meringolo M, Spagnolo PA, Badiani, A. The role of setting for ketamine abuse: clinical and preclinical evidence. Rev Neurosci 2012;23:769–780.
128. Schifano F, Corkery J, Oyefeso A, et al. Trapped in the "K-hole": overview of deaths associated with ketamine misuse in the UK (1993-2006). J Clin Psychopharmacol 2008;28:114–116.
129. Zhao C, Liu Z, Zhao D, et al. Drug abuse in China. Ann NY Acad Sci 2004;1025:439–445.
130. De la Torre R. Commentary on Morgan et al.(2010): ketamine abuse: first medical evidence of harms we should confront. Addiction 2010;105:134–135.
131. Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the Future National Results on Adolescent Drug Use; Overview of Key Findings, 2011. Ann Arbor: Institute for Social Research, The University of Michigan; 2012.
132. Bronstein AC, Spyker DA, Cantilena LR, et al. 2011 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th annual report. Clin Toxicol 2012;50:911–1164.
133. Florida Department of Law Enforcement. Drugs identified in deceased persons by Florida medical examiners. 2011 Report. Available at: https://www.fdle.state.fl.us/Content/getdoc/fa86790e-7b50-45f3-909d-c0a4759fefa8/2011-Drug-Report_Final.aspx
134. Florida Department of Law Enforcement. Drugs identified in deceased persons by Florida medical examiners. 2012 Report. Available at: https://www.fdle.state.fl.us/Content/getdoc/79241c67-253b-45eb-a238-1a07cf4a2a0c/2012-Drug-Report_Final.aspx
135. Substance Abuse and Mental Health Services Administration. Drug Abuse Warning Network, 2011: national estimates of drug-related emergency department visits. HHS Publication No. (SMA) 13-4760, DAWN Series D-39. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2013.
136. Li JH, Vicknasingam B, Cheung YW, et al. To use or not to use: an update on licit and illicit ketamine use. Subst Abuse Rehabil 2011;2:11–20.
137. Drug Enforcement Agency. Drug fact sheet: ketamine. 2015. Available at: http://www.dea.gov/druginfo/drug_data_sheets/Ketamine.pdf
138. Hill SL, Thomas SH. Clinical toxicology of newer recreational drugs. Clin Toxicol (Phila) 2011;49;705–719.
139. Morris H, Wallach J. From PCP to MXE: a comprehensive review of the non-medical use of dissociative drugs. Drug Test Anal 2014;6:614–632.

140. Helander A, Beck O, Backberg M. Intoxications by the dissociative new psychoactive substances diphenidine and methoxphenidine. Clin Toxicol (Phila) 2015;53:446–453.
141. Helander A, Backberg M, Hulten P, et al. Detection of new psychoactive substance use among emergency room patients: results from the Swedish STRIDA project. Forensic Sci Int 2014;243:23–29.
142. Backberg M, Beck O, Hulten P, et al. Intoxications of the new psychoactive substance 5-2(aminopropyl) indole (5-IT): a case series from the Swedish STRIDA project. Clin Toxicol (Phila) 2014;52:618–624.