Ketamine Abuse: Past and Present

Ming-Chyi Huang and Shih-Ku Lin

Abstract Ketamine is an anesthetic derivative of phencyclidine with dissociative, analgesic, and psychedelic properties. It is extensively used as an anesthetic drug in surgical procedures in pediatric, obstetric, and geriatric patients, as well as in veterinary settings. Since its approval for clinical use, the misuse and abuse of ketamine have been reported in scientific journals and in popular media globally, particularly in the last two decades. It has been used as a common club drug in dance, rave, and squat party scenes. Owing to its unique pharmacological properties, ketamine has been used as an antidepressant for the treatment of resistant depression. However, a long-term use of high doses of ketamine leads to numerous physical and psychological negative effects, such as abdominal pain, urinary system disorder, dependence/tolerance/withdrawal, cognitive impairment, psychosis, and depression. At present, no effective pharmacotherapy for managing compulsive drug-seeking behavior in patients with ketamine use disorder is available. Treatment that incorporates regular urine screening in addition to medications for psychiatric symptoms and craving may present favorable results.

Keywords Abuse · K-hole · Physical consequence · Psychological consequence · Regulation · Treatment

Ketamine is an anesthetic derivative of phencyclidine (or *N*-1-phenylcyclohexylpiperidine [PCP]) with dissociative, analgesic, and psychedelic properties. In the 1950s, the staff at Parke-Davis Industries developed two cylcoheximide drugs, PCP and *N*-ethyl-1-phenylcyclohexylamine chlorhydrate, as ideal anesthetic agents with analgesic effects (Domino 2010). PCP was commercialized in the United States; however, it was withdrawn from medical use in 1978 because of its

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K. Hashimoto et al. (eds.), *Ketamine*,
https://doi.org/10.1007/978-981-15-2902-3_1

"schizophrenomimetic" effects and abuse potential as a recreational drug (with a street name of "angel dust"). Due to the failure to synthesize and develop a less potent and rapidly metabolized derivative of PCP with lower "psychic effects," ketamine continues to be an alternative medicinal drug (Huang et al. 2014). Although classified as a hallucinogen in pharmacology, ketamine is extensively used in various anesthetic procedures in pediatric, obstetric, and geriatric patients due to its safety profile (White et al. 1982; Li and Vlisides 2016). In addition, the antidepressant effects of ketamine in the treatment of refractory depression have been reported in recent years (Berman et al. 2000; Krystal et al. 2013). In this chapter, we discuss ketamine abuse from past to present.

1 Ketamine Abuse

FDA approved ketamine as an anesthetic in 1970. In the following year, scholars raised the question that if ketamine is a hallucinogen, it may be abused or misused, similar to lysergic acid diethylamide (LSD) (Reier 1971). Although the nonmedical use of ketamine began on the West Coast of the United States in the early 1970s (Petersen and Stillman 1978), scientific reports of the phenomenon were very few until the early 1990s.

Ketamine was not considered a major drug of abuse in the past two decades, and relatively few cases were reported during the period (Hurt and Ritchie 1994; Jansen and Rracot-Cankovic 2001). Popular use of ketamine originated from the rave or party pill (ecstasy) – adulterant mixture (Jansen 1993). In Taiwan, the most common compounds found in the analyses of urine from people attending rave parties are 3,4-methylenedioxymethamphetamine (MDMA), methamphetamine, ephedrine, ketamine, acetaminophen, and caffeine (Lua et al. 2003). Following the ecstasy epidemic, ketamine use has become more popular in recent years globally, particularly as a party drug in dance, rave, and squat party scenes. It has also become popular in the UK (Morgan et al. 2004; Muetzelfeldt et al. 2008), Australia (Dillon et al. 2003), Hong Kong (Cheng et al. 2007; Ng et al. 2010), and Mainland China (Fang et al. 2006).

The Expert Committee on Drug Dependence of the WHO prereviewed ketamine in 2003 and conducted a critical review in 2006. The committee concluded that "this information was not sufficient to warrant scheduling." At a 2012 meeting, the committee decided that "bringing ketamine under international control is not appropriate." At the level of the European Union, in 2000, the European Commission concluded that it was not appropriate to introduce control measures and recommended further monitoring of ketamine use. In the latest World Drug Report by United Nations Office on Drugs Control 2019 (UNODC 2019), ketamine is classified under new psychoactive substances (NPSs), which are not under the control of international drug conventions but which may pose a threat to public health. The growing popularity of ketamine in South-East Asia could be, in part, due to its lower

status in regulatory systems and lower price point as a substitute for the increasingly expensive "ecstasy" or methamphetamine.

In recent years, ketamine has also become commonly abused in Taiwan, particularly among the youth and adolescents (Chen et al. 2009; Lua et al. 2003; Yen et al. 2007). Studies have reported that most ketamine users in Taiwan concomitantly used ecstasy (MDMA). MDMA and ketamine detection rates have been as high as 76% and 47%, respectively, among rave party participants in Taiwan (Lua et al. 2003). In addition, a focus group discussion conducted with club drug users revealed that there was a special drug use sequence extensively adhered to by Taiwanese polydrug users (Leung et al. 2008). In a single drug use episode, MDMA was often the first drug used, followed by ketamine, and then marijuana. This unique sequence of polydrug use in a single episode is called "trinity." A long-term use of ketamine may lead to dependence, and this disorder is diagnosed as "Other Hallucinogen Use Disorder" according to DSM-5 and as "Hallucinogen Abuse" based on the ICD-10 Code F16.1.

2 Psychedelic Effects of Ketamine

Contrary to the clinical doses for anesthesia (2 mg/kg) and depression (0.5 mg/kg), the abuse dose is quite high (>3 mg/kg). Most abusers snort ketamine powder directly, and other routes include smoking, ingestion, and rarely injection (Carmona-Huerta et al. 2019). The relatively rapid onset of the effects on the brain (approximately 5 min) and the short half-life (approximately 1–2 h) are believed to enhance binging use and the abuse potential of ketamine.

Ketamine is a noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist. It impairs working, episodic, and semantic memory acutely and causes psychotogenic and dissociative effects in healthy volunteers receiving a single dose. At high doses, ketamine can cause cardiovascular and respiratory toxicity while producing psychotropic effects, which become the primary experience, particularly in recreational users. The effect demonstrates a linear dose–effect relationship ranging from referential ideation, dissociation, and depersonalization to psychotic experiences, including a sensation of feeling light, body distortion, absence of time sense, novel experiences of cosmic oneness, and out-of-body experiences, often referred to as the "K-hole" (Curran and Monaghan 2001). According to the results of a structured interview to examine initiation experiences and the positive and negative effects of ketamine on recreational users (Muetzelfeldt et al. 2008), the most appealing aspects of ketamine were "melting into the surrounding," "visual hallucinations," "out-of-body experiences," and "giggliness," whereas the unappealing effects were "memory loss" and "decreased sociability." A user becomes trapped in a state of detachment from their physical environment and loses senses of time, space, and balance, as well as verbal skills.

In a survey of 1614 ketamine users, the common withdrawal symptoms reported were fatigue, poor appetite, drowsiness, cravings, anxiety, dysphoria, tremors,

palpitation, and sweating (Chen et al. 2014). In addition, female ketamine users self-reported significantly greater levels of severity in cognitive impairment and urinary discomfort than male users.

3 Physical Effects of Ketamine Abuse

Experimental results revealed that ketamine could induce neurotoxic events and promote neuronal apoptosis (Olney et al. 2002). Chronic ketamine users were reported to have reduced frontal gray matter (Liao et al. 2011) and white matter abnormalities (Liao et al. 2010).

Regular ketamine abusers have reported vague or intense abdominal pain, colloquially termed "K-cramps" (Jansen 2000). They often attempt to alleviate the pain by consuming more ketamine, which makes it even more difficult to quit ketamine use. Case studies have described the dilation of the common bile duct with a smooth tapered end, mimicking choledochal cysts (Wong et al. 2009). A recent study reported that 18 of 26 (69%) patients had fusiform dilatation of the common bile ducts without evidence of intrinsic or extrinsic obstruction, and the severity of bile duct dilatation was correlated with the duration of ketamine use (Yu et al. 2014). Although the exact mechanism of fusiform dilatation is unclear, it is potentially associated with NMDA receptor blockade in the smooth muscle. Ketamine may also act via the dorsal motor nucleus of the vagus nerve, which has fibers projecting into the gall bladder. Discontinuing ketamine use is key to managing the abdominal pain; otherwise, treatment options are nonspecific.

Another major physical side effect of long-term ketamine abuse is interstitial cystitis. This is a severe and chronic complication, and the symptoms include dysuria, increased frequency of small-volume micturition, suprapubic pain, and if severe, painful hematuria and obstructive nephropathy. The novel clinical phenomenon was first documented by Shahani et al. in 2007 when they reported a single case of a pediatric patient with ketamine-associated ulcerative cystitis (Shahani et al. 2007). Computed tomographic scans of the patient revealed marked thickening of the bladder wall, reduced bladder capacity, and perivesical inflammation, and cystoscopy revealed severe ulcerative cystitis. A successive study by Chu et al. found that 42 of 59 (71%) patients with a "ketamine bladder" had various degrees of epithelial inflammation, similar to that observed in the case of chronic interstitial cystitis (Chu et al. 2008).

Several hypotheses have been proposed to explain the cause of urological complications. First, ketamine and norketamine may have direct toxic effects on the bladder when excreted. Second, the effect of ketamine on the central nervous system may decrease the contractile responses of the smooth muscle of the bladder. Third, damage to the glycosaminoglycan layer of the urothelium and interstitial cells may cause inflammatory responses and induce interstitial fibrosis (Chu et al. 2008). The prevalence of cystitis and contracted bladder is believed to be high in individuals who use ketamine daily over an extended period. Approximately 30% of

recreational ketamine users report having urinary tract symptoms when using ketamine (Muetzelfeldt et al. 2008), and nearly half of the frequent users seek medical attention for cystitis. The prognosis of the disease varies, and one-third of cases resolve after ketamine use is discontinued, one-third remain in the same state, and the remaining one-third worsen (Cottrell and Gillatt 2008). A special term, "walking-stick ureters," has been used to describe the segmental beading from ureteral strictures and the straightening of both ureters in a case report (Huang et al. 2011). Nevertheless, abstaining from ketamine use is the milestone of treatment, followed by the administration of mucosal protective agents, such as pentosan polysulfate, or hyaluronic acid. Surgical intervention, such as augmentation enterocystoplasty or cystectomy with conduit diversion, is generally considered the last resort in patients who have persistent symptoms and hematuria despite the aforementioned therapies and abstinence from ketamine. However, the treatment outcomes depend on the severity of disease progression, similar to the case of interstitial cystitis (Chen et al. 2011).

4 Psychological Consequences of Ketamine Abuse

Over the last two decades, many reports have explored the negative psychological effects of chronic ketamine abuse. Most studies have focused on cognitive impairment; some have highlighted that chronic ketamine abuse may result in dependence, psychosis, and depression. In the following sections, we address the psychological consequences associated with chronic and heavy ketamine use.

4.1 Dependence

The peak effect of ketamine occurs within 20 min, with the desired effects dissipating within 90 min; the distribution half-life is 7–11 min, and the plasma half-life is approximately 2–4 h (Dillon et al. 2003; Moore and Bostwick 1999). The short half-life and pharmacokinetic properties of ketamine make it attractive but may also lay the ground for its abuse potential. The problem of ketamine dependence has gradually gained attention since the 1980s and has been highlighted in many case reports (Hurt and Ritchie 1994; Jansen 1990; Moore and Bostwick 1999; Pal et al. 2002; Kamaya and Krishna 1987; Ahmed and Petchkovsky 1980).

Animal studies have demonstrated that ketamine reinforces self-administration behavior and conditioned place preference (de Luca and Badiani 2011; Venniro et al. 2015). Acute treatment with ketamine increases extracellular dopamine concentrations, a key neurotransmitter underlying the reinforcing effects of drug abuse in the neural network of the reward system (the striatum and prefrontal cortex) (Breier et al. 1997; Smith et al. 1998; Vollenweider et al. 1997). It has been hypothesized that ketamine blocks NMDA glutamate receptors on gamma-aminobutyric

acid (GABA) neurons, which results in the disinhibition of dopaminergic neurons and the subsequent increase in dopamine release (Liu et al. 2016). Notably, the results of a recent study indicated that even at low doses, repeated administration of ketamine could enhance addiction-like behavior (Strong et al. 2017).

In humans, data from imaging studies have revealed that ketamine could cause the striatal release of dopamine. The reinforcing and rewarding properties may explain the propensity for ketamine addiction and the increasing ketamine abuse trend globally over the past few decades (Li et al. 2011; Bokor and Anderson 2014). In addition, stress-related systems, such as the hypothalamus–pituitary–adrenal gland axis, and orexin (Huang et al. 2019) and oxytocin (Huang et al. 2018) signaling pathways, which have been postulated to play a role in the neuroadaptational mechanisms underlying addiction development, have been reported to be dysregulated in ketamine-dependent patients.

4.2 Tolerance

On the basis of serial investigations on ketamine abuse, Morgan et al. first highlighted that tolerance is a common feature in individuals who used ketamine frequently, and tolerance tend to escalate the dose over time. They reported that there might be a 600% increase in the ketamine dose compared with their initial dose of the drug (Morgan et al. 2008). They proposed that tolerance may be due to the induction of liver enzymes that metabolize ketamine (Livingston and Waterman 1978) as well as neuroadaptational changes that occur following chronic ketamine exposure (Morgan et al. 2012). Clinical case reports have also revealed that ketamine abusers develop considerable tolerance to the drug with very high doses (reaching 2.5 g/day) (Goyal et al. 2014; Critchlow 2006; Moore and Bostwick 1999; Pal et al. 2002). In treatment-seeking ketamine-dependent patients, ketamine use at doses as high as 4 g per day have been observed before the seeking treatment (Huang et al. 2018, 2019; Cheng et al. 2018; Wang et al. 2018).

4.3 Withdrawal

No consensus has been reached yet regarding whether a specific withdrawal syndrome exists following the discontinuation of chronic and heavy ketamine use. In general, physical withdrawal symptoms are not considered to be prominent in case reports describing ketamine dependence (Goyal et al. 2014); however, some reports have highlighted that somatic and psychological symptoms such as anxiety, depression, shaking, sweating, palpitations, or sleep impairment may be substantial in some users (Critchlow 2006; Morgan et al. 2008; Lin et al. 2016). Future studies that systemically examine the symptoms and signs in individuals with ketamine

dependence should elucidate the clinical profile and characteristics of ketamine withdrawal.

5 Cognitive Impairment

Cognitive impairment is among the multiple adverse outcomes associated with ketamine abuse (Bokor and Anderson 2014; Morgan et al. 2010, 2012). The pharmacological effects of ketamine via a blockade of NMDA glutamate receptors, which is key to the mechanisms underlying learning and memory, could account for the disruption of cognitive function (Morgan et al. 2012). In addition, the effects on other neurotransmitter systems, for example, the inhibition of muscarinic acetylcholine receptor function (Durieux 1995) and induction of dopamine release (Rabiner 2007), could play a role.

A longitudinal study observed that increasing ketamine use over a year was correlated with decreasing performance in cognitive tasks, mainly spatial working memory and pattern recognition memory, suggesting that continued sustained ketamine use is harmful to cognitive function (Morgan et al. 2010). In addition, individuals who used ketamine actively (i.e., using ketamine 1–4 times per week and having the last dose within the preceding 1 month) exhibited deficits over an array of cognitive tests involving mental and motor speed, visual and verbal memory, and executive functions (Morgan et al. 2010; Tang et al. 2013), and the deficits seemed persistent (Morgan et al. 2010).

The cognitive function of treatment-seeking ketamine-dependent patients (i.e., those with a higher severity of ketamine use) was worse substantially compared with that of controls based on many cognitive tasks, including verbal memory, motor speed, verbal fluency, attention, and processing speed, as well as measures from the cognitive battery as a whole (Wang et al. 2018). Data from imaging studies have indicated that ketamine-dependent patients displayed damage in multiple brain areas, such as the frontal, parietal, occipital, limbic, and corpus striatum (Liao et al. 2011; Wang et al. 2013). In addition, the damage appears to be correlated dose dependently with the duration and cumulative dose of ketamine used (Liao et al. 2011), manifesting minute patches in the first year, and the patches became larger sites of atrophy by 4 years of heavy use (Wang et al. 2013). One animal study also showed that brain function was not altered after 1 month of ketamine use but was impaired significantly after 6 months of use (Sun et al. 2014). The observation of a correlation between the dose and cognitive deficit is in line with clinical reports that higher doses of ketamine use are associated with poorer verbal fluency (Wang et al. 2018) and that heavier lifetime ketamine use is correlated with verbal learning and verbal memory deficits (Chan et al. 2013). Such observations collectively suggest that chronic and heavy ketamine use might predispose individuals to more severe cognitive impairment, particularly under higher doses and longer administration. Whether the cognitive impairment would ameliorate following abstinence remains unknown despite evidence indicating a trend where a longer duration of abstinence

is associated with better cognitive performance (Wang et al. 2018). In addition, the cognitive impairment associated with current ketamine users was not observed in ex-users (Tang et al. 2013). Future investigations that track the alterations in cognitive ability following more extended periods of abstinence from ketamine use are required.

6 Psychosis

Previous evidence demonstrating similarity between the cognitive and behavioral effects of ketamine in animals and humans and the signs and symptoms of schizophrenia (SZ) in humans suggests that abnormalities in NMDA receptor function play a role in the etiology of SZ (Javitt et al. 2012; Abi-Saab et al. 1998; Krystal et al. 2003; Lahti et al. 2001). Recreational ketamine abuse is associated with some subtle psychopathology that resolves with abstinence (Morgan et al. 2012). Persistent mild delusional ideation (Morgan et al. 2009, 2010), sensory disturbances, and other subthreshold psychotic symptoms (Fine and Finestone 1973; Stone et al. 2014; Tang et al. 2015a) are common among individuals with chronic ketamine abuse. Approximately 3% of ketamine abusers even develop psychotic symptoms that persist far beyond the period of intoxication (i.e., beyond 2 h following drug administration) (Krystal et al. 1994; Kleinloog et al. 2015; Abi-Saab et al. 1998; Adler et al. 1998; Liang et al. 2015; Zhang et al. 2014). The symptom factor structure was similar to that of SZ to a greater extent in individuals with ketamine-induced psychosis than in healthy individuals receiving a single dose of ketamine (Xu et al. 2015).

In a recent study, chronic heavy ketamine abusers with persistent psychotic symptoms beyond ketamine discontinuation (KPP) had PANSS profile total scores or subscale (positive, negative, and general psychopathology) scores similar to those of SZ patients (Cheng et al. 2018). However, those without persistent psychotic symptoms (KNP) had significantly less severe symptoms compared with the patients with KPP or SZ. In addition, individuals with KNP performed better in cognitive tests than the patients with KPP or SZ, who exhibited similar cognitive impairment characteristics, in particular spatial problem solving and verbal memory. Spatial memory has been found to be impaired in SZ patients, and this impairment predicts the transition to overt psychosis in individuals with a high risk of psychosis (Bang et al. 2015). In addition, patients with KPP consumed less than two-thirds of the daily ketamine consumption of patients with KNP. Overall, such observations suggest that ketamine administration might unmask a latent vulnerability to SZ-like syndrome in a subset of ketamine users and support the glutamatergic dysregulation hypothesis of SZ. Whether vulnerability to KPP, for example, based on genetic factors, might be a manifestation of risk factors unique to the syndrome or shared with SZ should be clarified in future studies.

7 Depression

Recent research has revealed the rapid antidepressant effects of acute intravenous infusion of low-dosed ketamine (Berman et al. 2000; Murrough et al. 2013; Zarate et al. 2006). The effects are superior with a repeated treatment protocol as compared with a single infusion (Murrough et al. 2013). In addition, the antidepressant effects generated by low anesthetic doses (10 mg/kg) of ketamine were not observed in rats receiving high doses (80 mg/kg) (Trujillo et al. 2011). In addition, preclinical evidence indicated that acute ketamine exposure would produce different neurobiological alterations following prolonged exposure (Kittelberger et al. 2012), suggesting that long-term and heavy ketamine abuse might be associated with distinct features resulting from the acute effects of low-dosed ketamine.

Some studies have suggested a link between chronic ketamine use and depression (Kalsi et al. 2011; Morgan et al. 2010, 2012). In a 1-year follow-up study, individuals who used ketamine frequently were observed to have increased depression scores over 12 months (Morgan et al. 2010). In clinical samples of ketamine abusers, self-reported depressive symptoms are rather common, with as high as 72.5%–77.5% of them scoring above the cut-off scores of moderate to severe depression assessed based on the Beck Depression Inventory (Fan et al. 2016; Tang et al. 2013). The prevalence of major depressive disorder (MDD) in outpatient samples of ketamine abusers was 7.8% (Liang et al. 2015), and the prevalence was estimated to be 18.5% through a chart-review analysis (Tang et al. 2015b), based on a standardized instrument. For inpatient populations, our data, also based a standardized interview, revealed that 23.3% (nearly one-fourth) of treatment-seeking ketamine-dependent patients had the MDD comorbidity (Chen et al. 2020).

To date, compared with its antidepressant effects, considerably less evidence is available with regard to the pro-depressant effects of ketamine (Chang et al. 2016). Contradictory outcomes for long-term to acute effects have been observed in other abused substances. For instance, although cocaine acutely produces intense euphoria, chronic administration of the drug may gradually cause a panic level of anxiety or depression (Rounsaville 2004). Because comorbid depression plays a role in conferring a risk of a poorer treatment response, more adverse outcomes (Hedden et al. 2010), maintaining substance use behavior (Cheetham et al. 2010; Cohn et al. 2014), assessment and screening of depressive symptoms, should be highlighted in the clinical management of chronic ketamine abusers.

8 Treatment of Ketamine Abuse

Currently, there is no effective pharmacotherapy for managing compulsive drug-seeking behavior in patients with ketamine use disorder. Ketamine abusers usually do not seek treatment until they have developed psychological problems or physical disorders, or they are forced to visit a psychiatric clinic for cessation use under the

pressure of their family or law enforcement. In the search for substance use disorder treatment options, agents with "anticraving" properties have been proposed as an emerging class of psychotropic medication (O'Brien 2005). The antiepileptic lamotrigine has been proposed for the treatment of ketamine use disorder considering its pharmacological effect on glutamate release inhibition and the results of clinical case studies (Huang et al. 2016). Treatment that incorporates regular urine screening in addition to medication for psychiatric symptoms has revealed fair results. As ketamine abuse and dependence grow, addiction services need to be better informed on the drug and its effects. Additional studies should aim to address the health challenges experienced by this group of abusers and to explore best practices for the treatment of ketamine addiction.

9 Conclusion

Ketamine has had a turbulent history since its first use as a clinical anesthesia for humans in 1964 (Domino 2010). Considering its analgesic–anesthetic mechanisms and antidepressant effects, ketamine is associated with a high potential of abuse or dependence. The pros and cons of ketamine use as well as other uncertainties regarding its use (e.g., antidepressant effect) required further study in the future.

Ketamine users seldom seek help despite the awareness about the negative side effects of the drug, which may contribute to the severity of ketamine dependence that is complicated by the associated physical and mental harm. Therefore, additional studies are required to increase the availability and accessibility of effective treatment interventions as well as preventative public education.

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