# Chapter 2

# Ketamine

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## Abstract

Ketamine has become a popular drug of abuse in many countries. In China ketamine was the third most abused drug just after heroin and methamphetamine. Illegal ketamine use cause severe mental and physical impairments. To control the illegal use of ketamine attracts much attention from governments and researchers. Because ketamine can induce psychiatric symptoms, ketamine was proposed to be a pharmacological model to mimic schizophrenia and ketamine was also identified to have fast antidepressant effects in treatment of depression. All of these facets of ketamine make it an intriguing target both in psychiatry and neuroscience field. Ketamine's history, ketamine abuse epidemiology, pharmacology, ketamine related symptoms and ketamine related biological changes were reviewed in this chapter.

## History

Ketamine, a derivative of phencyclidine (PCP), was first synthesized in 1962 by the American chemist Calvin L. Stevens. A few years later, following the federal government's approval of ketamine for human use in 1970, ketamine anesthesia was first given to American soldiers during the Vietnam War [1]. Ketamine is also used widely in veterinary medicine or battlefield as an anesthetic in developing nations [2]. Ketamine is on the World Health Organization's List of Essential Medicines, which as the most important medications needed in a basic health system. Its hydrochloride salt is sold as Ketanest, Ketaset, and

Ketalar. Ketamine's hallucinogenic effects eventually made it a popular psychedelic in 1970. Its illicit use as a recreational drug of abuse was documented in the early 1970s in underground literature (e.g. The Fabulous Furry Freak Brothers). The drug was used in psychiatric and other academic research through the 1970s. Extraordinary phenomenology of ketamine intoxication was documented by John Lilly and Marcia Moore et al in 1978.

## Ketamine use Epidemiology

Ketamine use as a short acting, dissociative anesthetic in surgery began some years later in 1970. But even before its use in the medical community, observers had noted its non-medical use in the late 1960s. From the mid 1980s onwards, the recreational use of ketamine along with ecstasy gained popularity among young person has since spread to Europe, Canada, Asia, and Australia. Ketamine's rise in the dance culture was most rapid in Hong Kong by the end of the 1990s [3], and is the most popular recreational drug in Taiwan in youths [4]. In China, ketamine has become the third most common drug abused, there has been 190,000 registered ketmine abusers in 2013 [5]. Data from United Nations show that most global ketamine abusers are distributed mainly in China. Outside of Asia, the prevalence of ketamine use among "club drug" users increased from 25% to 40% in the United Kingdom from 1999 to 2003 [6].





Ketamine users are majorly men and tend to be young, and this phenomenon consistent with the profile of other substance abusers. Statistics from the fifty-ninth issue in a series of Central Registry of Drug Abuse (CRDA) Reports show that the number of ketamine users in Hong Kong has increased from 36.9% of young drug users under the age of 21 in 2000 to 84.3% in 2009. Since young users are more likely to inject ketamine intravenously therefore result in higher incidence of comorbid hepatitis C infection [7,8]. Illicit ketamine use is of great concern to many. Consequently, in 2004, ketamine was classified as a psychotropic substance in Schedule I in China (F.D.A., 2004). In Hong Kong ketamine is regulated under Schedule 1 of Hong Kong Chapter 134 Dangerous Drugs Ordinance in 2000. And that ketamine can only be used legally by health professionals, for university research purposes, or with a physician's prescription in Hong Kong.

Ketamine has over the past few years been thought of as a 'club drug' at nightclubs and "raves". Ketamine first appeared in the gay dance scene during the early 1990s in the UK. In the dance scene setting, ketamine is sold in either powdered or capsules and liquid form, where it can be bought over the counter in the marketable content [9]. Due to the complexity of its chemical synthesis, ketamine sold illicitly comes from diverted or theft of licit medical sources, primarily from veterinary clinics. Recreational use of ketamine mainly at home, dance hall, night club and hotel [10]. Ketamine is usually injected intravenously

or intramuscularly [11], but it is also effective when insufflated, smoked, or taken orally [12].

## Pharmacology (Pharmacodynamics, Pharmacokinetics and Side Effects)

The main pharmacological action of ketamine is as a non-competitive antagonist of the N-methyl-daspartate (NMDA) receptor [13]. Ketamine has central excitatory and inhibitory effects, as well as anti-anxiety, narcotic, hallucinogenic and generally psychotomimetic effects. Low-dose ketamine is effective in the treatment of complex regional pain syndrome (CRPS) [14,15], and especially involving in the treatment of neuropathic pain syndromes [16]. In medical settings, ketamine is used as an anesthetic, because it suppresses breathing much less than most other available anesthetics [17]. Ketamine is still used as a bronchodilator in the treatment of severe asthma for children [18]. In addition, it has been found that a single sub-anesthetic dose of intravenous ketamine has rapid-acting antidepressive effects in patients with depression [19,20].

The active enantiomer of ketamine is S (+)-ketamine. Ketamine is mostly metabolized into norketamine (80%). This metabolism does not simply involve the liver [21], the site of significant metabolism include: the kidneys, the intestine, and the lungs in animals [22]. Ketamine elimination half-life is 2–3 h. Its clearance may be 20% higher in women than in men [23].





When used in medicine ketamine is generally safe when administered by trained medical professionals [24]. Thus, the psychotropic side effects are less obvious, but the higher doses required can lead to disorienting side effects [25]. There are known side effects that include: arrhythmia, high blood pressure or low blood pressure in cardiovascular system; increased intracranial pressure (ICP) [26]. In addition, there are anaphylaxis (transient erythema, morbilliform rash), dependence, emergence reaction.

## Dependence and Withdrawal Symptoms

Ketamine is similar to other drugs linked with dependence including stimulants, opiates, alcohol, and cannabis. A common characteristic of ketamine dependence is that a short period of time of repeated overuse cause of the user indulging in the drug. A study in mice reported that acute and chronic ketamine administration significantly enhanced dopamine release, and chronic ketamine injection increasing dopamine receptor 1 and 2 gene expression [27]. It has been implied that the dopamine reward pathway may play an important role in developing ketamine dependence.

Thus far, little is known about ketamine withdrawal symptoms in humans. Few studies of withdrawal symptoms in ketamine addiction have been done. The most recent study reported that increased immobility during

force swimming test (FST) of mice persisted for 10 days after withdrawing ketamine [28]. A few case studies also show craving and somatic and psychological aspects of anxiety as withdrawal symptoms [29-31]. However, a specific ketamine withdrawal syndrome has not yet been described.

## Psychodysleptic Effects

Acute use of ketamine produces a dissociative state, disturbances of the visual and auditory, body image, time perceptions and mood. These disturbances characterised by a sense of detachment from one's physical body and derealization, of floating, or depersonalization, conscious dreams, or hallucinations [32,33]. Ketamine is very short-acting dissociatives comparing with phencyclidine (PCP) and dextromethorphan (DXM). It takes effect within about 10 minutes [34], while its hallucinogenic effects last 60 minutes or less, but following initial use, the user's senses, judgment, and coordination may be affected for up to 24 hours. In healthy volunteers, a linear dose-effect relationship between the progressive effects and ketamine concentration (concentrations between 50 and 200ng/ml) was demonstrated [35]. More severe effects (anxiety and paranoid feelings) appear around 500ng/ml [36]. At sufficiently high doses ketamine can lead to acute delirium with visual and auditory hallucinations. Ketamine is also commonly abused with other drugs to enhance their effects.





## Ketamine Induced Psychosis

Ketamine provokes distinctive pathopsychological symptoms in humans and rodents which have showed some similarities with those observed in schizophrenia patients [37,38]. Ketamine has thus been widely investigated as a potential pharmacological model to test the hypoglutamatergic function hypothesis for schizophrenia [39-41]. A single intravenous dose of ketamine infusion in healthy volunteers induces acute psychotic symptoms, and produces not only positive but also negative symptoms, as well as impairment of memory [39,42]. Morgan et al. found that frequent ketamine users exhibit delusional ideation which were persisted for up to one year and that delusions persisted even when ketamine was discontinued [43]. However, there is no evidence of persistent psychosis in a low dose, short-term ketamine administration [44].

In addition to perceptual changes and delusions, ketamine also causes prominent emotional blunting, anhedonia and social withdrawal. Ketamine may induce negative symptoms through direct inhibition of the NMDA receptor [45]. Ke et al. measured the psychotic symptom dimensions of ketamine users (acute and chronic) using the Positive and Negative Syndrome Scale (PANSS) comparing to schizophrenia patients (early and chronic stages). They found the items in negative factor (six common symptoms were: blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity

& flow of conversation and motor retardation) were most consistent across the four groups [46].

Even though studies on ketamine-induced psychosis are burgeoning, little is known about the underlying molecular mechanisms responsible for ketamine-associated psychosis. There was emerging evidence that the glutamate neuronal transmitters system was evolved in the pathogenesis in ketamine psychosis. Here, clarifing genetic variations impacting transcriptional control of NMDA Rs and full sequencing of NMDA receptor genes may help explain individual vulnerability to ketamine abuse and ketamine-associated psychosis [47].

## Ketamine Induced Cognition Impairments

The association between cognition impairments and ketamine abuse has been a research interest in the field of cognitive neuroscience over the last two decades [39,48-50]. Both animal and human studies have shown that ketamine can impair cognitive function, such as episodic memory, semantic memory, working memory, executive function and procedural learning [51-54]. In humans, a single dose of ketamine induces working and episodic memory impairments, as well as executive function [55]. Following 4 but not 2 weeks of daily injection ketamine of 5 mg/kg in mice, an impaired fear memory has been found [56]. Both short- and long-term memory impairments





are the most common characteristics of ketamine abusers [55]. Furthermore, in a longitudinal study, ketamine use caused impairments in visual recognition and spatial working memory that correlated with level of ketamine use over 12 months [57]. Krystal and colleagues assayed the effects of ketamine on the Wisconsin card sort task (WCST) and found that ketamine significantly increase the number of total errors and the number and percent of perseverative errors. Ketamine also increase distractibility, impaire recall, altere perception [58]. Similarly, the effect of ketamine on attentional measures has been explored [59-61]. For example, mismatch negativity (MMN). The results have shown that smaller MMN to both pitch and duration deviants was significantly correlated to ketamine use [60].

## Effects in Peripheral Systems

Ketamine can cause a variety of urinary tract problems. A group of urinary tract damage with the misuse of 'street K' was first reported by Chu in Hong Kong Medical Journal in 2007. They reported that long term use may result in damage to the liver or urinary bladder, or even lead to acute renal failure [62]. Some researchers propose that ketamine abuse leading to damage of urinary tract system is the consequence of the immune response. Thickening of the bladder wall, a small capacity, and perivesicular stranding were identified in daily ketamine users, which are consistent with severe inflammation [63]. Also

at cystoscopy ketamine users had severe ulcerative cystitis [63,64]. Bilateral hydronephrosis and renal papillary necrosis have also been reported in some cases [48,65]. Following dose reduction, the symptoms of the lower urinary tract remitted [48]. In addition, recent report found that liver enzyme abnormalities occurred following repeat treatment with ketamine infusions. It is suggested that liver enzymes must be monitored during involving higher doses and repeated exposure to ketamine [66].

## Biological Changes Related to Ketamine Use

It was showed that acute administration of ketamine produced fast behavioural antidepressant effects, decreased significantly the immobility time of rats in Forced Swimming Test (FST) compared to saline group [67]. Acute intravenous administration of low dose ketamine to depressed patients elicited a rapid antidepressant effect within 2 h, which sustained for 7-10days [68,69]. Studies showed that acute ketamine increased Brain Derived Neurotrophic Factor (BDNF) levels in hippocampus, cerebral cortex and antidepressant effect of ketamine was attenuated in BDNF knockout mice [70], which implicated the role of BDNF in the antidepresant effects of ketamine.

Work from laboratory went on to show that ketamine, through blockade of NMDA receptors, activated a specific intracellular signaling pathway to rapidly increase BDNF





protein expression. Low dose ketamine, by blocking the activation of NMDA receptors, decreased the influx of calcium through the receptor, thereby inhibiting eukaryotic elongation factor 2 kinase (eEF2K) [70]. Eukaryotic elongation factor 2 (eEF2), the substrate of eEF2K, phosphorylated by eEF2K, then suppressed protein translation [71]. Ketamine-mediated NMDAR blockade at rest inhibited eEF2K resulting in reduced eEF2 phosphorylation and de-suppression of BDNF translation, leading to a rapid increase in BDNF protein expression in the hippocampus.

Compared with those researches about acute administration of ketamine, the studies of chronic ketamine usage were not enough. While chronic use of ketamine may have opposite effects on Neurotrophic factors. One study showed that the serum BDNF and NGF concentrations were lower in chronic ketamine users than that in healthy control subjects and that the decrease of BDNF level was correlated with high frequency of ketamine intake [72]. It was also reported that serum levels of vascular endothelial growth factor (VEGF), a potent growth factor, were decreased in chronic ketamine users compared with healthy subjects [73].

Ketamine has also been showed to interfere with inflammatory response [74]. Previous studies showed that ketamine could suppress the syntheses of lipopolysaccharide (LPS)-induced proinflammatory cytokine, such

as TNF-α, IL-6 and IL-1β, suggesting a close relationship between ketamine and cytokine levels [74-76]. It was reported that serum IL-6 and IL-18 levels were significantly higher among ketamine users than those among healthy controls, whereas serum TNF-α level was significantly lower in ketamine users [77].

Long term use of ketamine have effects on brain structure. White matter changes associated with chronic ketamine use were found in bilateral frontal and left temporoparietal cortices and chronic ketamine use was indicated to associate with widespread disruption of white matter integrity [78,79]. And it was reported that chronic use of ketamine significant decrease gray matter volume in bilateral frontal cortex of ketamine users in comparison with control subjects [80].

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