MEDWIN PUBLISHERS
Committed to create value for Researchers

Advances in Clinical Toxicology
ISSN: 2577-4328

# Emerging Trends in the Abuse of Ketamine and its Side Effects on Health: Toxicology and Addiction Potential

**Zou J, Tan S***

*Department of Histology and Embryology, University of South China, PR China

***Corresponding author:** Sijie Tan, Department of Histology and Embryology, School of Medicine, University of South China, 28# West Chansheng Road, Hengyang, Hunan, PR China, 421001, Tel: +86 734 8281 388; E-mail: sijietan@126.com

**Review Article**

**Volume 1 Issue 1**

**Received Date**: July 19, 2016

**Published Date:** July 22, 2016

**DOI:** 10.23880/act-16000106

## Abstract

Ketamine, a noncompetitive N-methyl-d-asparate (NMDA) receptor antagonist, has been widely used in clinical settings as an anesthetic agent. However, ketamine also causes delirium and hallucination, which lead to its recreational use and abuse. Here, we reviewed the trends in ketamine abuse and its side effects on health, including the research advances in epidemiology, toxicology and its addiction potential. Due to the lower cost, ketamine have become the most popular abused drug in Eastern Asia, especially in the young people. Ketamine cause damages in the peripheral system as well as central nervous system (CNS). Both symptoms in the lower urinary tract such as cystitis and cardiac pathology have been noted. In the CNS, chronic ketamine causes neurodegeneration pathology as demonstrated in animal's studies. Several reports on the ketamine dependence in human cases and animals as well, which indicate the addiction potential of ketamine. To devise therapeutic approaches for ketamine abusers, future studies focusing on understanding the changes in the CNS during the formation ketamine dependence are desired.

**Keywords:** Ketamine; Abuse; Chronic Toxicity; Urinary Bladder; Central Nervous System

**Abbreviations:** NMDA: N-Methyl-D-Asparate; CNS: Central Nervous System; PCP: Phencyclidine; CRDA: Central Registry of Drug Abuse; CRDAR: Central Registry of Drug Abuse Report; $GABA_A$: Gamma-amino butyric Acid Type A; LDH: Lactate Dehydrogenase; LTP: Long-term Potentiation; TUNEL: Terminal dUTP Nick End Labeling;

## Introduction

Ketamine was developed in 1960s and initially known as Ci-581. After synthesis, it was introduced into medical use as a new dissociative anaesthetic [1]. Ketamine induced a state of dissociative anaesthesia by cutting off the connections between thalamic function and the limbic system. In the beginning, ketamine was thought to be a safer substitution of phencyclidine (PCP), which was developed as an anesthetic agent before 1960s but was not approved for clinical use. Ketamine had a short duration of action and its half-life in the liver was 2.5-3 hours [2], whereas PCP was more stable in human body with a longer half-life of 7-46 hours and it thus had many side effects, such as hallucinogenic and neurotoxic effects. Besides, ketamine showed less suppression effects on breathing and fewer propensities to produce convulsions than other anaesthetics. Ketamine received FDA approval in human in 1971. In 1970s, ketamine was first used in

soldiers in the Vietnam War and today it remains an alternative choice in pediatrics and veterinary medicine. In medical settings, ketamine was given through intravenous or intramuscular injection and the anaesthetic dosages of ketamine varied from 2 to 100mg/kg in different species. In mice, ketamine (80-100 mg/kg) and xylazine (15 mg/kg) was a common combination to induce anaesthesia [3]. In human, it was used in pediatric anesthesia, emergency medicine and local anaesthesia. The intravenous dose for anesthesia was 1 to 2 mg/kg whereas the intramuscular dose was 2 to 4 mg/kg. Anaesthesia started at 1 minute following ketamine injection and lasted for 5-10 minutes [4]. In emergency medicine such as burn patients, ketamine was regarded as the first choice for anesthesia and it was used intravenously at low dosage to relief from pain [5].

## Ketamine and abuse

Since 1970s, the side effects of ketamine had been increasingly recognized [6-8]. Psychologically, acute use of ketamine caused hallucination, symptoms of psychosis, delusion, agitation, confusion, and memory impairment [9]. Besides, many side effects, such as nausea and vomiting, bizarre dreams, were reported. These side effects have been documented in a dose-dependent fashion and some of them persisted for several days after administration. For example, recurrent of hallucinations appeared even 5 days after ketamine anaesthesia in a young boy [10]. After low doses of use, abusers had a mild feeling of floating outside their body. Following heavy ketamine use, abusers experienced a near death feeling, which was also known as “K hole” and “out of body” experiences. These stimulating effects of ketamine made it a popular recreational drug and were repeatedly used in at night clubs, dance parties, and rave scenes by the young people. In these locations, ketamine was sold illicitly either as white powder, pills or liquid, which known as the names of “Special K”, “Vitamin K” or “SuperK” [11]. Abusers took this drug by snorting (15-200 mg), orally (75-300 mg) or injected intramuscularly (25-125 mg) [12].

Since a few reports on non-medical use of ketamine in 1990s [13], abuse of ketamine has increased rapidly in many countries and areas, particularly in East and South-East Asia. Ketamine’s growth in popularity was thought to be because of its low price. During 2007 to 2009, the average price of ketamine was about HK$144 per pure gram in Hong Kong, which was cheaper than other drugs such as the main component of ecstasy methamphetamine. In Hong Kong, abuse of ketamine has been well documented by the Central Registry of Drug Abuse (CRDA) and the Central Registry of Drug Abuse Report (CRDAR) was released yearly. According to the CRDAR, the number of ketamine users in 2008 had doubled compared with that in 2004. Since 2008, ketamine has been the second-most popular abusive drug except heroin in Hong Kong. In 2011, it was reported that 31.5% of abused drugs was ketamine. In the newly reported drug abusers, ketamine accounted for about 60% in all reported drugs. Especially in the group of addicts aged under 21, ketamine dominated the abused drugs and accounted for more than 80% in all reported drugs [14]. In the United Kingdom, the recent data indicated that ketamine abusers increased from 85, 000 in 2006/07 to 113,000 in 2008/09. Around 4.0% of the population had used ketamine during their lifetime and ketamine abuse affected 1.7% of the population in 2009/10 [15]. Ketamine use related deaths were also reported in the UK and the number increased 10-folds from 1999 to 2008 [16]. In northern Italy, an investigation of 2015 subjects at musical events and raves found that 7% people had used ketamine [17]. In Canada, the prevalence of ketamine abuse was estimated as 2.2% in 2009. In Australia, 1% Australians at 14 years of age or older had used ketamine [18]. Ketamine abuse was also reported in Taiwan [19-20] and the United States [21].

## Pharmacological effects of ketamine

After intravenous administration, most of ketamine accumulated in the central nervous system (CNS) through the systemic circulation with a 6.5:1 brain-to-plasma ratio in rats [22]. Although increasing data has demonstrated ketamine interacted with other neurotransmitter receptors, ketamine is mostly known for a noncompetitive antagonist of a glutamate receptor, the N-Methyl-D- aspartate (NMDA) receptor. As a derivate of PCP, ketamine showed similar pharmacological effects with its predecessor. It can uncompetitively block NMDA receptor through binding on its PCP site and closed the ion channel to inhibit NMDA receptor mediated calcium ion influx [23]. Following ketamine administration, blockade of NMDA receptor was found in the brain as well as the spinal cord [24]. Besides the glutamate receptor, ketamine was known to interact with opioid receptors *in vitro* and *in vivo* [25-26]. In human neuroblastoma SH-SY5Y cells, it was found that ketamine interacted with μ(2) opioid receptors at clinically relevant concentration but no direct agonist activity on this receptor was observed [27]. Recent study showed that ketamine enhanced effects of opioid induced ERK1/2 signaling pathways and increased the effectiveness as well as the

duration of opiate-induced analgesia [28]. On top of this, ketamine also acted on cholinergic receptors. Durieux and colleagues [29] reported that keatmine inhibited muscarinic acetylcholine receptors and showed anticholinergic clinical effects. Ketamine interacted with nicotinic acetylcholine receptors at closed state [30]. Ketamine also potentiate gamma-aminobutyric acid type A ($GABA_A$) receptors, which form the major inhibitory neurotransmission in the CNS. Irifune and colleagues [30] reported that ketamine had $GABA_A$ receptors agonistic properties and ketamine-induced anesthesia could be partly mediated by $GABA_A$ receptors. In *in vitro* studies, ketamine at anesthetically relevant concentrations modulated alpha 6 containing $GABA_A$ receptors, which was mainly distributed in the cerebellum granular neurons. At higher concentrations, ketamine directly activated the receptors and induced an inward chloride ion current. These actions of ketamine caused hyperpolarization of the membrane thus inhibited the firing of action potentials [31-32].

## Toxic effects of ketamine on peripheral system

Toxicity of ketamine on the urinary system had been demonstrated in the kidney and urinary bladder. Infiltrations of mononuclear white cells were observed following 1 month of ketamine treatment in kidney. Mononuclear infiltration were demonstrated near to glomeruli, blood vessels forming perivascular cuffing [33]. Lower urinary tract symptoms in ketamine abusers were first reported in 2007 [34-35]. Chu and colleagues reported 10 patients, who had been taking ketamine for 1 to 4 years, presented to the hospital with urinary tract symptoms [34]. The main symptoms were dysuria, frequency, urgency, incontinence, pain, gross hematuria and decreased bladder capacity. Cystoscopy and bladder biopsy showed inflammation and vascular congestion on the bladder wall that was similar with cystitis. Shahani and colleagues reported 9 daily ketamine users presented with similar symptoms [35]. Cystoscopy showed that all the patients had severe ulcerative cystitis. Biopsies of 4 cases also revealed inflammation with eosinophilic infiltration and epithelial denudation. A larger scale survey revealed that the incidence of lower urinary tract symptoms in ketamine abusers was about 30% (29 of 97) [36]. More severely, a recent review of 96 cases showed that even 92 % of chronic ketamine users have some features of cystitis [37]. Severity of symptoms was associated with chronicity because slight symptoms started after 1 month of ketamine use while it developed more severe and obvious after 1 year use [38]. So far no effective medicinal treatment for these symptoms is available but the symptoms sometimes reduced or relieved after acquittal of the drug [34]. As ketamine and its metabolites norketamine were detected in urine, Howard proposed that these toxic components in urine caused damage to the epithelium layer and microvasculature through direct contact [39]. Histological examination on bladders in animal studies showed loss of muscle proportion and increase of connective tissue in the bladder [40], which confirmed that ketamine may also cause damage in the deep layers of the bladder wall.

Cardiotoxicity of ketamine has already been demonstrated. Following ketamine use, increased heart rate and the pulmonary venous pressure were observed in mice and human as well [41-42]. Long-term ketamine treated mice showed abnormal electrocardiogram with increased incidence of ST-segment elevation, especially in the prolonged (6 months) treated groups. Abnormal cardiovascular functions were further confirmed by histopathological changes in the heart muscle cells. For example, there were increased LDH reactive cells and degenerative changes such as vesiculation and lysis of cytoplasm in the cardiac cells of ketamine treated mice. Serum troponin levels, indications of cardiac failure and circulatory collapse, were largely increased in ketamine treated mice [43]. Interestingly, withdrawal from ketamine could partially reduced toxicity on the heart and kidney as well, while environmental enrichment during the period of abstinence greatly promoted the recovery [44].

Toxic effects of ketamine on liver and intestinal were also found. Sixteen weeks of ketamine treatment caused obvious damages to the liver. There were increased glutamic oxaloacetic transaminase, lactate dehydrogenase, and proliferative nuclear antigen in the liver. Fibrosis and fatty degeneration of liver cells were also observed in mice [45]. As well, chronic ketamine administration decreased proliferative cell nuclear antigen in the mucosa of the intestines, apoptosis or necrosis were observed in these cells [46].

## Effects of ketamine on the CNS

Previous studies also reported some adverse effects of ketamine on the CNS. Dundee and colleagues reported that increased postoperative serum enzymes levels were found in patients anaesthetised with ketamine infusions [47], which was similar to that happened in toxic hepatitis. Besides, a lot of studies had focused on the possible toxic effects of ketamine in neonatal animals due

to its widely use in pediatrics. During a particular developmental period (between 16-21 days old), exposure to combination of ketamine and xylazine induced corneal lesions in rats [48]. Ikonomidou and colleagues first reported that repeated doses ketamine and other NMDA receptor antagonists increased widespread neuronal apoptosis in the brain of 7-day-old rats [49]. Neurotoxic effects of ketamine on the developing CNS were further confirmed in the following studies in mice and monkeys [50-52]. The apoptogenic actions of ketamine were also observed in monkeys at both fetal and neonatal age. Ketamine exposure caused apoptosis of neurons were more obvious in fetuses than in neonates [53]. Although the immediately toxic effects of ketamine on the developing CNS were pronounced, the follow-up study did not find any associated adverse neurodevelopmental outcome and abnormal neurological or behavioral performance in early childhood [54-55].

The growing ketamine abuse raised concerns about its long-term adverse effects in adults. Frequent and chronic recreational use of ketamine tended to impair cognition. NMDA receptors played a vital role in mechanisms of long-term potentiation (LTP), which was believed to be a fundamental key facilitating synaptic plasticity and memory formation [56]. As a non-competitive NMDA receptor antagonist, the most notable effects of ketamine were on the learning and memory. Acute doses of ketamine caused impairments of working memory and cognitive function, through affecting recollective processes involved in retrieval and initial encoding of information [57-58]. Chronic use of ketamine led to aparent impairments on these functions [59]. On top of this, long-term of ketamine may lower motor acitivity. In habitual ketamine users, cerebellar activities were significantly downregulated when they were performing simple motor function tasks. In particular, alcohol enhanced ketamine induced the down regulation in cerebellum as ketamine users who drank alcohol before the test showed even less activated volume in the cerebella. Histological examination showed loss of purkinje cells and increased cell apoptosis in the cerebellum of the mice chronic treated ketamine and ketamine plus alcohol [60]. After 3 and 6 months ketamine administration, hyperphosphorylated tau proteins were significant increased in the prefrontal and entorhinal cortices of mice and monkeys brains. Furthermore, about 15% of hyperphosphorylated tau positive cells showed apoptosis as showed by terminal dUTP nick end labeling (TUNEL) staining [61]. These changes were regarded as ketamine induced neurodegeneration as hyperphosphorylated tau and apoptosis are the common characteristics in the brains of patients suffering from neurodegenerative diseases. These neurodegenerative changes may partly contribute to ketamine caused cognitive impairments. A large scaled screen of gene expression changes in the CNS following prolonged ketamine use in mice showed that $GABA_A$ receptors, which mediated the inhibitory neurotransmission, could also played roles in cognitive impairment induced by ketamine [62].

In recent years, many cases reports on prolonged ketamine abuse in human have been published, which raised the concern whether chronic use of ketamine would cause dependence and addiction [63-65]. In human, it was ported that the abuse of ketamine may last several years, while abstinence of ketamine cause anxiety like behaviors and sleep disorders [66-67]. Indeed, repeated administration of ketamine induced conditioned place preference in rats, which implicated the potential of addiction for ketamine [68]. Chronic ketamine use caused anxiety like behaviors in mice as demonstrated by the elevated plus maze test and the expression of drug dependence related genes were differentially expressed [69]. Although the mechanism is not well known, ketamene activated the dopaminergic pathway, the rewarding system in the CNS, which may be critical in the formation of dependence [70]. Huang and colleagues reported that blockade of GSK-3β decreased ketamine self-administration and reduced drug-seeking behavior after abstinence [71], which provided the potential target for treating ketamine addiction.

## Conclusion

Recreational use and abuse of ketamine, an NMDA receptor antagonist, has been increased rapidly. Abuse of ketamine raised concern about its side effects on human health. Indeed, toxic effects were noted in the peripheral system and the CNS. Symptoms in the lower urinary tract such as cystitis and cardiac pathology have been noted following prolonged ketamine use. In addition, ketamine dependence in human cases and animals studies pointed out its addiction potential. Future studies focused on better understanding of changes in the CNS during ketamine dependence are needed to devise therapeutic approaches for ketamine abusers.

## Acknowledgement

The authors would like to thank supporting from the National Science Foundation of China (81301144) and the

startup grant from the University of South China (2014XQD22).

## References

1. Domino EF, Chodoff P, Corssen G (1965) Pharmacologic effects of Ci-581, a new dissociative anesthetic, in man. Clin Pharmacol Ther 6: 279-291.

2. Hijazi Y, Boulieu R (2002) Contribution of CYP3A4, CYP2B6 and CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes. Drug Metab Dispos 30(7): 853-858.

3. Green CJ, Knight J, Precious S, Simpkin S (1981) Ketamine alone and combined with diazepam or xylazine in laboratory animals: a 10 year experience. Lab Anim 15(2): 163-170.

4. Sinner B, Graf BM (2008) Ketamine. Handb Exp Pharmacol 182: 313-333.

5. Ceber M, Salihoglu T (2006) Ketamine may be the first choice for anesthesia in burn patients. J Burn Care Res 27(5): 760-762.

6. Fine J, Finestone SC (1973) Sensory disturbances following ketamine anesthesia: recurrent hallucinations. Anesth Analg 52(3): 428-430.

7. Fischer R (1974) A pharmacological and conceptual reevaluation of hallucinations. Confin Psychiatr 17(3-4): 143-151.

8. MacLennan FM (1982) Ketamine tolerance and hallucinations in children. Anaesthesia 37(12): 1214-1215.

9. Knox JW, Bovill JG, Clarke RS, Dundee JW (1970) Clinical studies of induction agents. XXXVI: Ketamine. Br J Anaesth 42(10): 875-885.

10. Perel A, Davidson JT (1976) Recurrent hallucinations following ketamine. Anaesthesia 31(8): 1081-1083.

11. Wolff K, Winstock AR (2006) Ketamine: From medicine to misuse. CNS Drugs 20(3): 199-218.

12. Erowid (2000) Ketamine Basics. http://www.erowid.org/chemicals/ketamine/ketamine_basics.shtml

13. Dalgarno P J, Shewan D (1996) Illicit use of ketamine in Scotland. J Psychoact Drugs 28(2): 191-199.

14. Central Registry of Drug Abuse Sixty-fourth Report (2014) http://www.nd.gov.hk/en/drugstatistics.

15. Hoare J, Moon D (2010) Drug misuse declared: findings from the 2009/10. British Crime Survey England and Wales. Home Office Statistical Board. London: Home Office: 2010.

16. Morgan CJ, Curran HV (2012) Ketamine use: a review. Addiction 107(1): 27-38.

17. Pavarin RM (2006) Substance use and related problems: a study on the abuse of recreational and not recreational drugs in Northern Italy. Ann Ist Super Sanità 42(4): 477-484.

18. Degenhardt L, Copeland J, Dillon P (2005) Recent trends in the use of "club drugs": an Australian review. Subst Use Misuse 40(9): 1241-1256.

19. Wang YC, Lee CM, Lew-Ting CY, Hsiao CK, Chen DR, et al. (2005) Survey of substance use among high school students in Taipei: web-based questionnaire versus paper -and-pencil questionnaire. J Adolesc Health 37(4): 289-295.

20. Chen WJ, Fu TC, Ting TT, Huang WL, Tang GM, et al. (2009) Use of ecstasy and other psychoactive substances among school-attending adolescents in Taiwan: national surveys 2004-2006. BMC Public Health 9:27.

21. Maxwell JC (2005) Party drugs: properties, prevalence, patterns, and problems. Subst Use Misuse 40(9-10): 1203-1240.

22. Cohen ML, Chan SL, Way WL, Trevor AJ (1973) Distribution in the brain and metabolism of ketamine in the rat after intravenous administration. Anesthesiology 39(4): 370-376.

23. Irifune M, Shimizu T, Nomoto M, Fukuda T (1992) Ketamine-induced anesthesia involves the N-methyl-D-aspartate receptor-channel complex in mice. Brain Res 596(1-2): 1-9.

24. Collins JG, Kendig JJ, Mason P (1995) Anesthetic actions within the spinal cord: contributions to the state of general anesthesia. Trends Neurosci 18(12): 549-553.

25. Smith DJ, Bouchal RL, deSanctis CA, Monroe PJ, Amedro JB, et al. (1987) Properties of the

interaction between ketamine and opiate binding sites in vivo and in vitro. Neuropharmacology 26(9): 1253-1260.

26. Baumeister A, Advokat C (1991) Evidence for a supraspinal mechanism in the opioid-mediated antinociceptive effect of ketamine. Brain Res 566(1-2): 351-353.

27. Hirota K, Sikand KS, Lambert DG (1999) Interaction of ketamine with mu2 opioid receptors in SH-SY5Y human neuroblastoma cells. J Anesth 13(2): 107-109.

28. Gupta A, Devi LA, Gomes I (2011) Potentiation of μ-opioid receptor-mediated signaling by ketamine. J Neurochem 119(2): 294-302.

29. Durieux ME (1995) Inhibition by ketamine of muscarinic acetylcholine receptor function. Anesth Analg 81(1): 57-62.

30. Irifune M, Sato T, Kamata Y, Nishikawa T, Dohi T, et al. (2000) Evidence for GABA(A) receptor agonistic properties of ketamine: convulsive and anesthetic behavioral models in mice. Anesth Analg 91(1): 230-236.

31. Anis NA, Berry SC, Burton NR, Lodge D (1983) The dissociative anaesthetics, ketamine and phencyclidine, selectively reduce excitation of central mammalian neurones by N-methyl-aspartate. Br J Pharmacol 79(2): 565-575.

32. Hevers W, Hadley SH, Lüddens H, Amin J (2008) Ketamine, But Not Phencyclidine, Selectively Modulates Cerebellar GABAA Receptors Containing α6 and δ Subunits. J Neurosci 28(20): 5383-5393.

33. Yeung LY, Rudd JA, Lam WP, Mak YT, Yew DT (2009) Mice are prone to kidney pathology after prolonged ketamine addiction. Toxicol Lett 191(2-3): 275-278.

34. Chu PS, Kwok SC, Lam KM (2007) 'Street ketamine'-associated bladder dysfunction: a report of ten cases. Hong Kong Med J 13(4): S1-3.

35. Shahani R, Streutker C, Dickson B, Stewart RJ (2007) Ketamine-associated ulcerative cystitis: a new clinical entity. Urology 69(5): 810-812.

36. Chu PS, Ma WK, Wong SC, Chu RW, Cheng CH, et al. (2008) The destruction of the lower urinary tract by ketamine abuse: A new syndrome? BJU Int 102(11): 1616-1622.

37. Chan YC (2012) Acute and Chronic Toxicity Pattern in Ketamine Abusers in Hong Kong. J Med Toxicol 8(3): 267-270.

38. Tsai TH, Cha TL, Lin CM, Tsao CW, Tang SH, et al. (2009) Ketamine-associated bladder dysfunction. Int J Urol 16(10): 826-829.

39. Howard SS (2010) Ketamine-Induced Urologic Insult (KIUI). Pain Physician 13: E343-E346.

40. Tan S, Chan WM, Wai MS, Hui LK, Hui VW, et al. (2011) Ketamine effects on the urogenital system--changes in the urinary bladder and sperm motility. Microsc Res Tech 74(12): 1192-1198.

41. Spotoft H, Korshin JD, Sørensen MB, Skovsted P (1979) The cardiovascular effects of ketamine used for induction of anaesthesia in patients with valvular heart disease. Can Anaesth Soc J 26(6): 463-467.

42. Droogmans S, Lauwers R, Cosyns B, Roosens B, Franken PR, et al. (2008) Impact of anesthesia on valvular function in normal rats during echocardiography. Ultrasound Med Biol 34(10): 1564-1572.

43. Chan WM, Liang Y, Wai MS, Hung AS, Yew DT (2011) Cardiotoxicity induced in mice by long term ketamine and ketamine plus alcohol treatment. Toxicol Lett 207(2): 191-196.

44. Li X, Li S, Zheng W, Pan J, Huang K, et al. (2015) Environmental enrichment and abstinence attenuate ketamine-induced cardiac and renal toxicity. Sci Rep 5: 11611.

45. Wai MS, Chan WM, Zhang AQ, Wu Y, Yew DT (2012) Long-term ketamine and ketamine plus alcohol treatments produced damages in liver and kidney. Hum Exp Toxicol. Hum Exp Toxicol 31(9): 877-886.

46. Wong YW, Lam LH, Tang HC, Liang Y, Tan S, et al. (2012) Intestinal and liver changes after chronic ketamine and ketamine plus alcohol treatment. Microsc Res Tech 75(9): 1170-1175.

47. Dundee JW, Fee JP, Moore J, McIlroy PD, Wilson DB (1980) Changes in serum enzyme levels following ketamine infusions. Anaesthesia 35(1): 12-16.

48. Guillet R, Wyatt J, Baggs RB, Kellogg CK (1988) Anesthetic-induced corneal lesions in developmentally sensitive rats. Invest Ophthalmol Vis Sci 29(6): 949-954.

49. Ikonomidou C, Bosch F, Miksa M, Bittigau P, Vickler J, et al. (1999) Blockade of NMDA receptors and apoptotic neurodegeneration in the developing brain. Science 283(5398): 70-74.

50. Hayashi H, Dikkes P, Soriano SG (2002) Repeated administration of ketamine may lead to neuronal degeneration in the developing rat brain. Paediatr Anaesth 12(9): 770-774.

51. Slikker W Jr, Zou X, Hotchkiss CE, Divine RL, Sadovova N, et al. (2007) Ketamine-induced neuronal cell death in the perinatal rhesus monkey. Toxicol Sci 98(1): 145-158.

52. Zou X, Patterson TA, Divine RL, Sadovova N, Zhang X, et al. (2009) Prolonged exposure to ketamine increases neurodegeneration in the developing monkey brain. Int J Dev Neurosci 27(7): 727-731.

53. Brambrink AM, Evers AS, Avidan MS, Farber NB, Smith DJ, et al. (2012) Ketamine-induced neuroapoptosis in the fetal and neonatal rhesus macaque brain. Anesthesiology 116(2): 372-384.

54. Rozé JC, Denizot S, Carbajal R, Ancel PY, Kaminski M, et al. (2008) Prolonged sedation and/or analgesia and 5-year neurodevelopment outcome in very preterm infants. Arch Pediatr Adolesc Med 162(2): 728-733.

55. Guerra GG, Robertson CM, Alton GY, Joffe AR, Cave DA, et al. (2011) Neurodevelopmental outcome following exposure to sedative and analgesic drugs for complex cardiac surgery in infancy. Paediatr Anaesth 21(9): 932-941.

56. Li F, Tsien JZ (2009) Memory and the NMDA Receptors. N Engl J Med 361(3): 302-303.

57. Curran HV, Morgan CJ (2000) Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. Addiction 95(4): 575-590.

58. Morgan CJ, Mofeez A, Brandner B, Bromley L, Curran HV (2004) Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. Neuropsychopharmacology 29(1): 208-218.

59. Morgan CJ, Curran HV (2006) Acute and chronic effects of ketamine upon human memory: a review. Psychopharmacology (Berl) 188(4): 408-424.

60. Chan WM, Xu J, Fan M, Jiang Y, Tsui TY, et al. (2012) Downregulation in the human and mice cerebella after ketamine versus ketamine plus ethanol treatment. Microsc Res Tech 75(3): 258-264.

61. Yeung LY, Wai MS, Fan M, Mak YT, Lam WP, et al. (2010) Hyperphosphorylated tau in the brains of mice and monkeys with long-term administration of ketamine. Toxicol Lett 193(2): 189-193.

62. Tan S, Rudd JA, Yew DT (2011) Gene Expression Changes in GABAA Receptors and Cognition Following Chronic Ketamine Administration in Mice. PLoS ONE 6(6): e21328.

63. Lim DK (2003) Ketamine Associated Psychedelic Effects and Dependence. Singapore Med J 44: 31-34.

64. Goyal S, Ambekar A, Ray R (2014) Ketamine dependence in an anesthesiologist: an occupational hazard? Indian J Psychol Med 36(3): 335-337.

65. Critchlow D (2006) A case of ketamine dependence with discontinuation symptoms. Addiction 101(8): 1212-1213.

66. Tang J (2015) Sleeping problems in Chinese illicit drug dependent subjects. BMC Psychiatry 15: 28.

67. Liu JX, Zerbo E, Ross S (2015) Intensive ketamine use for multiple years: a case report. Am J Addict 24: 7-9.

68. Xu DD, Mo ZX, Yung KKL (2006) Individual and Combined Effects of Methamphetamine and Ketamine on Conditioned Place Preference and NR1 Receptor Phosphorylation in Rats. Neurosignals 15(6): 322-331.

69. Tan S, Zou J, Li M, Yew DT (2015) Chronic effects of ketamine on gene expression changes in neurotransmitter receptors and regulators-A PCR-array study. Molecular & Cellular Toxicology 11(4): 395-400.

70. Tan S, Lam WP, Wai MSM, Yu AWH, Yew DT (2012) Chronic ketamine administration

modulates midbrain dopamine system in mice. PLoS ONE 7(8): e43947.

71. Huang X, Huang K, Zheng W, Beveridge TJ, Yang S, et al. (2015) The effects of GSK-3β blockade on ketamine self-administration and relapse to drug-seeking behavior in rats. Drug Alcohol Depend 147: 257-265.