

**Ketamine Bibliography and Summary of Medical Articles
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Tishler LC, Gordon LB., *Ethical Parameters of Challenge Studies Inducing Psychosis with Ketamine.*, *Ethics Behav* 1999;9(3):211-217.

Researchers routinely induce psychosis in healthy volunteers via ketamine infusion to expand their knowledge of schizophrenia. We question the ethics of the nature and procedures of such studies. We also address safeguards for ethically conducting and reporting such pursuits, including recruitment, screening, available treatment, and follow-up.

Moore KA, Sklerov J, Levine B, Jacobs AJ., *Urine Concentrations of Ketamine and Norketamine Following Illegal Consumption.*, *J Anal Toxicol*, 2001 Oct;25(7):583-588.

Ketamine, an anesthetic agent primarily used in veterinary medicine and pediatrics, continues to gain in popularity in the drug abuse scene or 'Rave Wave' of all-night dance clubs. The Division of Forensic Toxicology Laboratory (Office of the Armed Forces Medical Examiner) at the Armed Forces Institute of Pathology, as the primary analytical laboratory for criminal investigative agencies in the Department of Defense (DOD), has seen requests for ketamine analysis rise from 1 in 1997 to 116 in 2000. This increasing abuse has led the DOD Urine Drug Testing Laboratories to consider adding ketamine screening to their random urinalysis program. However, before ketamine testing can be implemented as standard policy, concentrations of ketamine and metabolites in urine need to be evaluated after actual drug use. There is very little information regarding the pharmacokinetics of ketamine, especially concentrations of the drug or its two major metabolites, norketamine and dehydronorketamine, that can be expected in urine. In fact, dehydronorketamine has been believed to be an analytical artifact caused by the high temperatures of gas chromatography. In this paper, we attempt to resolve this issue with the development of a liquid chromatography-mass spectrometry (LC-MS) method. The urine concentrations of ketamine, norketamine and dehydronorketamine (presumptive) detected in 33 "positive" cases received in our laboratory since 1998 are reported. Quantitations were accomplished with LC-MS. Ketamine concentrations ranged from 6 to 7744 ng/mL. Norketamine concentrations ranged from 7 to 7986 ng/mL and dehydronorketamine (presumptive) concentrations ranged from 37 to 23,239 ng/mL.

Lahti AC, Weiler MA, Tamara Michaelidis BA, Parwani A, Tamminga CA., *Effects of Ketamine in Normal and Schizophrenic Volunteers.*, *Neuropsychopharmacology* 2001 Oct;25(4):455-467.

This study evaluates the effects of ketamine on healthy and schizophrenic volunteers (SVs) in an effort to define the detailed behavioral effects of the drug in a psychosis model. We compared the effects of ketamine on normal and SVs to establish the comparability of their responses and the extent to which normal subjects might be used experimentally as a model. Eighteen normal volunteers (NVs) and 17 SVs participated in ketamine

interviews. Some (n = 7 NVs; n = 9 SVs) had four sessions with a 0.1-0.5 mg/kg of ketamine and a placebo; others (n = 11 NVs; n = 8 SVs) had two sessions with one dose of ketamine (0.3 mg/kg) and a placebo. Experienced research clinicians used the BPRS to assess any change in mental status over time and documented the specifics in a timely way. In both volunteer groups, ketamine induced a dose-related, short (<30 min) increase in psychotic symptoms. The scores of NVs increased on both the Brief Psychiatric Rating Scale (BPRS) psychosis subscale (p =.0001) and the BPRS withdrawal subscale (p =.0001), whereas SVs experienced an increase only in positive symptoms (p =.0001). Seventy percent of the patients reported an increase (i.e., exacerbation) of previously experienced positive symptoms. Normal and schizophrenic groups differed only on the BPRS withdrawal score. The magnitude of ketamine-induced changes in positive symptoms was similar, although the psychosis baseline differed, and the dose-response profiles over time were superimposable across the two populations. The similarity between ketamine-induced symptoms in SVs and their own positive symptoms suggests that ketamine provides a unique model of psychosis in human volunteers. The data suggest that the phencyclidine (PCP) model of schizophrenia maybe a more valid human psychosis/schizophrenia drug model than the amphetamine model, with a broader range of psychotic symptoms. This study indicates that NVs could be used for many informative experimental psychosis studies involving ketamine interviews.

Jansen KL, Darracot-Cankovic R., *The Nonmedical Use of Ketamine, Part Two: A Review of Problem Use and Dependence.*, J Psychoactive Drugs 2001 Apr-Jun;33(2):151-8

This is the second part of a review of the nonmedical use of ketamine. Part one discussed the history of ketamine, the sought-after effects for which it is taken in a nonmedical context, how these are produced, common adverse effects, the ketamine schizophrenia model and the neurotoxicity issue. Part two reviews what is currently known about problem use of ketamine, ketamine dependence, treatment options and harm minimization issues. Some ketamine users become dependent on the drug in a manner resembling cocaine dependence, with craving and a high tolerance but no evidence of a physiological withdrawal syndrome. The likely mechanisms of this dependence are discussed in terms of what is known about the neurochemistry of ketamine, its psychological effects, and published case histories in both the formal and informal literature. The conclusions are that ketamine dependence is linked with effects that this complex drug has in common with not only cocaine and amphetamine but also with opiates, alcohol and cannabis, as well as the psychological attractions of its distinctive psychedelic properties.

Curran HV and Monaghan L, "*In and Out of the K-hole: A Comparison of the Acute and Residual Effects of Keetamine in Frequent and Infrequent Ketamine Users,*" *Addiction*, May 2001, 96(5):749-760.

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, produces acute impairment of working, episodic and semantic memory along with psychotogenic and dissociative effects when a single dose is given to healthy volunteers. In recreational users, Curran and Morgan

showed that ketamine produced the same acute effects but that 3 days after ingestion, ketamine users showed persisting memory impairment and elevated psychotogenic symptoms compared with controls. To explore whether such persisting effects reflect chronic effects of ketamine use, the present study compared frequent with infrequent users of ketamine on the night of drug use and again 3 days later. Eighteen frequent and 19 infrequent ketamine users were assessed on each test day on a range of cognitive tasks tapping memory and attentional function and on subjective scales (schizotypal, symptomatology, dissociation, mood). Groups were broadly matched for polydrug use apart from ketamine which frequent users took significantly more often and in larger quantities than infrequent users. Acute effects on day 0 replicated previous findings. On day 3, frequent users showed significant impairments on tasks tapping episodic and semantic memory but there was no evidence of persisting dissociative or schizotypal symptoms. Conclusion: These findings indicate that frequent use of ketamine produces long-lasting impairments in episodic memory and aspects of retrieval from semantic memory. Such effects accord with animal evidence of the effects of NMDA receptor blockade on memory. Those using, or contemplating using ketamine should be informed of these persisting, detrimental effects of the drug upon human memory.

Weiner AL et.al., "Ketamine Abusers Presenting to the Emergency Department: A Case Series," J.Emerg.Med., May 2000, 18(4):447-451.

Ketamine hydrochloride, familiar to emergency physicians as a dissociative anesthetic, has been abused as a hallucinogen for almost 30 years. The drug produces effects similar to those of PCP but with much shorter duration of effect. Since 1996, an increasing number of patients have presented to Connecticut Emergency Departments (Eds) after the intentional abuse of ketamine. Because the medical literature contains almost no information on the consequences of ketamine abuse, we have compiled a series of ketamine abusers presenting to the ED. Among the 20 patients in this series, commonly presenting complaints included anxiety, chest pain, and palpitations. Tachycardia was the most common physical examination finding. Nystagmus, a common finding after PCP use, was seen in only three cases. The most frequent complications after ketamine abuse were severe agitation and rhabdomyolysis. The symptoms of ketamine intoxication appear to be short-lived, with 18 of the 20 patients discharged from the ED within 5 h. of presentation. Emergency physicians should include ketamine in the differential diagnosis of drug- or toxin-induced hallucinations. Methods for detecting this drug in biologic fluids are reviewed as are treatment recommendations for managing the patient who presents to the ED after abusing ketamine.

Curran HV and Morgan C, "Cognitive, Dissociative, and Psychotogenic Effects of Ketamine in Recreational Users on the Night of Drug Use and 3 Days Later," Addiction, April 2000, 95(4):575-590.

Recreational use of the N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine, is increasing. The present study aimed to examine both the acute and residual effects of this drug on cognitive function, dissociation and schizotypal symptomatology in recreational users. A parallel group design was used to compare 20 volunteers who reported having taken ketamine with 19 volunteers who reported no consumption of ketamine on the relevant night (day 0). All 39 participants were tested on day 0 and again 3 days later.

On each test occasion a battery of tests was administered which tapped a wide range of memory functions, attention, dissociation, schizotypal symptomatology and mood. Groups were broadly matched for polydrug use apart from ketamine. Acute effects on day 0 replicated previous laboratory studies showing a broad spectrum of cognitive impairments following ketamine administration as well as marked dissociative effects and schizotypal symptomatology. Three days later, ketamine users had significantly higher scores than controls on both dissociation and schizotypal symptomatology. On some cognitive measures there were no group differences on day 3; however, on tests tapping semantic memory, the ketamine users showed persisting impairments compared with controls.

Conclusions: Ketamine appears to induce acute and severe impairments of working, episodic, and semantic memory as well as psychogenic and dissociative effects. Three days after drug ingestion, recreational users display semantic memory impairment and dissociative and schizotypal symptomatology which could reflect chronic or residual effects of taking the drug or pre-existing differences in ketamine users.

Gill JR and Stajic M, "Ketamine in Non-hospital and Hospital Deaths in New York City," J.Forensic Sci., May 2000, 45(3):655-658.

We reviewed all ketamine-positive deaths (87) examined at the New York City Office of Chief Medical Examiner over a two-year period (1997-1999). There were 15 non-hospital deaths with 12 due to acute multidrug intoxications, one due to sarcoidosis, and two due to physical injury (blunt and thermal). In no instance was a fatal intoxication caused exclusively by ketamine. Opiates (10/15), followed by amphetamines (7/15) and cocaine (6/15), were the most frequent co-intoxicants. Ethanol was found in only one death. The race of all decedents was white and the majority were men (11/15) between the ages of 18 and 30 years. The remaining 72 instances of positive ketamine findings were hospital deaths following surgical procedures or burns.

Weiner AL., Emerging Drugs of Abuse in Connecticut, Conn.Med., January 2000, 64(1):19-23.

During the past decade, several new drugs of abuse have emerged as public health concerns in Connecticut. These include ketamine, gamma-hydroxybutyrate, Ritalin and "Illy." Two trends stand out when one looks at these new drugs of abuse. First, drugs that have legitimate medical indications are being increasingly diverted for illicit purposes. Second, much of the information needed to acquire, synthesize and use these drugs can be found on the Internet. While none of these newer agents is abused to the extent of heroin or cocaine, all of them have the potential to cause serious morbidity, and occasionally death. The goal of this article is to make Connecticut physicians aware of these emerging drugs of abuse. Emphasis is placed on recognizing the signs and symptoms produced by these drugs and on managing the complications that are associated with their use.

Newcomer JW et.al., "Ketamine-induced NMDA Receptor Hypofunction as a Model of Memory Impairment and Psychosis," Neuropsychopharmacology, February 1999, 20(2):106-118.

N-methyl-D-aspartate (NMDA) glutamate receptor antagonists are reported to induce schizophrenia-like symptoms in humans, including cognitive impairments. Shortcomings of most previous investigations include failure

to maintain steady-state infusion conditions, test multiple doses and/or measure antagonist plasma concentrations. This double-blind, placebo-controlled, randomized, within-subjects comparison of three fixed sub-anesthetic, steady state doses of intravenous ketamine in healthy males (n=15) demonstrated dose-dependent increases in Brief Psychiatric Rating Scale positive (F[3,42]=21.84; p<0.0001) and negative symptoms (F[3,42]=2.89; p=0.047), and Scale for the Assessment of Negative Symptoms (SANS) total scores (F[3,42]=10.55; p<0.0001). Ketamine also produced a robust dose-dependent decrease in verbal declarative memory performance (F[3,41]=5.11; p=0.004), and preliminary evidence for a similar dose-dependent decrease in nonverbal declarative memory, occurring at or below plasma concentrations producing other symptoms. Increasing NMDA receptor hypo-function is associated with early occurring memory impairments followed by other schizophrenia-like symptoms.

Delgarno PJ and Shewan D., "Illicit Use of Ketamine in Scotland," J.Psychoactive Drugs, April 1996; 28(2);191-199.

Semistructured interviews were carried out with 20 illicit users of ketamine in Scotland. Participants had used a wide range of illegal drugs. Scottish drug agencies reported limited contacts with ketamine users; however, subjects were knowledgeable regarding the licit purpose of ketamine, its effects, and its legal status. Ketamine was usually obtained through diversion from legitimate sources. Three participants reported extensive use, indicating the potential for psychological dependence. A standard dose of ketamine was typically 1/8g, usually taken intranasally. Participants reported the ketamine experience as being extremely intense and dissociative, usually lasting for approximately one hour. All participants reported using ketamine in a carefully preplanned setting, emphasizing comfort, security, and familiarity. Participants identified potential problems arising from using ketamine in a public place, or in unfamiliar surroundings and also suggested that novice users may encounter problems through lack of knowledge concerning the intense nature of the experience. Accurate information concerning the effects and nature of ketamine as well as the importance of set and setting should be made available. However, publicizing the drug should be avoided as widespread interest could cause greater problems than currently exist.

Lahti AC et.al., Subanesthetic Doses of Ketamine Stimulate Psychosis in Schizophrenia," Neuropharmacology, August 1995; 13(1) 9-19.

We administered ketamine to schizophrenic individuals in a double-blind, placebo-controlled design using a range of subanesthetic doses (0.1, 0.3, 0.5 mg/kg) to evaluate the nature, dose characteristics, time course, and neuroleptic modulation of N-methyl-D-aspartate (NMDA) antagonist action on mental status in schizophrenia. Ketamine induced a dose-related, short (<30 minutes) worsening in mental status in the haloperidol-treated condition, reflected by a significant increase in BPRS total score for the 0.3 mg/kg (p=0.005) and 0.5 mg/kg (p=0.01) challenges. Positive symptoms (hallucinations, delusion, thought disorder), not negative symptoms accounted for these changes. These ketamine-induced psychotic symptoms were strikingly reminiscent of the subject's symptoms during active episodes of their illness. Results from six patients who were retested in the same design after being neuroleptic free for 4 weeks failed to indicate that haloperidol blocks ketamine induced psychosis. Several subjects

evidenced delay or prolonged (8-24 hours) psychotomimetic effects such as worsening of psychosis with visual hallucinations. These data suggest that antagonism of NMDA-sensitive glutamatergic transmission in brain exacerbates symptoms of schizophrenia.

Dillmann JM. "Substance Abuse in the Perioperative Setting," AORN.J., July 1995; 62(1):111-112.

Published information and extensive anecdotal reports from perioperative nurses reveal an alarming amount of substance abuse in the perioperative setting. In addition to the familiar controlled substances (eg. Narcotics, tranquilizers), practitioners must be familiar with the potential abuse of anesthesia induction agents such as ketamine, nitrous oxide, and general inhalation anesthetics. Perioperative nurses need to be aware of the problem of substance abuse in the perioperative setting, increasing their knowledge of substance abuse practices, be alert to signs and symptoms of chemical dependency, and have plans for responding to reported substance abuse situation when on duty.

Jansen KL, "Ketamine - Can Chronic Use Impair Memory," Int.J.Addict., Feb 1990, 25(2):133-139.

Ketamine, a congener of PCP, can produce a range of psychological effects which have led to its non-medical use. Recent discoveries concerning the effects of ketamine and similar substance in the brain suggest that they may interfere with memory processes when given acutely and may affect synaptic plasticity when given chronically in high doses in certain animal models. It is thus of interest to examine the consequences, if any, of chronic use in humans. A case is here presented of long-term, high-dose ketamine use, in which the user described impaired recall and attention, and a subtle visual anomaly persisting after cessation of the habit. This history is considered in the context of other relevant studies.