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Review Article

# Effects of ketamine on psychomotor, sensory and cognitive functions relevant for driving ability

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ABSTRACT

Ketamine is a dissociative anesthetic. The misuse of ketamine as a recreational drug has increased over the last decade, especially in rave parties or clubs. Short-term ketamine pilot protocols have been undertaken for treatment-resistant depressive clients. In this study, we review and comment on the evidence relating to the potential of ketamine as a causative/contributory factor in traffic accidents. To determine the causal role of ketamine in traffic accidents, a literature search on the psychomotor, cognitive, visual and perceptual functions related to safe driving was conducted. Furthermore, to interpret related data better, an overview of ketamine and its congeners' clinical pharmacology issues, recreational psychoactive effects, and identification in biological specimens is also provided.



**Contents**



## 1. Introduction

Misuse of dissociative drugs is a popular phenomenon and a cause for clinical concern [1–3]. Of these molecules, ketamine hydrochloride (KET), known as "special K" in the recreational drug scene, is most typically administered in pediatric surgery, in patients at risk for hypotension and bronchospasm, and in veterinary medicine. More recently, short-term ketamine pilot protocols have been undertaken for treatment-resistant depressive clients [4]. Most illicit ketamine is diverted from medical supplies/veterinary clinics and evaporated to obtain a powder form. Because ketamine synthesis presents some technical difficulties, users may alternatively acquire it online or import the drug from countries where it is legally manufactured [5]. Ketamine misuse as a recreational drug has remarkably increased over the last decade and is now being reported from many different countries [6–8]. 'Special K' is especially popular among youngsters and is self-administered in rave parties or clubs [9–11] either alone or in combination with other drugs [12–14].

Notwithstanding the popularity of 'special K' as a recreational drug, only a small number of epidemiological studies have investigated driving under the influence of KET [15,16]. The Crime

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Survey for England and Wales (CSEW) project, involving self-administration of questionnaires by subjects notified for driving under the influence of psychoactives, suggested that 40% of participants disclosed their previous experiences of ketamine intake, either alone or in combination with other drugs [17]. In a report published in 2012, 13 out of 853 oral fluid specimens taken from random roadside testing in Victoria were found positive for ketamine [18]. More recently, 14 of 376 suspected cases of driving under the influence were reported to be ketamine-positive individuals [19]. In this study, ketamine was not included in the standard panel and was assessed only if suspected. The mean and median concentrations of KET detected in those cases were 421 and 385 ng/mL, respectively, and the mean and median concentrations of norketamine, the main metabolite, were 605 and 410 mg/mL, respectively. Another survey [20] found that 10 of 3038 blood samples collected from impaired drivers were KET-positive. Two further studies reported 45% KET positivity among intoxicated drivers involved in non-fatal traffic accident [21] and 9% positivity among those involved in fatal crashes [22].

The aim of this paper is to review and discuss the evidence relating to the potential of ketamine as a recreational drug contributing to the occurrence of traffic accidents. To better interpret related data, an overview of ketamine and its congeners' clinical pharmacology issues, recreational psychoactive effects, and identification in biological specimens will also be provided.

## 2. Methods/literature search strategy

A literature search on the psychomotor, cognitive, visual and perceptual functions related to safe driving was completed. In accordance with related international consensus guidelines [23], we focused on objective findings achieved in human experiments in which previously set and declared ketamine doses were administered or target concentrations were maintained. Furthermore, only studies in which doses or concentrations were within the range of abused doses were included. To better interpret the related data, further animal behavioral/cognitive psychopharmacology studies were considered. The search was conducted within key databases, including PubMed, together with a focused Internet search for the identification of remaining relevant documents. In reviewing psychomotor functions, we searched phrase keywords including ketamine and "psychomotor performance", "driving ability", "driving skills", "motor function", "attention", and "executive functions", which yielded more than 500 hits regarding studies published within last 20 years. We also search-crossed our results using references in the selected papers. We excluded studies that did not consider the effects of KET on healthy subjects, studies considering the effects of chronic treatment only, non-controlled studies, and studies with no full-text available. For epidemiological data, we search ketamine and "epidemiology", "traffic accident", "car crash", and "traffic injury". When available, data from systematic reviews and randomized controlled trials were used. No filters were applied to limit the retrieval by study type, although there was a specific focus on human population data. The search was not restricted to English language documents. Personal archives of references were also used, and consultation with experts occurred when necessary.

## 3. Ketamine pharmacodynamics and pharmacokinetics

The hallucinogenic effects of ketamine are related to central serotonin receptor (5-HT2A) agonism [24] and NMDA (N-methyl-D-aspartate) receptor antagonism [25,26], which accounts for most of its analgesic [27,28], amnestic [29] and motor [31] effects as well as part of its sensory and psychotic effects [30]. Ketamine has a high affinity for mu/delta/sigma opioid receptors [12,32,33] that could contribute to its analgesic effect [34,35]. Furthermore, certain effects could be mediated by ketamine's activity on the cholinergic [32], i.e., postanesthetic delirium and, possibly, memory learning attention [36], adrenergic and dopaminergic systems [37,38]. This activity is thought to be a major contributor to the psychomimetic effects of KET [39–41]. Hence, ketamine is thought to modulate cognitive processes, emotional responses, memory and learning; however, the relative contributions of the various mechanisms of action of KET are far from clearly elucidated. When misused, ketamine can be most typically snorted but also injected, smoked, or administered rectally in a dosage range of 25–300 mg [6,42,43]. Following intranasal/snorting and oral intake, ketamine bioavailability is reported to be approximately 25–50% [9,44,45] and 17–20% [46,47], respectively, with the onset of effects occurring within 5–20 min of administration and the oral route being associated with longer-lasting effects[48]. Ketamine half-life can be in the range of 1–3 h and is contingent upon the route of administration, presenting with a bi- or tri-exponential pattern of elimination and a protein binding of approximately 60% [49]. Due to its relatively short half-life, re-dosing is common. Ketamine is mainly metabolized in the liver by CYP3A4 [50]. Nevertheless, active metabolites can produce prolonged, various and variable effects [51,52]. Approximately 90% of a dose is excreted in the urine during 72 h (~2% as the native compound, ~2% as norketamine, ~16% as dehydronorketamine and ~80% as conjugated metabolites [53]). Following intravenous/nasal [45]/intramuscular route [47] intake, equivalent ketamine and norketamine concentrations are reached within ~2 h, with ketamine blood levels progressively decreasing, while norketamine levels increase. Conversely, oral intake is associated with a rapid, steep increase in norketamine concentration so that the blood levels of norketamine are higher than those of KET by the time of absorption [47]. A linear correlation between KET concentration and its related effects is found within a range of 50–200 ng/mL [54].

## 4. Ketamine recreational effects

The psychotropic effects of ketamine include referential thinking, dissociation, depersonalization, euphoria, anxiety [55], paranoid thoughts/psychotic experiences [54,56], and out-of-the-body/near death experiences (e.g., the "K-hole" [1,14,57]). Further effects may include slurred speech, vomiting, confusion, drowsiness [30], reduced/increased motor activities with stereotypes and mannerisms [58]; lack of coordination; dystonia [59]; and motor paralysis/rigidity/ataxia [56]. Visual acuity may be affected with blurred vision and visual field narrowing having been reported [28,60]. High dosage self-administration may be associated with both cardiovascular and respiratory toxicity [1,61]. In the long term, tolerance, dependence, withdrawal signs and flashbacks are described, with schizotypal symptoms and perceptual distortions possibly persisting after cessation [62]. Approximately one-third of patients with long-term recreational ketamine use present with both urological ("k bladder", e.g., dysuria, suprapubic pain, hematuria, decreased bladder capacitance, abnormal bladder histology, and hydronephrosis) [63–66] and intestinal ("k cramps") [12,64,67] problems. Numbness, muscle weakness and impaired perception can result in falls, trauma or burns. Some reports of associated fatalities have been described; recreational use risks have also included drowning, death from hypothermia due to lying outside in winter, traffic accidents and increased likelihood of becoming a crime victim [1,61,68–70].

## 5. Ketamine congeners

Due to the number of untoward effects associated with 'special K' ingestion and to elude legislative sanctions, a number of