The Green Light on Ketamine: Considerations for On-Road Safety

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Ketamine (2-(2-chlorophenyl)-2-(methylamino) cyclohexanone) is a phenylcyclidine derivative originally developed in the 1960's as a medication to initiate and maintain optimum anaesthesia in veterinary and paediatric surgery [1]. Ketamine functions as an N-methyl-d-aspartate (NMDA) receptor antagonist, and in low or sub-aesthetic doses, has proven efficacy as an analgesic, sedative, and novel antidepressant [2]. The administration of ketamine reliably produces dose-related deficits in several functional cognitive domains, and the associated psychoactive properties of the substance have been described in some detail [3-5]. Despite this, the impact on translatable facets of neurobehavioural functioning associated with ketamine use, such as driving ability, is not well described, and thus assumptions regarding the implications of the use of this drug on measures of traffic safety are equivocal [6]. Epidemiological studies have noted an increase in both the clinical application and concurrent recreational use of ketamine, and thus effective assessments of both the direct and peripheral effects of this substance are of high clinical importance.

Ketamine has been used extensively among clinical settings for its analgesic and anesthetising properties, and emerging research has promoted the use of the substance for its antidepressant effects [7]. Pharmacologically, ketamine acts as a non-competitive glutamate antagonist, and also has peripheral effects on other receptor cites, such as dopamine [8]. As an anaesthetic substance, ketamine has been shown to be a potent 'dissociative' substance, which produces effective analgesia and amnesia without concurrent respiratory or cardiovascular depression sometimes observed in other analgesics [3]. Due to the typically rapid mechanism of action, ketamine has proven efficacy as an antidepressant in cases of treatment-resistant depressive illness, and treatment with this drug has been shown to effectively reduce disease remission among affected individuals [9]. Despite these generally advantageous properties and clinical use of ketamine, side effects associated with use of this substance have also been noted, such as delusions, hallucinations, delirium and confusion, to more severe 'out-of-body' or 'near-death' experiences [8]. Perhaps paradoxically, it appears that it is these effects which are considered to appeal to individuals seeking to use ketamine on a non-medical platform.

A low dose of non-medically administered ketamine (.15 mg/lb or .33mg/kg), which is often inhaled or injected intravenously, induces distortions of time, space and reality, and produces visual and auditory hallucinations and mild dissociative effects. When used in large doses (1 mg/lb or 2.22 mg/kg), it induces a more severe dissociation, colloquially referred to as a 'K-hole', wherein individuals report detachment from reality and severe distortions in consciousness [10]. In addition to these effects, research has also noted significant neurobehavioural performance deficits in aspects of sustained and divided attention [11], reaction time [12], and subjective assessments of alertness [12]. Further, these reported effects have been noted to persist up to three days post-ingestion [3]. Although limited explicit data exist on the prevalence of recreational ketamine use, road-side motor-vehicle drug tests have noted a high prevalence among drivers detained for these tests where urine and saliva tests are employed [13], and, of particular concern, this number is considered to be increasing.

The direct effect of ketamine on driving ability is unclear, as assessments of the relative impact of sub-anaesthetic doses of the drug on driving parameters are largely limited to observational road-side drug studies only. Road trauma has been cited as a peripheral risk associated with ketamine use [10], however, the mechanistic properties of this association are unclear. Given the aforementioned deficits in neurocognitive and psychomotor abilities linked to ketamine use, it is possible that these impairments reduce an individuals' ability to effectively and simultaneously interpret and organise incoming visual, auditory and tactile information and, and concurrently impede appropriate behavioural reactions, which in turn may contribute to higher rates of crashes *via* increased lane deviation, reduced reaction and braking time, and greater steering deviations. As such, controlled examination of Ketamine's modulatory effect on driving ability in similar controlled circumstances to previous studies examining drugs of abuse is necessary [14]. It is unclear, however, whether a dose-response relationship exists with regard to medically indicated dosage or when used on a non-medical platform, whether the relative risk is mediated by the mechanism of administration (*i.e.* intravenously or orally), or if this is differentially represented among populations of men and women, and between previous users and treatment naïve individuals.

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Ketamine presents as a novel, albeit understudied therapeutic aid, and is gaining popularity across a number of clinical platforms. Of concern, however, is the lack of studies describing peripheral implications for cognitive, affective and neurobehavioural functioning, despite indication that the use of this substance is increasing. Assumptions as to the relative impact on complex everyday tasks, such as driving, are typically derived from peripheral deficits in functional cognitive domains, or observational road-traffic research, and thus the directly translatable effects of ketamine use on several neurobehavioural domains are unclear. As highlighted, numerous areas of enquiry exist; which need to be addressed in a systematic, controlled and representative manner if definitive conclusions regarding these associations are to be effectively described. In this context, explicit assessments of the acute effects of ketamine use on driving parameters are essential.

CONFLICT OF INTEREST

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