# Ketamine for chronic noncancer pain: concerns regarding toxicity

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**Purpose of review**
Ketamine misuse and abuse is on the increase. This review focuses on recent studies on ketamine toxicity in recreational users and possible implications for the use of ketamine in chronic pain therapy.

**Recent findings**
Urological toxicity, hepatotoxicity and cognitive deficits are all reported as adverse effects of the recreational use of ketamine. Urological toxicity and hepatotoxicity have been reported as adverse effects of ketamine in pain therapy.

**Summary**
These findings may have implications for the clinical use of ketamine in chronic noncancer pain conditions. Until safety issues are resolved, it is suggested that chronic pain treatment involving higher doses and repeated exposure to ketamine be restricted to the context of randomized, controlled trials or clinical audits.

**Keywords**
adverse effects, chronic pain, ketamine, toxicity

## INTRODUCTION

Although there is only limited evidence for short-term effect and no convincing evidence for long-term effect and improved function, ketamine is increasingly being used in the treatment of chronic noncancer pain conditions such as complex regional pain syndrome (CRPS) type I. A number of authors have reported the use of ketamine infusions in the treatment of chronic pain [1–3].

A simple search of the *PubMed* database 26th December 2011 using the term 'ketamine', with limits 'Humans' and 'Published in the last year' gave 184 hits. Further restricting the search to 'Randomized controlled trials' gave a total of 37 hits. Surprisingly, none of these were efficacy trials in chronic pain. The 184 studies included trials on perioperative ketamine, results of experimental studies and trials of adverse effects. The growing number of ketamine-related toxicity studies will be the primary focus of this review.

## KETAMINE FOR CHRONIC PAIN: SHOULD WE BE READING THE ADDICTION LITERATURE?

Ketamine is a phencyclidine (PCP, 'angel dust') derivative, which has multiple pharmacological effects due to interaction with many channels and receptors, including nicotinic and muscarinic acetylcholine receptors, opioid receptors, monoaminergic and voltage-sensitive calcium channels and sodium channels. Ketamine has a direct effect on the *N*-methyl-D-aspartate (NMDA) receptor, binding to the PCP-binding site in the NMDA channel, and inhibiting glutamate activation of the channel in a noncompetitive manner. The antihyperalgesic effects of ketamine are thought to be due to this antagonistic effect on the NMDA receptor.

The psychotomimetic adverse effects of ketamine in anaesthetic dose are well documented, whereas reports of ketamine-related urotoxicity, hepatoxicity and memory deficit are of more recent date and are primarily to be found in the addiction literature. Whether the toxic effects which arise as a result of ketamine abuse are relevant for the use of ketamine in chronic pain treatment is a question

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## KEY POINTS

- Increasing knowledge about the adverse effects of ketamine in recreational users may have implications for the use of ketamine in chronic pain.
- High doses and repeated exposure to ketamine are associated with urotoxicity, hepatotoxicity and cognitive deficits.
- Until safety issues are resolved, chronic pain treatment involving high doses of ketamine and repeated administration should be reserved for randomized, controlled trials or clinical audits.

best answered by taking a closer look at the ketamine regimens recommended for the treatment of refractory chronic pain conditions. Sigtermans *et al.* [3] treated CRPS patients with 4 day infusions of S(+) ketamine with individually titrated doses and a mean ketamine infusion rate of $22.2 \pm 2.0$ mg/h per 70 kg. Although this treatment provided pain relief, it did not improve the functional status of the patients and the authors suggested that more prolonged or repetitive ketamine treatments might be required to induce longer periods of pain relief and improvement in functional status. Schwartzman *et al.* [4] prematurely terminated a multiday 4 h daily infusion trial with racemic ketamine employing a maximum infusion rate of 25 mg/h in CRPS patients because their outpatient practice indicated that a higher dose (50 mg/h) would provide greater pain relief for a longer period of time. Noppers *et al.* [5▪▪] recently published the results of a pilot study examining possible time frames for the readministration of S(+) ketamine infusion therapy in patients with CRPS type 1. In this study, CRPS patients were given two infusions of S(+) ketamine with a dose range of 10–30 mg/h with an interval of 16 days between infusions. Kappural *et al.* [6] evaluated repeated 3–6 weekly infusions with racemic ketamine initiated at the rate of 10 mg/h in patients with chronic nonmalignant pain and high opioid requirements. The infusion rate was increased as tolerated until patients reported no pain or until the infusion rate reached 100 mg/h. Infusions were continued for 3 h or as long as tolerated.

From these studies it is reasonable to conclude that ketamine treatment of refractory chronic pain conditions may involve high doses of ketamine, intravenous administration and repeated exposure. Alternative treatment regimens may also be in clinical practice without being reported in the literature. This author knows of one patient who was instructed by the pain physician to self-administer ketamine injections as needed. With these facts in mind, toxicity reports and cautions from the addiction literature may provide information relevant to the use of ketamine in the chronic, noncancer pain setting.

## UROLOGICAL TOXICITY

A recent review on the recreational use of ketamine describes ketamine-related ulcerative cystitis as a major physical harm [7▪▪]. The first studies on urological toxicity came from the addiction literature [8,9]. In 2007, Shahani *et al.* [8] described nine patients who were chronic users of ketamine and who developed severe genitourinary symptoms. The first case presented with a 6-month history of painful haematuria, dysuria, urgency and postmictural pain. The symptoms began after the patient had started to use ketamine on a daily basis. Urine cultures, urine analysis and urine cytology were normal but computed tomography revealed marked inflammatory changes and reduced bladder capacity. The haematuria ceased after the patient stopped using ketamine, but symptoms of urgency and frequency persisted. The remaining patients had similar symptoms and findings.

A small number of reports of ketamine–associated urotoxicity in pain patients subsequently appeared in the scientific literature. Grégoire *et al.* [10] described the case of a 16-year-old patient with CRPS type I who developed cystitis following the use of oral ketamine (8 mg/kg per day) as an adjuvant analgesic. The symptoms developed after only 9 days of treatment with ketamine. Storr *et al.* [11] reported three cases in which palliative care pain patients receiving treatment with oral ketamine (330–1000 mg per day) developed significant urological symptoms. Persson [12] described a patient with persistent low back and leg pain after an operation for disc herniation who developed increased urinary frequency after 1 year of treatment with oral ketamine. The symptoms diminished on dose reduction. Persson reflected that urinary toxicity may ultimately prove to be the most serious limitation to long-term analgesic treatment with ketamine.

The mechanism by which ketamine causes urotoxicity is not fully understood but in-vitro studies have shown a direct interaction between ketamine and the bladder urothelium [13▪▪]. It has been speculated that ketamine-related cystitis is due to high concentration of ketamine metabolites in the bladder, although there are currently little data to support this hypothesis [13▪▪]. Ketamine-associated urotoxicity appears to be dose related and it was initially thought that symptoms would improve or

resolve entirely on the cessation of ketamine treatment/use. However, a recent prospective, longitudinal, observational study in 40 female ex-ketamine abusers and age-matched controls found that although there was some symptom improvement, overall 90% of ex-ketamine abusers at a mean of 8 months after cessation of use still had active urinary symptoms with increased frequency, lower maximum voided volume and lower bladder capacity, compared with controls [14▪]. The increasing number of cases of ketamine-related urological toxicity has led to the establishment of a specific collaboration of urologists in the United Kingdom interested in addressing this problem [13▪▪].

## HEPATIC TOXICITY

The pilot study by Noppers *et al.* [5▪▪] was prematurely ended after 13 patients had been included due to hepatotoxic adverse effects. Five of the six patients randomized to receive two continuous 100 h infusions of S(+) ketamine (infusion rate 10–20 mg/h) with a 16-day interval between treatments, developed severe adverse effects prior to, or during the second exposure to ketamine. Three of these patients developed hepatotoxic adverse effects. All three exhibited considerably raised liver enzymes, with two patients developing an itchy rash, one of whom developed petechiae. Liver enzyme levels declined rapidly on cessation of ketamine treatment.

This study was accompanied by a commentary whose author noted the number of reports of ketamine-related hepatoxicity in the addiction literature [15▪]. A recent case report describes cholangiopathy in a 32-year-old female who had inhaled ketamine for recreational use over a period of years [16]. Repeated endoscopic retrograde cholangiopancreatography showed multiple long-segment strictures and narrowing in the intrahepatic ducts of both liver lobes. In 2009, Wong *et al.* [17] described three cases of dilated common bile ducts in ketamine abusers.

The mechanism by which ketamine causes liver injury is not fully understood, but may be related to metabolic events causing increased lipid peroxidation and the formation of free radicals [15▪]. A preclinical study found that ketamine increases flow resistance across the sphincter of Oddi [18], but a more recent study in humans using ketamine in a single dose of 20 mg did not significantly affect sphincter of Oddi parameters [19]. A study from Singapore describes three cases of chronic ketamine abuse in young men who presented with obstructive jaundice and biliary tract abnormality which resolved over time with abstinence from ketamine [20]. The authors of this study suggested that the NMDA receptor antagonist effect of ketamine may cause smooth muscle relaxation and subsequent dilatation of the biliary tree, together with gallbladder dyskinesia via a central pathway, and that abnormal liver function tests in the absence of biliary dilatation might be caused by direct ketamine hepatotoxicity.

## ADDICTION POTENTIAL

Ketamine is a drug of abuse. The incidence of dependency is unknown, but craving for ketamine, compulsive behaviour and rapid development of tolerance are common in frequent users [7▪▪]. After opioids, ketamine is one of the most frequently abused drugs in addicted anaesthetists [21]. The United Nations World Drug Report 2010 described the spread of ketamine abuse across Asia, Australia, North America and Europe [22]. Ketamine was recently reported to be the most commonly misused drug amongst patients referred to a regional hospital substance abuse clinic in Hong Kong [23]. Currently, ketamine appears to be the fourth most popular club drug in the United Kingdom, after cannabis, ecstasy and cocaine [7▪▪]. Both preclinical and clinical studies in the anaesthesia setting have demonstrated that repeated doses of ketamine are associated with rapid development of tachyphylaxis [7▪▪].

As yet, ketamine-related addiction and abuse have not been described in the pain-patient population, although anecdotal reports exist. It is not inconceivable that repeated intravenous administration of ketamine in pain therapy could give rise to dependency in susceptible individuals.

## PSYCHOTOMIMETIC AND COGNITIVE ADVERSE EFFECTS

A study summarizing the potential adverse effects of ketamine concluded that although ketamine has a good safety record in anaesthesia, it should be used judiciously in the clinical and experimental setting due to cognitive and psychotomimetic adverse effects [24].

Psychotomimetic adverse effects such as hallucinations and panic attacks are dose dependent and are commonly observed after intravenous administration of ketamine. In the study by Noppers *et al.* [5▪▪] three of five patients in the treatment group developed psychotomimetic adverse effects. One of these experienced hallucinations and panic attacks, and refused further treatment, despite good pain relief. Another developed severe psychotropic adverse effects which improved on reducing the dose of ketamine, whereas the third patient

developed similar adverse effects in connection with both infusions, but the symptoms were generally less pronounced under the second infusion.

Several PET studies in healthy volunteers have shown that ketamine infusions in subanaesthetic doses in healthy volunteers elicit psychotomimetic features such as hallucinations, disorganized thought and paranoia. In these studies, ketamine was found to increase glucose metabolism in the prefrontal cortex. Prefrontal glucose metabolism was positively correlated with disorganised thought and schizophrenia-like symptoms [25,26].

The repeated recreational use of ketamine appears to affect prefrontal dopaminergic transmission [27]. In experimental models, ketamine produces cognitive deficits in humans in tasks involving attention and memory. In a recent structural MRI study, Liao *et al.* [28▪] found reduced dorsal prefrontal grey matter in chronic recreational users of ketamine. Morgan *et al.* [29] performed a 1-year longitudinal study in users of ketamine and found that frequent self-administration of ketamine (at least four times a week) was associated with considerable cognitive deficits in the form of decreasing performance on spatial working memory and pattern recognition memory tasks.

Ketamine-related cognitive adverse effects such as memory deficit have not been reported (or controlled for) in trials or audits assessing repeated administration of ketamine for chronic pain. This is a topic which deserves further attention.

## CONCLUSION

Ketamine's pharmacological profile makes it an interesting and useful drug for the treatment of refractory pain. At the same time, high doses and repeated administration of ketamine are associated with potentially serious and possibly persistent toxic effects. The adverse effects of ketamine are dose dependent and there are good arguments for restricting doses. The accumulating body of knowledge on urological and hepatic toxicity, together with ketamine's potential for addiction, make consideration of these issues a priority. As ketamine-related urotoxity and cognitive deficits have only recently been identified, there is a possibility that these types of adverse effects may have gone unrecognized in pain patients and have been underreported in the pain literature. In my opinion, until safety issues are resolved, chronic pain treatment involving repeated infusions of ketamine should be reserved for well designed, randomised, controlled trials or clinical audits, with careful monitoring and reporting of all adverse effects.

### Acknowledgements

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### Conflicts of interest

*There are no conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 291–292).

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