

Ketamine for Chronic Pain: Risks and Benefits

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Running head: Ketamine risks and benefits

Keywords: Pain, Chronic Pain, Neuropathic pain, Ketamine, NMDA receptor antagonist,
ketamine abuse

Word count: Abstract = 248, Main text = 4677

Number of tables: 1

Number of figures: 2

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bcp.12094

Summary

The anesthetic ketamine is used to treat various chronic pain syndromes, especially those that have a neuropathic component. Low-dose ketamine produces strong analgesia in neuropathic pain states, presumably by inhibition of the *N*-methyl-D-aspartate receptor although other mechanisms are possibly involved, including enhancement of descending inhibition and anti-inflammatory effects at central sites. Current data on short-term infusions indicate that ketamine produces potent analgesia during administration only, while three studies on the effect of prolonged infusion (10-14 days) show long-term analgesic effects up to 3 months following infusion. Ketamine's side-effects noted in clinical studies include psychedelic symptoms (hallucinations, memory defects, panic attacks), nausea/vomiting, somnolence, cardiovascular stimulation, and in a minority of patients hepatotoxicity. The recreational use of ketamine is increasing and comes with a variety of additional risks ranging from bladder and renal complications to persistent psychotypical behaviour and memory defects. Blind extrapolation of these risks to clinical patients is difficult, because of the variable, high and recurrent exposure to the drug in ketamine abusers and the high frequency of abuse of other illicit substances in this population. In clinical settings, ketamine is well tolerated, especially when benzodiazepines are used to tame the psychotropic side-effects. Irrespective, close monitoring of patients receiving ketamine is mandatory, particularly aimed at CNS, hemodynamic, renal and hepatic symptoms as well as abuse. Further research is required to assess whether the benefits outweigh the risks and costs. Until definite proof is obtained ketamine administration should be restricted to patients with therapy-resistant severe neuropathic pain.

Introduction

In the last decades, there is a growing number of patients being diagnosed with some form of chronic pain.[1] The treatment of chronic pain is based on a trial-and-error approach with anti-depressants, anti-epileptics and opioids as drugs of first choice. Irrespective of treatment, efficacy is limited with just 30-40% of patients showing adequate to good pain relief. The remaining population either displays no effect or responds poorly.[2,3]

Anesthesiologists and other pain physicians started using the anesthetic ketamine, at subanesthetic doses, to treat therapy-resistant chronic pain syndromes, especially those syndromes that have a neuropathic component, such as complex regional pain syndrome type 1 (CRPS-1), postherpetic neuralgia and neuropathic pain from peripheral nerve damage.[4-6] The recent increase in use of low-dose ketamine in chronic pain is due to the positive effects observed during treatment and possibly due to the fact physicians now add benzodiazepines and/or α_2 -agonists to minimize psychotropic side-effects. The first paper that showed the ability to “tame” ketamine with benzodiazepines was published in 1973.[7]

Ketamine was first synthesized in the early 1960s as a safer alternative to phencyclidine.[8]

In 1965 its anaesthetic properties were identified. Ketamine is a dissociative anaesthetic that produces profound analgesia and amnesia. Its use in contemporary anesthesia is limited taken the occurrence of a variety of side effect most importantly the induction of a psychedelic state causing agitation, hallucinations and panic attacks (*ie*, emergence and excitation symptoms). And although these side-effects may be prevented or treated (see above), the availability of alternatives has limited the use of ketamine in anesthesia to specific indications (*eg.*, pediatric and trauma anesthesia). However, since its first synthesis, the interest in ketamine is still growing with in 2011 alone 588 publications in PubMed.

In this short review, we will provide an overview of the relevant literature on the benefits and risks of ketamine. Note that ketamine, just like opioid analgesics, is a drug of abuse. Our review therefore has also relevance to the population of recreational ketamine users. In fact, many of the side-effects and complications from ketamine use, were first discovered in ketamine abusers.

Pharmacology

Ketamine is a phenylpiperidine derivative structurally related to phencyclidine (PCP, “angel dust”) with 2(2-chlorophenyl)-2-(methylamino)-cyclohexanone as chemical structure. The chiral center on the C-2 atom of the ketamine cyclohexane ring gives cause to 2 stereoisomers, S(+)- and R(-)-ketamine.[8,9] Commercially two different forms of ketamine are available: the racemic mixture (Ketalar®, Pfizer Inc.; available in the US since 1966) and the S(+)- enantiomer (S-ketamine or Ketanest-S®, Pfizer Inc.; available in a number of European Community member states since 1994).[8] After intravenous administration the volume of distribution is nearly 3 L/kg, redistribution half-life 7-15 minutes, clearance 15 ml/kg per min and elimination half-life 2-3 hours [8,10,11]. Ketamine rapidly passes the blood-brain barrier (blood-effect-site equilibration half-life, $t_{1/2k_{e0}}$, 1-10 min) ensuring a rapid onset of acute analgesic effect.[12-14] With respect to long-term ketamine treatment for chronic pain relief, the analgesic onset/offset half-life of ketamine ($t_{1/2}$, exceeds that of acute pain relief and a $t_{1/2}$ of 11 days has been estimated in CRPS-1 patients treated with 100-h of 20-30 mg/h of S-ketamine.[4,15]

Ketamine is a cytochrome P450 dependent drug. It is metabolized in the liver by CYP3A4, CYP2B6 and CYP2C9 to norketamine (via *N*-demethylation) with subsequent metabolism of norketamine into 4-, 5-, and 6-hydroxynorketamine (by CYP2A6 and CYP2B6). Norketamine is produced within minutes after intravenous administration of ketamine and may exceed

ketamine concentration particularly after long-term infusion.[4,8,12] Elimination of norketamine and the hydroxynorketamines occurs after glucuronidation in the liver, through the kidney and bile.[16-18] Inhibitors of the CYP enzymes involved in the metabolism of ketamine increase ketamine plasma concentration.[19] In contrast, induction of the CYP system has limited effect on the plasma concentration of ketamine as the hepatic clearance of ketamine before induction is high and approaches liver blood flow.[20] After termination of intravenous ketamine administration, ketamine concentrations drop rapidly and norketamine concentrations exceed ketamine concentration. In humans, the analgesic properties of norketamine have not been studied directly, however a recent human study on the effect of variations in norketamine concentration (induced via manipulation of its metabolism with rifampicin) on acute ketamine analgesia predicts no or even a negative contribution of norketamine to acute pain relief.[20,21] Possibly during prolonged ketamine infusion the downstream metabolites may contribute to effect.[22]

Chronic neuropathic pain and ketamine

In a series of excellent recent reviews the pathophysiology of chronic neuropathic pain development is discussed; see for example refs. [23-28]. As outlined and stated by Costigan et al.[26], neuropathic pain results from lesions of the somatosensory nervous system causing alterations in structure and function so that pain occurs spontaneously and responses to noxious and innocuous stimuli are amplified. Various neurochemical processes lie at the basis of the complex transition from nerve/neuronal damage to chronic neuropathic pain causing peripheral and central sensitization (which manifests itself as allodynia, hyperalgesia, enhanced temporal summation and spontaneous pain). Important mechanisms of chronic (neuropathic) pain development include phosphorylation and upregulation of the *N*-methyl-D-aspartate receptor (NMDAR), loss of descending inhibition,

plastic changes in the spinal cord and activation of immune cells in the spinal cord with the release of pro-inflammatory cytokines.[23-28]

Ketamine produces strong analgesia in neuropathic pain states, presumably by inhibition of the NMDAR.[8,23] The NMDAR is an excitatory glutamatergic receptor present at spinal and supraspinal sites and involved in the afferent transmission of nociceptive signals. In chronic pain states prolonged nociceptive stimulation causes activation and upregulation of the NMDAR at dorsal horn synapses resulting in enhanced and amplified trafficking of pain signals to the brain (central sensitization). This phenomenon is an important factor in the process of perseverance and eventually chronification of pain. There is now ample evidence that NMDAR antagonists that block the NMDAR, such as ketamine, are able to halt the excessive barrage of nociceptive input to the brain and are therefore potential alternatives to existing treatments of chronic pain syndromes.[4,23] Other effects of ketamine that may contribute to its analgesic behaviour include enhancement of descending inhibition (see below) and anti-inflammatory effects.[29-31]

Additional to its effect at the NMDAR, ketamine interacts with other receptor systems as well, including opioidergic, muscarinic, and monoaminergic receptors. Relatively little is known about the contributions of these receptor systems to the various effects of ketamine.[32] Studies in mice lacking the μ -opioid receptor suggest a role of the μ -opioid receptor in ketamine-induced acute analgesia.[33] However acute pain relief may also be induced by inhibition of presynaptic spinal dorsal horn neurons. Activation of NMDAR at these presynaptic sites cause the enhanced release of excitatory substances including glutamate and Substance P.[34]

Descending inhibition and ketamine

There is new evidence that ketamine is able to influence descending (*ie.* top-down) inhibitory pathways. Chronic pain patients often have a defect in their ability to engage descending inhibition of pain.[27] This may be an additional cause of chronification of pain (see above). Evidence that ketamine is able to activate descending inhibitory pathways arising from supraspinal sites and inhibit dorsal horn nociceptive neurons comes from two sources. (1) Using the technique of resting-state functional MRI (RS-fMRI) it was observed that low-dose ketamine activates the anterior cingulate cortex, the orbital frontal cortex, the insula and brainstem in healthy volunteers.[29] These areas are involved in descending inhibition of pain.[23] See also figure 1. (2) In a behavioural study in neuropathic pain patients due to small-fibre neuropathy, low-dose ketamine enhanced or re-activated an important experimental expression of descending inhibition, conditioned pain modulation (CPM, formerly known as diffuse noxious inhibitory controls or DNIC).[30] CPM is the central inhibition of a focal stimulus by administering a second noxious stimulus at a remote area (*ie.* pain inhibits pain). Without ketamine no CPM was detected in this population of neuropathic pain patients, while following ketamine treatment CPM responses were larger than following placebo or morphine treatment. In this study the magnitude of CPM activation was directly associated with the magnitude of spontaneous pain relief. Although these CPM data contrast earlier findings in volunteers (where ketamine enhanced pain facilitation rather than inhibition),[34] the RS-fMRI and patient CPM data collectively suggest, that ketamine is able to influence (*ie.* re-activate) the descending inhibitory system under specific circumstances (*eg.* under conditions of neuropathic pain) and consequently is able to restore the physiological balance between pain inhibition and facilitation.

Ketamine for Chronic Pain

Current interest in ketamine focuses on its ability to alleviate chronic pain, especially when chronic pain has a neuropathic component. Table 1 gives a list of neuropathic pain conditions in which ketamine has been used to alleviate neuropathic pain (all RCTs, see ref. [9] for the references). There is, however, no consensus on the administration protocol. While most studies show that short-term ketamine infusion is indeed associated with pain relief during infusion only a few studies examined the prolonged effect of ketamine following infusion. Taken its side-effects and the high cost of inpatient treatment, we believe that it is imperative to induce sustained analgesia and not just induce analgesia during infusion or in a few hours following treatment. There is evidence that the duration of infusion determines the duration of analgesic effect.[9] For example, in a randomized active placebo (midazolam)-controlled study in fibromyalgia patients a relatively high dose of S-ketamine (0.5 mg/kg), given over 30-min, produced analgesia no longer than 45 min.[36] In contrast, Sigtermans et al.[4] show that treating CRPS type 1 patients with a 100-h infusion of S-ketamine (dose titrated up to 20-30 mg/h) results in long-term pain relief lasting up to 3 months following treatment. Similar observations were made by Schwartzman et al. following a daily 4-h infusion of ketamine for 10 days in CRPS patients.[37] It therefore seems that long-term infusions are required before analgesia is observed in the days following treatment. However, while consistent, the number of placebo-controlled randomized controlled trials (RCTs) on long-term ketamine treatment (meaning 10 to 14 days) is limited. Just three RCTs examined the effect of long-term ketamine infusion in CRPS type 1 (two studies) and spinal cord injury (1 study).[4,37,38] We performed a meta-analysis on the analgesic effects of these studies at weeks 1 and 4 following ketamine treatment and observed a mean effect size (standardized difference in means) in the first week following treatment of 1.22 (95% confidence interval 0.82 to 1.61, $P < 0.001$) and in week 4 of 0.39 (95% confidence interval 0.03 to 0.75, $P = 0.036$). While these effect sizes are relatively

large, indicating that the effect of ketamine treatment persists for at least 4 weeks, they show a rapid decline in effect, an indication that retreatment is required within 4-6 weeks following the initial treatment period. This then requires another admission to the hospital that is costly and an additional burden to the patient. Furthermore, repetitive administrations may induce damage to internal organs (see below). A final remark on these long-term ketamine treatment studies is that while pain relief was present during the weeks following ketamine treatment little or no improvement in functionality was observed.[4] This is remarkable as loss of function is often related to spontaneous pain and allodynia.

It is of interest to speculate whether ketamine could prevent the occurrence of chronic pain states, such as may occur following surgery. Few qualitatively good studies have addressed this issue. Wilson *et al.* assessed the effect of ketamine to reduced chronic pain development following lower limb amputation (with a known incidence of persistent pain in up to 80% of patients).[39] They compared the effect of epidural racemic ketamine and bupivacaine *versus* epidural saline and bupivacaine and although they observed superior analgesia directly postoperative in the ketamine group, no significant difference occurred in persistent pain (for both stump pain and phantom limb pain) with respect to severity and incidence, one year following surgery. Similar observations were made for prevention of chronic post-thoracotomy pain.[40,41] These data suggest no pre-emptive effect of ketamine on development of chronic postoperative pain. However, before definitive conclusions can be drawn additional good quality randomized trials testing the effect of pre-emptive ketamine for a variety of indications using standardized techniques are required.

The most effective treatment of chronic pain is by multimodal approach. Ketamine is often administered together with opioid-analgesics, postoperatively and in the treatment of chronic cancer pain. A 2005 Cochrane review on perioperative ketamine use showed that

ketamine reduced morphine consumption in 27/37 studies with concomitant less pain and less nausea and vomiting.[42] Similarly, ketamine improves the efficacy of opioid treatment in cancer pain.[43] The mechanisms through which ketamine improves opioid efficacy are multiple: (i) Ketamine's ability to reduce the neuropathic pain is superior to that of opioids and as such ameliorates the pain state of cancer patients with a neuropathic pain component; (ii) Ketamine is an analgesic on its own right and interacts with opioids additively or synergistically, probably within descending inhibitory pathways; (iii) Animal data indicate that NMDAR antagonists prevent development of opioid-induced hyperalgesia.[44-46] Opioid-induced hyperalgesia is the paradoxical increase in pain perception that may become manifest during both acute and chronic opioid treatment and consequently makes adequate pain treatment more difficult and sometimes even impossible. The ability of ketamine to reduce the incidence (and severity) of opioid side-effects is important as side-effects reduce patient compliance. For example, most patients prefer to be in pain rather than being nauseated. These data suggest that an opioid-ketamine combination may be useful in non-neuropathic pain states (*eg.* in the palliative setting) or in mixed nociceptive/neuropathic pain states (*eg.* in cancer pain).

Recent evidence shows that ketamine has potent antidepressant qualities.[47,48] In fact, clinical studies show that one subanesthetic dose of ketamine produces almost immediate antidepressant effects (within 1 h). Ketamine has a positive effect on depressive symptoms in otherwise therapy-resistant patients. In rats, Li *et al.* showed that ketamine, by inhibiting the NMDAR, activates the mTOR (mammalian target of rapamycin) pathway increasing the expression of synaptic proteins and the density of dendritic spines, and causing an antidepressant response within one day.[49] Many chronic pain patients cope with depression or depression-like symptoms and depression and chronic pain share common mechanistic pathways. Hence the treatment of chronic pain may serve two purposes, treat

the pain and ameliorate the depressive symptoms. Whether the pain is cured and the depression resolves as a consequence, or the reverse is true, is of minor relevance to the chronic pain patient. However, despite these academic contemplations, no evidence was found for an improvement of depressive symptoms following long-term ketamine treatment in CRPS patients.[4] Possibly, the antidepressant effects of ketamine in chronic pain patients are short-lived. Further studies on this important issue are needed.

Finally, there are reports that ketamine has anti-inflammatory, neuroprotective and anti-tumour effects.[31] These reports (mostly derived from experimental studies) are at best preliminary and large randomized controlled trials in chronic pain patients are required to address these issues.

Ketamine - The Risks

As mentioned before a large body of evidence regarding the risks of ketamine comes from studies on the recreational use and chronic abuse of ketamine. Still, there is a large body of evidence from controlled studies in volunteers and patients as well as case reports that delineate the risks and side-effects of ketamine use.

Clinical use of ketamine. The side-effects from clinical ketamine-use may be divided into central nervous system (CNS)-related, cardiovascular, and hepatic.

CNS-related ketamine effects. Most important CNS effects are psychotropic or psychedelic.[50-52] Although psychedelic side-effects occur in a dose dependent fashion they already present themselves at relatively low doses, used in the treatment of chronic pain (20-30 mg/h). Both internal and external perception of reality are affected (Figure 2), causing auditory hallucinations, paranoid ideas, anxious feelings (panic attacks) and inability

to control thoughts (internal perception), and derealisation in time and space, visual hallucinations, increased awareness of sound and colour (external perception). Furthermore an intense sense of drug high is often perceived that some patients experience as extremely unpleasant, while others have an intense feeling of euphoria. Other CNS side-effects include dizziness, blurred vision, vertigo, nausea/vomiting, dysphasia, nystagmus, nightmares or vivid dreams, impaired motor function and memory deficits.[32,53,54] Psychedelic effects decrease rapidly after termination of ketamine administration, although Bagrove *et al.* [55] report that in the three nights following ketamine administration the incidence of unpleasant dreams was significantly increased compared to placebo. Taken these effects, ketamine is used to induce a schizophrenia-like state to investigate this syndrome in healthy volunteers.[56,57] As stated before, complete prevention of psychedelic effects is not possible but taming of the effect is feasible using benzodiazepines or α_2 -adrenergic receptor agonists (*eg.*, clonidine).[7,58] Especially the use of clonidine deserves further study as it may also counteract the cardiovascular stimulatory effects of ketamine (see below).

An analyses of cognition and memory function during short-term ketamine administrations demonstrated impairment in working memory and decrements in the encoding of information into episodic memory. Furthermore, in contrast to other amnestic drugs, ketamine impairs semantic memory.[53, 59-61] After the termination of these short time and single ketamine infusions, memory function reverted to normal, which indicates that in naive ketamine users ketamine-induced memory loss is self-terminating. However, the effects of the long-term use of low-dose ketamine for the treatment of chronic pain on memory function are poorly studied and consequently unknown (see below). The only study that examined the safety of high dose long-term ketamine in CRPS patients (anesthetic doses over 5 days) demonstrated no severe cognitive defects.[62] However, no data on long-term cognitive function were given.

To diminish the possibility of overt CNS-related side-effects, all patients should have an extensive psychiatric evaluation prior to ketamine treatment to rule out schizophrenia (and related disorders) and manic-depression (and related disorders). Also patients with a past history of drug abuse should be excluded from ketamine treatment.

Cardiovascular ketamine effects. Ketamine has a direct negative inotropic effect and an indirect stimulatory effect on the cardiovascular system.[12,63] Stimulation is due to activation of the sympathetic system and is related to the systemic release of catecholamines, inhibition of the vagal nerve, inhibition of norepinephrine re-uptake at peripheral nerves and non-neuronal tissues such as the myocardium, and norepinephrine release from sympathetic ganglia. Myocardial depression is observed after high dose ketamine infusion or during repeated (within minutes to hours) dosing of ketamine. Cardiovascular stimulation already occurs after low dose-ketamine infusion and is characterized by tachycardia, systemic and pulmonary hypertension, and increases in cardiac output and myocardial oxygen consumption.[12,32,63,64] Hence, these data indicate that monitoring is required when treating chronic pain patients with cardiovascular disease with low-dose ketamine. Whether treatment with clonidine or β -blockade improves hemodynamics following ketamine treatment seems plausible but has not been studied so far.

Hepatic ketamine effects. There are some reports showing an elevated liver enzyme profile following anesthetic and subanesthetic ketamine treatment. [65-68] For example, in a randomized controlled trial, Noppers *et al.* [68] observed that a second exposure to S-ketamine just 3 weeks following a 100-h treatment in CRPS-1 patients caused liver enzyme elevations of such magnitude that the trial was terminated. In 3 of 6 treated patients alanine

transaminase, alkaline phosphatase, aspartate transaminase, and γ -glutamyl transferase, all increased 3-times over the upper limit of normal. Upon termination of the ketamine infusion the enzymes slowly returned to normal (normal values reached within 3 months). Similar observations were made by others, using repetitive low-dose or continuous high-dose ketamine infusions with liver enzyme elevations in about 10% of patients that returned to normal within 3 months.[37,67] The mechanism of ketamine-induced liver injury is not fully understood. Possible factors include: a decrease in hepatic oxygen delivery, increase lipid peroxidation with the formation of free radicals, and allergic hepatitis. Irrespective of the mechanism, these data indicate that the use of repeated ketamine infusions require careful follow-up of the liver enzymes and cessation of treatment, if liver injury occurs. Single treatment designs seem to be less damaging to the liver. For example in the study of Sigtermans et al. no liver enzyme elevations were detected in 50 patients receiving a single 100-h ketamine infusion.[4]

Clinical data. In clinical practice, ketamine is considered safe, and in general, side-effects are well tolerated. We recently treated 50 CRPS-1 patients with a 100-h intravenous treatment of low-dose ketamine and concluded that the benefit from ketamine administration exceeded the risks.[4] Cvrček [54] evaluated the side-effects of a 3-month oral ketamine treatment (30 mg five times a day) in patients with diabetic polyneuropathy and postherpetic neuralgia. Drowsiness and dizziness were the most common site effects occurring in 25% and 22% of patients, respectively, followed by sedation (19%), dry mouth (19%), nausea and vomiting (9%) and memory deterioration (9%). During the study period 16% withdrew from the treatment due to failure of the therapy and 13% due to non-tolerated side-effects like dizziness, sedation, nausea and vomiting. Cvrček concluded that ketamine treatment, while not optimal, is acceptable for treatment of chronic pain.

Recreational use of ketamine. While the psychedelic side-effects limit ketamine's use in clinical practice, it is the main reason for ketamine's popularity in the recreational drug scene. Ketamine causes psychological rather than physical dependence as no physical withdrawal state is observed after cessation of long-term abuse.[64] In the UK, ketamine is a Class C drug (since 2006); in the US, ketamine is placed in Schedule III of the US Controlled Substance Act. Ketamine is ingested, snorted or injected at relatively high doses and the experience lasts for no longer than 2 hours. When the dissociative effects of ketamine are severe the experience is commonly referred to as the *K-hole* where schizophrenia-like symptoms dominate with perceived perceptions completely separate from reality (such as near-death experiences). At lower doses, the drug induces a state of mild dissociation with vivid hallucinations and the distortion of time and space (such as *melting into the surrounding* and out-of-body experience). [32,64]

Patients may present with a variety of symptoms at the emergency department (ED). For example, a US study in 20 patients showed that the majority of ketamine abusers visit the ED with complaints of anxiety, chest pain, palpitations, confusion and memory loss. Observed physical symptoms were hypertension, tachycardia, nystagmus, hallucinations and slurred speech.[69] In an ED study from China (Hong Kong) [70] reviewing 233 cases of ketamine abuse most important symptoms included impaired consciousness (45%), abdominal pain (21%), lower urinary tract symptoms (12%) and dizziness (12%). Some patients were agitated, aggressive and displayed paranoid behaviour. Furthermore due to the depersonalisation and derealisation the patients were more prone to automutilation. The management of acute ketamine toxicity is supportive and symptoms usually resolve spontaneously within several hours. Fatal outcomes are rarely reported and if they occur they are often related to aspiration of gastric contents.[64]

An important observation in recreational ketamine users that is not reported in clinical patients is the occurrence of urological symptoms. In frequent drug abusers ketamine may induce ulcerative cystitis that presents with symptoms of high urgency and frequency of urination, dysuria, urge incontinence and haematuria.[71,72] Mak *et al.*[73] showed that ketamine users that abuse ketamine over 2 years for at least 3 times a week have altered bladder function with sometimes severe urological complaints. The aetiology of ketamine-induced ulcerative cystitis is unclear, but appears to be associated to abuse frequency. In three retrospective case series covering 93 patients with urological symptoms due to ketamine abuse, reduced bladder volume was reported in 33% and hydronephrosis in 50%.[64,74-76] Reduced bladder volume was associated with bladder wall thickening, detrusor instability and vesicoureteric reflux. Acute renal failure secondary to these urological problems has been reported.[74] Mostly, the urological symptoms improve after cessation of ketamine use, however after long-term misuse symptoms may be present for a long period after cessation of the drug.[77] Also other organ systems seem to be affected by long-term ketamine abuse. Some reports describe ketamine-induced biliary tract dilatation with abnormal liver enzyme values consisted with post-hepatic obstruction in the absence of an obstructing lesion.[78,79] Furthermore, Poon *et al.* [80] identified that out of 37 ketamine abusers with urological complaints, 28 patients also had upper gastro-intestinal symptoms. Fourteen of the 28 patients underwent an upper bowel endoscopy that showed gastritis in twelve patients and gastroduodenitis in one.

In contrast to the clinical use of ketamine, ketamine abuse is associated with defects in memory function that persists after abstinence.[53,81,82] Also the presence of schizotypal symptoms like delusional thinking, superstitious conditioning, dissociation and depression may persist or recur regularly (*ie.*, *K-hole* flash-back).[83,84] This suggests more permanent damage to the brain in recurrent ketamine abusers. Evidence that ketamine is neurotoxic

comes from animal studies that show apoptotic neurodegeneration induced by NMDAR antagonists in the developing rodent brain. Neuronal injury is caused by the loss of inhibition of inhibitory pathways leading to enhancement of excitatory neuronal activity. Drugs like benzodiazepines and α_2 -agonists have shown protective effects in the development of neuronal damage.[58,85,86] In adults, toxic effects of ketamine on the brain were observed by Liao *et al.* in two studies.[87,88] They compared brain volumes of chronic ketamine abusers with healthy volunteers and found decreased grey and white matter volumes in the bilateral frontal cortex and white matter degeneration in the left temporoparietal cortex in persons abusing ketamine. These changes in the brain may well be associated with the memory defects in healthy volunteers (effects on working, episodic and semantic memory) and the schizotypal symptoms.

Overall, these data indicate harmful effects of ketamine when used in uncontrolled circumstances. Extrapolating the deleterious effects of ketamine to the use in clinical circumstances is difficult, since the observed effects in frequent drug users are present after usage of high doses of ketamine. Contamination of the drug with other substances may also play a role. Furthermore, it is difficult to determine whether all these effects are directly linked to the use of ketamine per se since illicit drug users often misuse several drugs of abuse simultaneously (*eg*, XTC, cocaine). Still, we should keep in mind that also chronic pain patients, treated with ketamine for longer periods of time, might experience similar adverse effects. Therefore, patients should be monitored closely and ketamine treatment should be terminated immediately when severe adverse effects are observed.

Conclusions

There is evidence that long-term treatment of chronic pain (particularly in pain with a neuropathic component) with ketamine will cause prolonged pain relief, although the

evidence comes from just a limited number of RCTs ($n = 3$). Of importance is further that no effect on functionality or on depressive symptoms was observed. Still, although ketamine treatment is linked to a variety of side-effects (which include CNS-related symptoms (development of a schizoid-like state, somnolence, dizziness, drug-high, memory defects), cardiovascular stimulation and in a minority of patients liver injury), it is the impression of the treating physicians (and of many of the patients) that the benefits outweigh the risks in specific patient populations. In order to substantiate these impressions, additional placebo or active-comparator controlled studies are required that indeed show that prolonged ketamine-infusions produce long-term analgesia with an acceptable risk-benefit ratio (as measured by a composite index that takes multiple outcome parameters into account). Additional ketamine risks have been observed in recreational ketamine users: urological symptoms and persistent or recurrent schizotypal behaviour and memory defects. And while we cannot extrapolate these findings in these recurrent users of often high-doses of ketamine to our patients, the possible long-term effects of ketamine in chronic pain patients on memory and cognition need further study. Until definite proof is obtained that ketamine benefits are greater than its risks, we argue that ketamine administration should be restricted to patients with severe and therapy-resistant neuropathic pain, such as in the case of refractory CRPS pain.[67] Hence, until further evidence is presented, ketamine should not be considered first or second choice in the treatment of neuropathic pain states, irrespective of its cause.

A final issue is the fact that chronic pain patients are treated in an inpatient setting. This is expensive and there is an urgent need for a reliable oral or transmucosal ketamine preparation. However, the use of ketamine outside of the hospital will come at the price of a reduced ability to monitor the patient during treatment and an enhanced probability of toxicity and abuse. Smart dosing regimens, patient (and doctor) training, frequent patient-

doctor contacts and close monitoring of drug dispensing are required to make at-home ketamine treatment a success.

Conflict of interest. The authors declare no conflict of interest regarding the topic of this review paper.

Accepted Article

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Accepted Article

Legend to the figures.

Figure 1. A-C. Resting-state fMRI areas of connectivity in the brain during low-dose ketamine exposure in healthy volunteers relative to network of interest 1 (NOI1). The data are linked to the antinociceptive properties of the drug by assessment of pain relief to a heat pain stimulus and incorporation of pain relief as regressor in the statistical model. The statistical map gives the variations in connectivity explained by ketamine (yellow) and by pain relief (green). These green areas indicate that pain relief was associated with increased connectivity in the anterior cingulate cortex (ACC), orbitofrontal cortex, brain stem and amygdala in relation to the network of interest (in blue). These regions are involved in pain sensing, pain processing and activation of descending inhibition of pain. (Adapted from Ref. [29] with permission).

Figure 2. Psychotropic effects observed during intravenous low-dose ketamine (circles) and placebo (squares) treatment. A. Drug high. B. Changes in internal perception (inner feelings that do not correspond with reality). C. Changes in external perception (misperceptions of an external stimulus or change in the awareness of the surroundings). NRS =numerical rating scale. (Adapted from Ref. [29] with permission).

Table 1. List of chronic pain syndromes from 37 randomized controlled trials on the efficacy of ketamine on chronic pain relief (2009-2012).[9]

Syndrome	number of studies
Acute and chronic migraine	2
Breakthrough (non)-cancer pain	1
Central neuropathic pain	2
Chemotherapy-induced neuropathy	1
Chronic neuropathic pain (various causes)	9
Complex regional pain syndrome	3
Fibromyalgia	3
Painful limb ischemia	2
Peripheral nerve injury (traumatic)	4
Phantom limb pain	1
Postherpetic neuralgia	1
Spinal cord injury	2
Temporomandibular pain	2
Trigeminal neuropathic pain	1
Whiplash	3

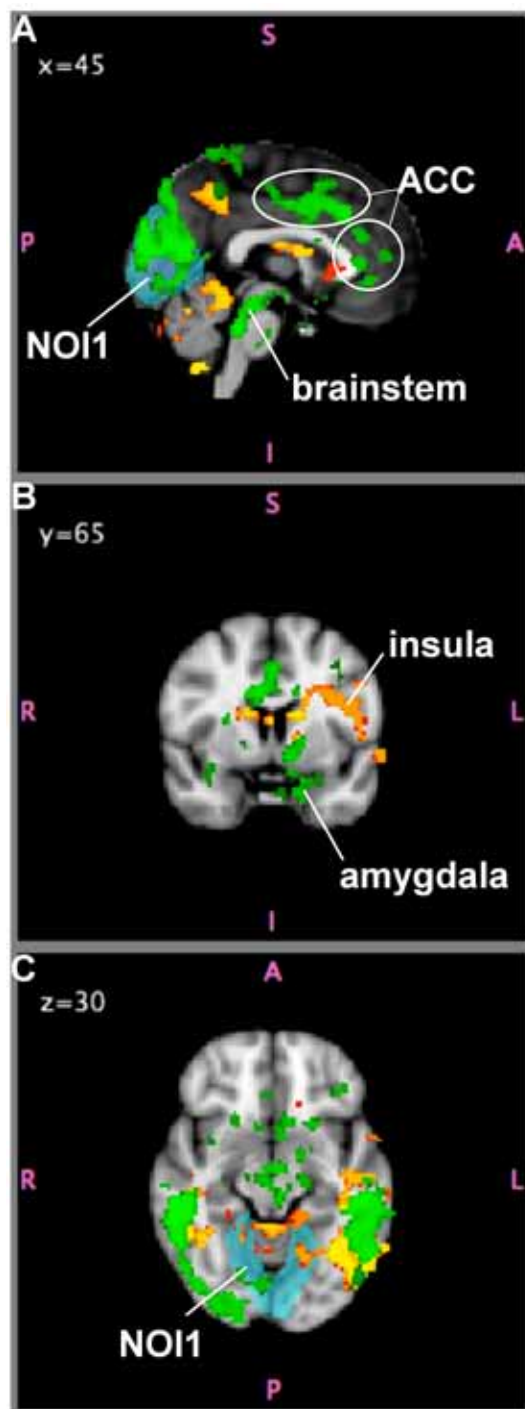


FIG 1

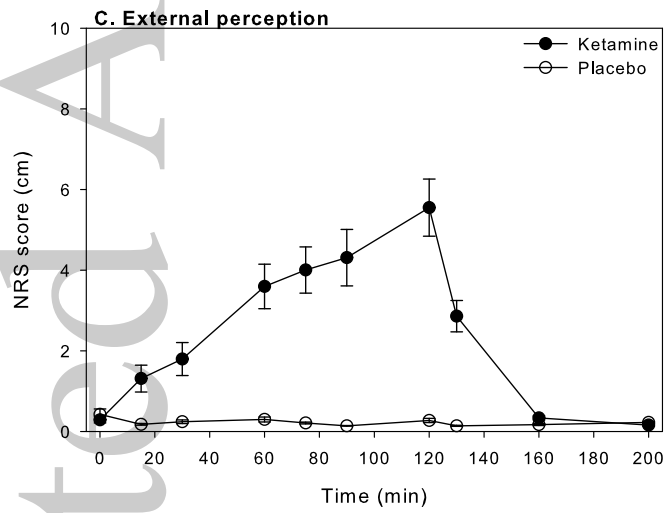
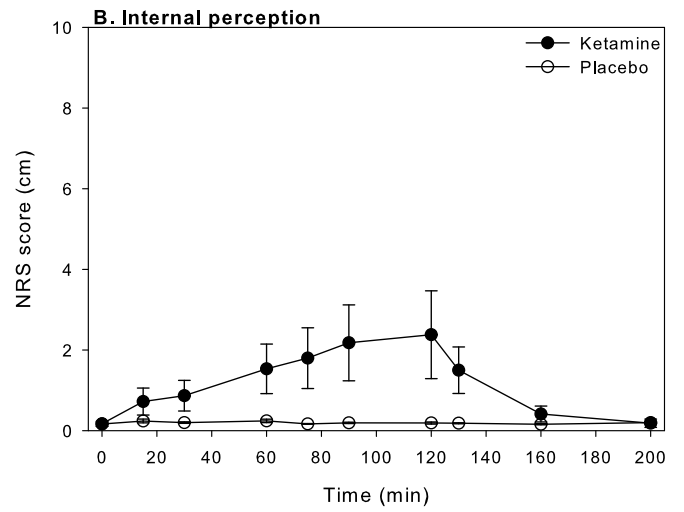
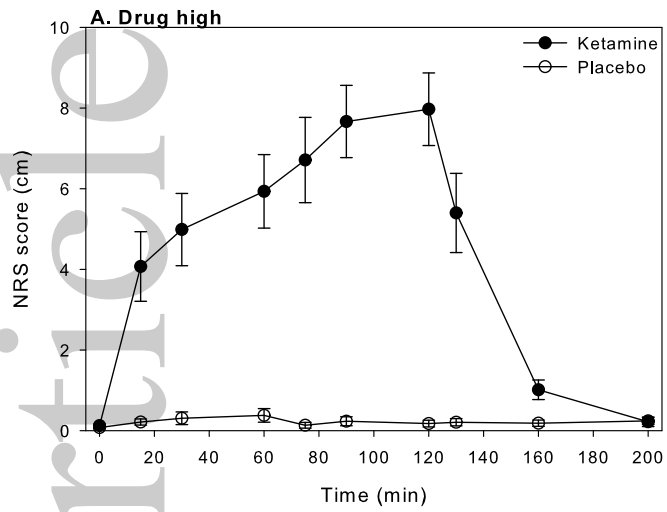


FIG 2