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Ketamine for chronic pain: risks and benefits

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The anaesthetic 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 (4–14 days) show long-term analgesic effects up to 3 months following infusion. The side effects of ketamine noted in clinical studies include psychedelic symptoms (hallucinations, memory defects, panic attacks), nausea/vomiting, somnolence, cardiovascular stimulation and, in a minority of patients, hepatoxicity. 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, haemodynamic, 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 has been 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 antidepressants, 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]. Anaesthesiologists and other pain physicians started using the anaesthetic ketamine, at subanaesthetic 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), post-herpetic 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-adrenoceptor 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 anaesthesia is limited given the occurrence of a variety of side effects, most importantly the induction of a psychedelic state causing agitation, hallucinations and panic attacks (i.e. emergence and excitation symptoms). Although these side effects may be prevented or treated (see above), the availability of alternatives has limited the use of ketamine in anaesthesia

to specific indications (e.g. paediatric and trauma anaesthesia). 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 its chemical structure. The chiral centre on the C-2 atom of the ketamine cyclohexane ring gives rise to two 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^{-1}, redistribution half-life 7–15 min, clearance 15 ml kg^{-1} min^{-1} and elimination half-life 2–3 h [8, 10, 11]. Ketamine rapidly passes the blood–brain barrier (blood–effect site equilibration half-life, $t_{1/2}k_{e0}$, 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 $t_{1/2}$ of ketamine 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^{-1} 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 the 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 concentrations [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 the 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 the 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, [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 monaminergic 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 (i.e. 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: (i) 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) and (ii) 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 (i.e. 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 with earlier findings in volunteers (where ketamine enhanced pain facilitation rather than inhibition) [35], the RS-fMRI and patient CPM data collectively suggest that ketamine is able to influence (i.e. re-activate) the descending inhibitory system under specific circumstances (e.g. 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 [9] for the references). There is, however, no consensus on the administration

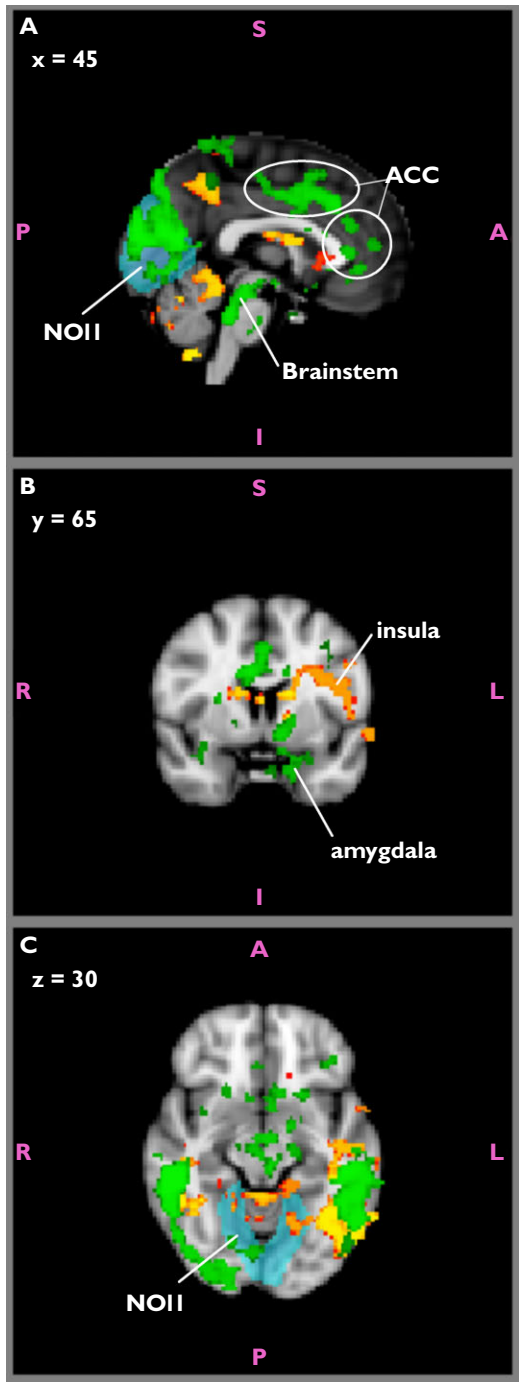

Figure 1

A-C. Resting state MRI 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 is 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 [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 ischaemia	2
Peripheral nerve injury (traumatic)	4
Phantom limb pain	1
Post-herpetic neuralgia	1
Spinal cord injury	2
Temporomandibular pain	2
Trigeminal neuropathic pain	1
Whiplash	3

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. Given 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 for 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^{-1}), given over 30 min, produced analgesia no longer than 45 min [36]. In contrast, Sigtermans *et al*. [4] showed that treating CRPS type 1 patients with a 100 h infusion of S-ketamine (dose titrated up to 20–30 mg h^{-1}) resulted 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 4 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 (one 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 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 *vs.* epidural saline and bupivacaine and although they observed superior analgesia directly post-operatively 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, 1 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 post-operative 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, post-operatively and in the treatment of chronic cancer pain. A 2005 Cochrane review on peri-operative ketamine use showed that ketamine reduced morphine consumption in 27/37 studies with concomitant less pain and less nausea and vomiting [42]. Similarly, ketamine improved 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 feel nauseated. These data suggest that an opioid-ketamine combination may be useful in non-neuropathic pain states (e.g. in the palliative setting) or in mixed nociceptive/neuropathic pain states (e.g. in cancer pain).

Recent evidence shows that ketamine has potent antidepressant qualities [47, 48]. In fact, clinical studies show that one subanaesthetic 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 mammalian target of rapamycin (mTOR) pathway increasing the expression of synaptic proteins and the density of dendritic spines, and causing an antidepressant response within 1 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, treating the pain and ameliorating 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 delineates 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 The 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^{-1}). 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 derealization 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 3 nights following ketamine administration the incidence of unpleasant dreams was significantly increased compared with placebo. Given 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 (e.g. clonidine) [7, 58]. The use of clonidine especially 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 (anaesthetic 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

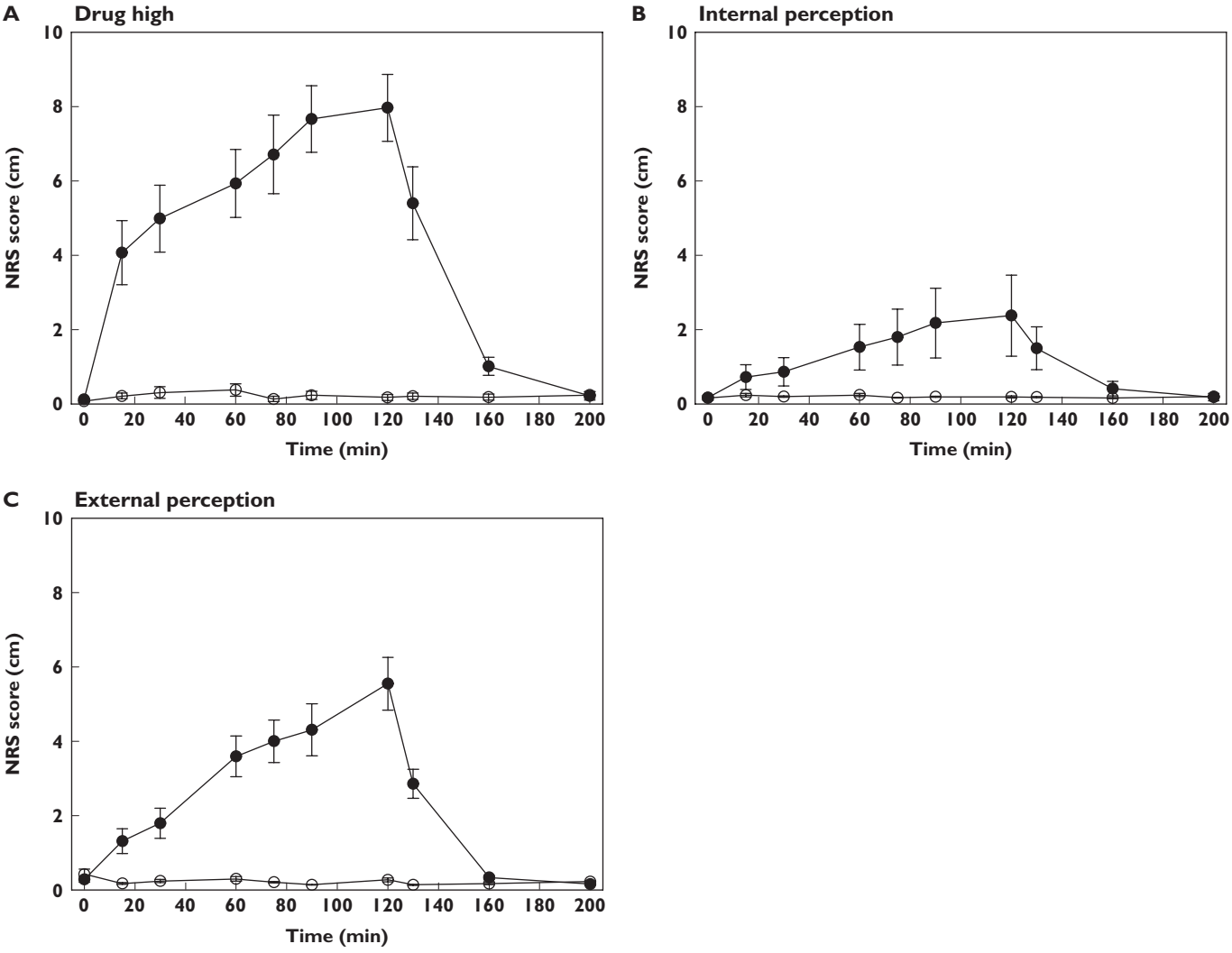

Figure 2

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

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-adrenoceptor blockade improves haemodynamics 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 anaesthetic and subanaesthetic 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 three of six treated patients alanine transaminase, alkaline phosphatase, aspartate transaminase and γ-glutamyl transferase all increased three 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 post-herpetic 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 h. 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 surroundings 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 are hypertension, tachycardia, nystagmus, hallucinations and slurred speech [69]. In an ED study from China (Hong Kong) [70] reviewing 233 cases of ketamine abuse the 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 depersonalization and derealization 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 three 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 with 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 consistant 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 12 patients and gastroduodenitis in one.

In contrast to the clinical use of ketamine, ketamine abuse is associated with defects in memory function that persist after abstinence [53, 81, 82]. Also the presence of schizotypical symptoms like delusional thinking, superstitious conditioning, dissociation and depression may

persist or recur regularly (i.e. *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-adrenoceptor 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 schizotypical 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 (e.g. XTC, cocaine). Still, we should also keep in mind that 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 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 schizotypical behaviour and memory defects. 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 the benefits of ketamine 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.

Competing Interests

We hereby declare that all authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1 Okie S. A flood of opioids, a rising tide of deaths. N Engl J Med 2010; 363: 1981–5.

2 Dworkin RH, O'Connor AB, Audette J, Baron R, Gourlay GK, Haanpää ML, Kent JL, Krane EJ, Lebel AA, Levy RM, Mackey SC, Mayer J, Miaskowski C, Raja SN, Rice AS, Schmader KE, Stacey B, Stanos S, Treede RD, Turk DC, Walco GA, Wells CD. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc 2010; 85: S3–14.

3 Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain 2005; 118: 289–305.

4 Sigtermans MJ, van Hilten JJ, Bauer MCR, Arbous MS, Marinus J, Sarton EY, Dahan A. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. Pain 2009; 145: 304–11.

5 Eide PK, Jorum E, Stubhaug A, Bremnes J, Breivik H. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparisonwith morphine and placebo. Pain 1994; 58: 347–54.

6 Kvarnstrom A, Karlsten R, Quiding H, Emanuelsson BM, Gordh T. The effectiveness of intravenous ketamine and lidocaine on peripheral neuropathic pain. Acta Anaesthesiol Scand 2003; 47: 868–77.

7 Coppel DL, Bovill JG, Dundee JW. The taming of ketamine. Anaesthesia 1973; 28: 293–6.

8 Domino EF. Taming the ketamine tiger. Anesthesiology 2010; 113: 876–86.

9 Noppers I, Niesters M, Aarts L, Smith T, Sarton E, Dahan A. Ketamine for the treatment of chronic non-cancer pain. Expert Opin Pharmacother 2010; 11: 2417–29.

10 Yanagihara Y, Ohtani M, Kariya S, Uchino K, Hiraishi T, Ashizawa N, Aoyama T, Yamamura Y, Yamada Y, Iga T. Plasma concentration profiles of ketamine and norketamine after administration of various ketamine preparations to healthy Japanese volunteers. Biopharm Drug Dispos 2003; 24: 37–43.

11 Reves JG, Glass PSA, Lubarsky DA, McEvoy MD. Intravenous nonopioid anesthetics. In: Miller's Anesthesia, 6th edn, ed. Miller RD. Philadelphia, PA: Elsevier, Churchill, Livingstone, 2005; 319.

12 Sigtermans M, Dahan A, Mooren R, Bauer M, Kest B, Sarton E, Olofsen E. S(+)-ketamine effect on experimental pain and cardiac output: a population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. Anesthesiology 2009; 111: 892–903.

13 Schüttler J, Stanski DR, White PF, Trevor AJ, Horai Y, Verotta D, Sheiner LB. Pharmacodynamic modeling of the EEG effects of ketamine and its enantiomers in man. J Pharmacokinet Biopharm 1987; 15: 241–53.

14 Herd DW, Anderson BJ, Keene NA, Holford N. Investigating the pharmacodynamics of ketamine in children. Ped Anesth 2008; 18: 36–42.

15 Dahan A, Olofsen E, Sigtermans M, Noppers I, Niesters M, Aarts L, Bauer M, Sarton E. Population pharmacokinetic-pharmacodynamic modeling of ketamine-induced pain relief of chronic pain. Eur J Pain 2011; 15: 258–67.

16 Hijazi Y, Boulieu R. Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes. Drug Metab Dispos 2002; 30: 853–8.

17 Leung LY, Baillie TA. Comparative pharmacology in the rat of ketamine and its two principal metabolites, norketamine and (Z)-6-hydroxynorketamine. J Med Chem 1986; 29: 2396–9.

18 Woolf TF, Adams JD. Biotransformation of ketamine, (Z)-6-hydroxyketamine, and (E)-6-hydroxyketamine by rat, rabbit, and human liver microsomal preparations. Xenobiotica 1987; 17: 839–47.

19 Hagelberg NM, Peltoniemi MA, Saari TI, Kurkinen KJ, Laine K, Neuvonen PJ, Olkkola KT. Clarithromycin, a potent inhibitor of CYP3A, greatly increases exposure to oral S-ketamine. Eur J Pain 2010; 14: 625–29.

20 Noppers I, Olofsen E, Niesters M, Aarts L, Mooren R, Dahan A, Kharasch E, Sarton E. Effect of rifampicin on S-ketamine and S-norketamine plasma concentrations in healthy volunteers after intravenous S-ketamine administration. Anesthesiology 2011; 114: 1435–45.

21 Olofsen Olofsen E, Noppers I, Niesters M, Kharasch E, Aarts L, Sarton E. Estimation of the contribution of norketamine to ketamine-induced acute pain relief and neurocognitive impairment in healthy volunteers. Anesthesiology 2012; 117: 353–64.

22 Goldberg ME, Torjman MC, Schwartzman RJ, Mager DE, Wainer IW. Pharmacodynamic profiles of ketamine (R)- and (S)- with 5-day inpatient infusion for the treatment of complex regional pain syndrome. Pain Physician 2010; 13: 379–87.

23 Petrenko AB, Yamakura T, Baba H, Shimoji K. The role of *N*-methyl-D-aspartate (NMDA) receptors in pain: a review. Anesth Analg 2003; 97: 1108–16.

24 Marchand F, Perretti M, McMahon SB. Role of immune system in chronic pain. Nat Rev Neurosci 2005; 6: 521–32.

25 Watkins LR, Maier SF. Immune regulation of central nervous system functions: from sickness responses to pathological pain. J Int Med 2005; 257: 139–55.

26 Costigan M, Scholz J, Woolf CJ. Neuropathic pain: a maladaptive response of the nervous system to damage. Annu Rev Neurosci 2009; 32: 1–32.

27 Ossipov MH, Dussor GO, Porreca F. Central modulation of pain. J Clin Invest 2010; 120: 3779–87.

28 Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011; 152: S2–15.

29 Niesters M, Khalili-Mahani N, Martini C, Aarts L, van Gerven J, van Buchem MA, Dahan A, Rombouts S. Effect of subanesthetic ketamine on intrinsic functional brain connectivity: a placebo controlled functional magnetic resonance imaging study in healthy volunteers. Anesthesioloy 2012; 117: 868–77.

30 Niesters M, Aarts L, Sarton E, Dahan A. Influence of ketamine and morphine on descending pain modulation in chronic pain patients: a randomized placebo controlled cross-over study. Br J Anaesth 2013. [Epub ahead of print].

31 Hirota K, Lambert DG. Ketamine: new uses for an old drug? Br J Anaesth 2011; 107: 123–6.

32 Wolff K, Winstock AR. Ketamine: from medicine to misuse. CNS drugs 2006; 20: 199–218.

33 Sarton E, Teppema LJ, Olievuer C, Nieuwenhuijs D, Matthes HWD, Kieffer BL, Dahan A. The involvement of the μ-opioid receptor in ketamine-induced respiratory depression and antinociception. Anesth Analg 2001; 93: 1495–500.

34 Boyce S, Wyatt A, Webb JK, O'Donnell R, Mason G, Rigby M, Sirinathsinghji D, Hill RG, Rupniak NM. Selective NMDA NR2B

antagonists induce antinociception without motor dysfunction: correlation with restricted localisation of NR2B subunits in dorsal horn. Neuropharmacology 1999; 38: 611–23.

35 Niesters M, Dahan A, Swartjes M, Noppers I, Fillingim RB, Aarts L, Sarton EY. Effect of ketamine on endogenous pain modulation in healthy volunteers. Pain 2011; 152: 656–63.

36 Noppers I, Niesters M, Swartjes M, Bauer M, Aarts L, Geleijnse N, Mooren R, Dahan A, Sarton E. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. Eur J Pain 2011; 15: 942–9.

37 Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. Pain 2009; 147: 107–15.

38 Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: a prospective, randomized, double blind trial. Pain Physician 2010; 13: 245–9.

39 Wilson JA, Nimmo AF, Fleetwood-Walker SM, Colvin LA. A randomised double blind trial of the effect of pre-emptive epidural ketamine on persistent pain after lower limb amputation. Pain 2008; 135: 108–18.

40 Mendola C, Cammarota G, Netto R, Cecci G, Pisterna A, Ferrante D, Casadio C, Della Corte F. S(+)-ketamine for control of perioperative pain and prevention of Post Thoracotomy Pain Syndrome: a randomized, double blind study. Minerva Anestesiol 2012; 78: 757–66.

41 Dualé C, Sibaud F, Guastella V, Vallet L, Gimbert YA, Taheri H, Filaire M, Schoeffler P, Dubray C. Perioperative ketamine does not prevent chronic pain after thoracotomy. Eur J Pain 2009; 13: 497–505.

42 Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev 2006; (1): CD004603.

43 Bell RF, Eccleston C, Kalso E. Ketamine as adjuvant to opioids for cancer pain. A qualitative systematic review. J Pain Symptom Manage 2003; 26: 867–75.

44 Juni A, Klein G, Kest B. Morphine hyperalgesia in mice is unrelated to opioid activity, analgesia, or tolerance: evidence for multiple diverse hyperalgesic systems. Brain Res 2006; 1070: 35–44.

45 Juni A, Klein G, Pintar JE, Kest B. Nociception increases during opioid infusion in opioid receptor triple knock-out mice. Neuroscience 2007; 147: 439–44.

46 van Dorp E, Kest B, Kowalczyk WJ, Morariu AM, Waxman AR, Arout CA, Dahan A, Sarton E. Morphine-6β-glucuronide rapidly increases pain sensitivity independently of opioid receptor activity in mice and humans. Anesthesiology 2009; 110: 1356–63.

47 Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, Charney DS, Krystal JH. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000; 47: 351–4.

48 Zarate CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, Charney DS, Manji HK. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006; 63: 856–64.

49 Li N, Lee B, Liu RJ, Banasr M, Dwyer JM, Iwata M, Li XY, Aghajanian G, Duman RS. mTOR-dependent synapse formation underlies rapid antidepressant effects of NMDA antagonists. Science 2010; 329: 959–64.

50 Bowdle AT, Radant AD, Cowley DS, Kharash ED, Strassman RJ, Ray-Byrne PP. Psychedelic effects of ketamine in healthy volunteers. Anesthesiology 1998; 88: 82–8.

51 Pomarol-Clotet E, Honey GD, Murray GK, Corlett PR, Absalom AR, Lee M, McKenna PJ, Bullmore ET, Fletcher PC. Psychological effects of ketamine in healthy volunteers. Phenomenological study. Br J Psychiatry 2006; 189: 173–9.

52 Coull JT, Morgan H, Cambridge VC, Moore JW, Giorlando F, Adapa R, Corlett PR, Fletcher PC. Ketamine perturbs perception of the flow of time in healthy volunteers. Psychopharmacology 2011; 218: 543–56.

53 Morgan CJ, Curran VH. Acute and chronic effects of ketamine upon human memory: a review. Psychopharmacology 2006; 188: 408–24.

54 Cvrček P. Side effects of ketamine in the long-term treatment of neuropathic pain. Pain Med 2008; 9: 253–7.

55 Blagrove M, Morgan CJ, Curran VH, Bromley L, Brandner B. The incidence of unpleasant dreams after sub-anaesthetic ketamine. Psychopharmacology 2009; 203: 109–20.

56 Stefanovic A, Brandner B, Klaassen E, Cregg R, Nagaratnam M, Bromley LM, Das RK, Rossell SL, Morgan CJ, Curran HV. Acute and chronic effects of ketamine on semantic priming: modeling schizophrenia? J Clin Psychopharmacol 2009; 29: 124–33.

57 Honey GD, O'Loughlin C, Turner DC, Pomarol-Clotet E, Corlett PR, Fletcher P. The effects of a subpsychotic dose of ketamine on recognition and source memory for agency: implications for pharmacological modeling of core symptoms of schizophrenia. Neuropsychopharmacology 2006; 31: 413–23.

58 Bergman SA. Ketamine: review of its pharmacology and its use in pediatric anesthesia. Anesth Prog 1999; 46: 10–20.

59 Morgen CJ, Rossell S, Pepper F, Smart J, Blackburn J, Brandner B, Curran HV. Semantic priming after ketamine acutely in healthy volunteers and following chronic self-administration in substance users. Biol Psychiatry 2006; 59: 265–72.

60 Morgan CJ, Mofeez A, Brandner B, Bromley L, Curran VH. Acute effects of ketamine on memory systems and psychotic symptoms in healthy volunteers. Neuropsychopharmacology 2004; 29: 208–18.

61 Adler CM, Goldberg TE, Malholtra AK, Pickar D, Breier A. Effects of ketamine on thought disorder, working memory, and semantic memory in healthy volunteers. Biol Psychiatry 1998; 43: 811–6.

62 Koffler SP, Hampstead BM, Irani F, Tinker KRT, Rohr P, Schwartzman RJ. The neurocognitive effects of 5 day

anesthetic ketamine for the treatment of refractory complex regional pain syndrome. Arch Clin Neuropsychol 2007; 22: 919–29.

63 Timm C, Linstedt U, Weiss T, Zenz M, Maier C. Sympathicomimetische Effekte auch bei niedriger Dosierung von Esketamin. Anaesthetist 2008; 57: 338–46.

64 Kalsi SS, Wood DM, Dargan PI. The epidemiology and patterns of acute and chronic toxicity associated with recreational ketamine use. Emerg Health Threats J 2011; 4: 7107. doi: 10.3402/ehtj.v4i0.7107.

65 Blunnie WP, Zacharias M, Dundee JW, Doggart JR, Moore J, McIlroy PD. Liver enzymes with continuous intravenous anaesthesia. Anaesthesia 1981; 36: 152–6.

66 Dundee JW, Fee JP, Moore J, McIlroy PD, Wilson DB. Changes in serum enzyme levels following ketamine infusions. Anaesthesia 1980; 35: 12–6.

67 Kiefer RT, Rohr P, Ploppa A, Dietrich HJ, Grothusen J, Koffler S, Altemeyer KH, Unertl K, Schwartzman RJ. Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II study. Pain Med 2008; 9: 1173–201.

68 Noppers IM, Niesters M, Aarts LP, Bauer MC, Drewes AM, Dahan A, Sarton E. Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients: a report of 3 cases. Pain 2011; 152: 2173–8.

69 Weiner AL, Vieira L, McKay CA Jr, Bayer MJ. Ketamine abusers presenting to the emergency department: a case series. J Emerg Med 2000; 18: 447–51.

70 Ng SH, Tse ML, Ng HW, Lau FL. Emergency department presentation of ketamine abusers in Hong Kong: a review of 233 cases. Hong Kong Med J 2010; 16: 6–11.

71 Morgan CJ, Curran VH. Ketamine use: a review. Addiction 2011; 107: 27–38.

72 Middela S, Pearce I. Ketamine-induced vesicopathy: a literature review. Int J Clin Pract 2011; 65: 27–30.

73 Mak SK, Chan MT, Bower WF, Yip SK, Hou SS, Wu BB, Man CY. Lower urinary tract changes in young adults using ketamine. J Urol 2011; 186: 610–4.

74 Chu PS, Ma WK, Wong SC, Chu RW, Cheng CH, Wong S, Tse JM, Lau FL, Yiu MK, Man CW. The destruction of the lower urinary tract by ketamine abuse: a new syndrome? BJU Int 2008; 102: 1616–22.

75 Mason K, Cottrell AM, Corrigan AG, Gillatt DA, Mitchelmore AE. Ketamine-associated lower urinary tract destruction: a new radiological challenge. Clin Radiol 2010; 65: 795–800.

76 Tsai TH, Cha TL, Lin CM, Tsao CW, Tang SH, Chuang FP, Wu ST, Sun GH, Yu DS, Chang SY. Ketamine-associated bladder dysfunction. Int J Urol 2009; 16: 826–9.

77 Cheung RY, Chan SS, Lee JH, Pang AW, Choy KW, Chung TK. Urinary symptoms and impaired quality of life in female ketamine users: persistence after cessation of use. Hong Kong Med J 2011; 17: 267–73.

78 Lo RS, Krishnamoorthy R, Freeman JG, Austin AS. Cholestasis and biliary dilatation associated with chronic ketamine abuse: a case series. Singapore Med J 2011; 52: e52–5.

79 Wong SW, Lee KF, Wong J, Ng WW, Cheung YS, Lai PB. Dilated common bile ducts mimicking choledochal cysts in ketamine abusers. Hong Kong Med J 2009; 15: 53–6.

80 Poon TL, Wong KF, Chan MY, Fung KW, Chu SK, Man CW, Yiu MK, Leung SK. Upper gastrointestinal problems in inhalational ketamine abusers. J Dig Dis 2010; 11: 106–10.

81 Curran VH, Monaghan L. In and out of the K-hole: a comparison of the acute and residual effects of ketamine in frequent and infrequent ketamine users. Addiction 2001; 96: 749–60.

82 Morgan CJ, Riccelli M, Maitland CH, Curran VH. Long-term effects of ketamine: evidence for a persisting impairment of source memory in recreational users. Drug Alcohol Depend 2004; 75: 301–8.

83 Morgan CJ, Monaghan L, Curran VH. Beyond the K-hole: a 3-year longitudinal investigation of the cognitive and subjective effects of ketamine in recreational users who have substantially reduced their use of the drug. Addiction 2004; 99: 1450–61.

84 Freeman TP, Morgan CJ, Klaassen E, Das RK, Stefanovic A, Brandner B, Curran VH. Superstitious conditioning as a model of delusion formation following chronic but not acute ketamine in humans. Psychopharmacology 2009; 206: 563–73.

85 Sikker W, Zou X, Hotchkins CE, Divine RL, Sadovova N, Twaddle NC, Doerge DR, Scallet AC, Patterson TA, Hanig JP, Paule MG, Wang C. Ketamine-induced neuronal cell death in perinatal rhesus monkey. Toxicol Sci 2007; 98: 145–58.

86 Jevtovic-Todorovic V, Carter LB. The anesthetics nitrous oxide and ketamine are more neurotoxic to old than to young rat brains. Neurobiol Aging 2005; 26: 947–56.

87 Liao Y, Tang J, Corlett PR, Wang X, Yang M, Chen H, Liu T, Chen X, Hao W, Fletcher PC. Reduced dorsal frontal gray matter after chronic ketamine use. Biol Psychiatry 2011; 69: 42–8.

88 Liao Y, Tang J, Ma M, Wu Z, Yang M, Wang X, Liu T, Chen X, Fletcher PC, Hao W. Frontal white matter abnormalities following chronic ketamine use: a diffusion tensor imaging study. Brain 2010; 133: 2115–22.