Ketamine for the treatment of chronic non-cancer pain

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Importance of the field: Worldwide the number of patients affected by chronic pain is growing and conventional treatment is often insufficient. Recently the importance of the *N*-methyl-D-aspartate receptor (NMDAR) in the mechanisms and maintenance of chronic pain was established. Ketamine (introduced in the 1960s as an anesthetic) is the most studied NMDAR antagonist in the treatment of various chronic pain syndromes.

Areas covered in this review: The pharmacology, safety and toxicology of ketamine are discussed. Further, electronic databases were scanned for prospective, randomized controlled trials that assessed ketamine's analgesic effect in patients with chronic pain. The focus of this review is on trials published after 2008 that applied long-term intravenous infusions.

What the reader will gain: While most studies on intravenous ketamine show acute analgesic effects, three recent trials on long-term ketamine treatment (days to weeks) demonstrate the effectiveness of ketamine in causing long-term (months) relief of chronic pain. Despite these positive results, further studies are needed on safety/toxicity issues. Other administration modes are less effective in causing long-term pain relief.

Take home message: There is now evidence form a limited number of studies that pain relief lasting for months is observed after long-term intravenous ketamine infusion, suggesting a modulatory effect of ketamine in the process of chronic pain, possibly via blockade of upregulated NMDAR.

Keywords: analgesia, chronic pain, CRPS, ketamine, NMDA receptor antagonist, pain

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1. Introduction

Worldwide, the number of patients affected by chronic pain is growing. Presently, in the US alone, chronic pain affects over 70 million people, costing the economy more than US$100 million per year [1]. Management of chronic pain syndromes is characterized by a trial-and-error approach, with interventions including psychotherapy, physiotherapy, drug treatment (including opioids, antidepressants, antiepileptics, NSAIDs, and their combinations) and spinal cord stimulation, often with limited success. Recently, the importance of the *N*-methyl-D-aspartate receptor (NMDAR) in the etiology and perseverance of chronic pain was established [2]. In chronic pain, the NMDAR is activated and upregulated in the dorsal horn of the spinal cord (sensitization), which causes enhanced signal transmission in the pain circuitry and leads to chronic pain that is often coupled with allodynia and hyperalgesia [2,3]. Consequently, drugs that block the NMDAR may be able to relieve chronic pain and possibly modulate the underlying disease process. The most studied NMDAR antagonist currently available is ketamine (**Box 1**) [4].

Here we will discuss the use of low-dose ketamine in the treatment of chronic non-cancer pain, reviewing the complete ketamine database and highlighting recent

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Box 1. Drug summary.

Drug name (generic)	Ketamine
Phase	Phase IV
Indication	Anesthesia, acute and chronic pain
Mechanism of action	*N*-methyl-D-aspartate receptor antagonist
Route of administration	Intravenous, oral, intranasal, topical
Chemical structure	2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone
Pivotal trials	Sigtermans *et al.*, Pain 2009 [10] Schwartzman *et al.*, Pain 2009 [12] Amr, Pain Physician 2010 [11]

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clinical and preclinical studies (published after 2008). While ketamine was initially marketed as anesthetic agent, it recently began its second life in the treatment of chronic and acute (perioperative) pain [5-9]. In chronic pain, ketamine is used in the treatment of cancer and non-cancer pain. A major problem with the use of ketamine is the development of psychotropic side effects, especially when used at high dose, while animal data suggest that high-dose and long-term ketamine infusion may be associated with neurotoxicity [7].

Recent studies (published after 2008) focusing on long-term infusion of low-dose ketamine in the treatment of chronic pain non-cancer demonstrated efficacy and safety of the ketamine infusion, although the patients were not followed for > 3 months [10-12]. Previous reviews have addressed the efficacy of ketamine in acute pain, cancer pain and chronic non-cancer pain (covering studies until 2008), predominantly of studies employing short-term administration paradigms [5-8].

2. Chemistry

Ketamine (2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone) is an arylcyclo-alkylamine molecule, a phenylpiperidine derivative that is structurally related to phencyclidine (PCP). It was first synthesized in the early 1960s and initially introduced as safer alternative to PCP. In 1965 the anesthetic properties of ketamine became apparent. At anesthetic doses it causes a dissociative anesthetic state (dissociation between the thalamus and limbic system), while at subanesthetic doses it is a potent analgesic. Ketamine exists in two stereoisomeric forms, S(+) and R(-), due to the presence of a chiral center located on C-atom 2 of the cyclohexane ring (**Figure 1**) [5]. The S(+) variant has about two and four times greater analgesic potency compared with the racemic mixture and the S(-) enantiomer, respectively [5]. There are two different commercial forms of ketamine available: the racemic mixture (Ketalar™, Pfizer, Inc.) and in some countries (such as The Netherlands, Germany, Austria) the S(+) enantiomer (S-ketamine or Ketanest-S™, Pfizer, Inc.).

3. Pharmacokinetics and metabolism

Few studies have addressed the pharmacokinetics of ketamine in chronic pain patients using an extended administration paradigm [10]. Studies on acute (short-term) administration show limited bioavailability after oral, sublingual and rectal administration (20 – 30%), partly because of the large first-pass effect, while bioavailability is somewhat higher after intranasal application (45%), with no differences between the two enantiomers of the racemic mixture [13]. Peak concentration after oral ketamine ingestion is reached after 20 – 30 min. The pharmacokinetics after a single or short-term infusion have well been described: volume of distribution, distribution and elimination half-life are 0.3 l/kg, 15 min and 2 – 3 h, respectively [14,15]. After intravenous infusion of the racemic mixture, the

R(-) enantiomer inhibits the elimination of the S(+) variant (magnitude of effect ~ 30%) [16]. Furthermore, for the S(+) enantiomer a sex difference in pharmacokinetics has been observed, with a 20% greater clearance in women [15]. Ketamine rapidly passes the blood–brain barrier due its high lipophilicity (blood–effect–site equilibration half-life 1 – 3 min), ensuring a rapid onset of analgesic effect [15,17].

Ketamine is extensively metabolized by the hepatic cytochrome P450 enzyme system (by CYP3A4, CYP2B6 and CYP2C9 enzymes) [18,19]. The main pathway is *N*-demethylation to norketamine with subsequent metabolism of norketamine into 6-hydroxynorketamine. Norketamine and the hydroxy-product are glucuronidated and eliminated via the kidney and bile [20,21]. Induction of the CYP system will have limited effect on the ketamine concentration, as its hepatic clearance before induction is high and approaches liver blood flow (1 l/min) [15]. Drugs that inhibit CYP enzymes involved in ketamine's metabolism (such as clarithromycin) will increase ketamine plasma concentrations, in particular after oral administration [22]. Norketamine appears within minutes in plasma after the intravenous administration of ketamine, and, particularly after long-term infusions, reaches values similar to or even greater than that of

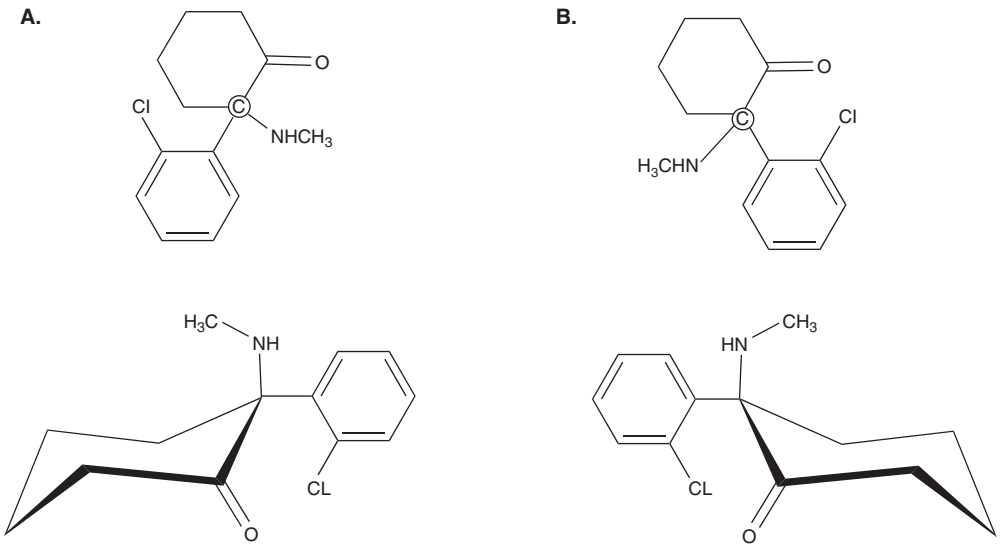

Figure 1. Structure of ketamine. A. S(+)-ketamine; **B.** R(-)-ketamine. The chiral center (C) is at C-atom 2 of the cyclohexane ring.

ketamine [10,15,17]. Upon the termination of ketamine infusion, the plasma concentrations drop rapidly and norketamine concentrations exceed ketamine concentrations [10,15,17].

4. Mechanism of action

While ketamine acts at multiple receptor systems (such as the μ-opioid receptor and the HCN1 pacemaker cell), the analgesic effect of ketamine in chronic pain is attributed to its effects at the NMDAR [2,10,23,24]. The NMDAR is an excitatory ionotropic glutamate receptor present in the spinal cord and the brain. In the resting state, the receptor is blocked by Mg^{2+} ions. The block is lost upon strong and sustained nociceptive activation of the receptor by presynaptic release of glutamate (in the presence of the co-agonist, glycine). This results in a neuronal influx of positive ions (Na^+, Ca^{2+}) and an increase in discharge of dorsal horn nociceptive neurons (causing enhanced pain perception). Prolonged activation of the NMDAR results in plastic changes in the spinal cord with upregulation of NMDAR and central sensitization leading to the chronification of pain [2,3,25]. Ketamine is a noncompetitive antagonist of the NMDAR, reverting the NMDAR to its resting state and consequently causing the impairment of nociceptive signal propagation to the brain and, especially after long-term administration, restoration of the physiological balance between pain inhibition and facilitation [10]. Of further interest is that ketamine's metabolite, norketamine, is a noncompetitive antagonist of the NMDA receptor [26]. Animal data indicate that norketamine passes the blood–brain barrier, has about one-third the potency of ketamine, and is thought to be involved in ketamine's analgesic effect as well as (though to a lesser extent) the development of psychotropic side effects [26]. No data are presently available to substantiate this in humans.

5. Clinical efficacy

5.1 Randomized clinical trials (RCTs): 1992 – 2010

Most studies published on the effect of ketamine on chronic pain are open-label studies, case series or case reports. We searched seven electronic databases (PubMed, EMBASE, Web of Science, the Cochrane Library, CINAHL, PsychINFO and Academic Search Premier) in June 2010 for papers assaying ketamine's analgesic effect in chronic pain patients using a prospective, randomized, controlled design. Key words included pain, chronic pain, chronic disease, neuralgia, neuropathic pain, complex regional pain syndrome, fibromyalgia, neuropathic pain, neuropathy, low back pain, diabetic neuropathy, migraine, multiple sclerosis, postherpetic neuralgia, trigeminus neuralgia, phantom limb, ketamine, S-ketamine, ketanest, ketalar, ketaset, ketanest, calipsol, kalipsol calypsol, 2-(2-Chlorophenyl)-2-(methylamino)-cyclohexanone, CI 581. Limits included human, English, French, German and Dutch.

We retrieved 36 RCTs (first publication date 1992, six published after 2008) of which the majority (21) were on i.v. ketamine (20 using the racemic mixture, 2 S(+)-ketamine) [9-11,27-61]. See **Tables 1** and **2** for the study characteristics. The infusion duration of ketamine in studies on i.v. administration varied from single injections to multiple day infusions (max. infusion duration 2 weeks) with large variations in doses (**Tables 1** and **2**). We refrained from performing a meta-analysis, as the heterogeneity between studies was large and the quality of the majority of studies poor to

Table 1. Randomized controlled trials on the effect of intravenous ketamine on chronic pain (in chronological order).

[Ref.] Year	N*	Chronic pain disease	Crossover	Design and treatment	Results
[11] 2010	20	Neuropathic pain from SCI		20 patients received 80 mg KET infusion in 5 h for 1 week + 3 times/day gabapentin vs 20 patients received a PBO infusion + 3 times/day gabapentin	KET caused effective analgesia in weeks 1 and 2 following treatment
[12] 2009	9	Complex regional pain syndrome		KET 4-h infusion (n = 9) vs PBO (n = 10) infusions for 10 days. Max. infusion = 0.35 mg/kg/h	KET NRS from 7.66 to 6.13 ($p < 0.05$ at weeks 3 – 4) vs PBO NRS from 7.7 to 7.5. Other pain indices improved for ≥ 12 weeks
[10] 2009	30	Complex regional pain syndrome		4.2 day S-KET infusion (increasing dose, max. 20 mg/h, n = 30) vs PBO (n = 30)	KET caused analgesic effects lasting up to 11 weeks. Maximum effect during treatment week
[49] 2007	20	Whiplash	+	4 treatment combinations: PBO/PBO, PBO/remifentanil, KET/PBO, KET/remifentanil. i.v. TCI system with target KET concentration of 100 ng/ml. Infusion duration 65 min	KET/PBO and KET/remifentanil reduced VAS scores from 3.9 to 1.8 and 3.5 to 1.0 cm ($p < 0.001$) during infusion
[40] 2006	20	Nerve injury pain	+	0.24 mg/kg KET over 30 min vs lidocaine (5 mg/kg) vs PBO	Spontaneous pain reduction by KET only; evoked pain reduced by both drugs
[48] 2005	30	Whiplash	+	0.3 mg/kg KET infusion vs 0.3 mg/kg morphine vs 5 mg/kg lidocaine vs PBO. Infusion duration 30 min	KET = 14 responders; duration of effect ≤ 1 – 1.5 h
[46] 2004	10	SCI and neuropathic pain below the level of injury	+	KET 0.4 mg/kg injection vs lidocaine 2.5 mg/kg vs PBO	KET responders 5/10 vs 1/10 after lidocaine and 0/10 after PBO. KET effect = 38% VAS reduction (lidocaine = 10% and PBO = 3%, $p = 0.01$)
[44] 2003	12	Chronic neuropathic pain	+	KET i.v. 60 μg/kg bolus + 6 μg/kg/min for 20 min vs alfentanil vs PBO	KET (and alfentanil) produced significant reductions of pain and hyperalgesia but not cold pain detection threshold
[45] 2003	12	Peripheral neuropathic pain of traumatic origin	+	Single KET 0.4 mg/kg injection vs lidocaine 2.5 mg/kg vs PBO	KET response in 7/12 patients: KET caused a 55% reduction in VAS vs 34% and 22% for lidocaine and PBO ($p = 0.009$)
[54] 2002	18	Painful limb ischemia		KET infusion + opioid vs PBO infusion + opioid. KET dose 0.6 mg/kg infused over 4 h	Improved pain relief by KET of 65% 1 day post-treatment and 69% 5 days post-treatment. Also significant effects on general activity and quality of life
[50] 2001	12	Post-nerve injury	+	KET TCI concentration 50, 100 and 150 ng/ml vs alfentanil (TCI 25, 50 and 75 ng/ml) vs PBO	KET reduced hyperalgesia
[41] 2000	29	Fibromyalgia	+	0.3 mg/kg KET over 30 min vs PBO in 29 patients	17/29 patients showed pain relief > 50%
[58] 1998	8	Pain from arteriosclerosis of the lower extremities	+	KET bolus injection 0.15, 0.30 or 0.45 mg/kg vs morphine 10 mg bolus injection	Dose-dependent analgesic effect from KET with greater effect than morphine at 0.3 and 0.45 mg/kg
[60] 1997	18	Fibromyalgia	+	KET 0.3 mg/kg infusion over 30 min vs PBO vs 0.3 mg/kg morphine vs 5 mg/kg lidocaine	KET responders = 8, nonresponders = 8. Effect in responders 1 – 5 days

*Number of patients receiving ketamine.

KET: Ketamine; NRS: Numerical rating scale; NS: Not significant; PBO: Placebo; QST: Quantitative sensory testing; SCI: Spinal cord injury; S-KET: S(+)-ketamine; TCI: Target controlled intravenous infusion; VAS: Visual analogue score.

Table 1. Randomized controlled trials on the effect of intravenous ketamine on chronic pain (in chronological order) (continued).

[Ref.] Year	N*	Chronic pain disease	Crossover	Design and treatment	Results
[56] 1997	81	Chronic migraine with a temporal pattern	+	KET infusion 0.15 – 1 mg/kg per 24 h for 2 weeks vs PBO	Chronic migraine became episodic in 76/81 patients with a reduction of intake of co-analgesics
[57] 1996	11	Phantom limb pain	+	KET 0.1 mg/kg bolus injection followed by 7 μg/kg/min for max. 45 min vs PBO	KET reduced stump and phantom pain by 100%
[36] 1995	10	Peripheral neuropathic pain	+	KET (0.2 mg/kg bolus + 0.3 mg/kg over 1 h) vs magnesium (bolus + cont. infusion)	KET produced a 57% reduction of pain and 33% reduction of area of allodynia
[53] 1995	8	Chronic post-traumatic pain and widespread mechanical allodynia	+	KET infusion for 2 h (mean dose 58 mg) vs alfentanil (11 mg) vs PBO	Pain relief: KET 65%, alfentanil 46%, PBO 22% ($p < 0.01$). Similar observations for relief of allodynia. Pain relief disappeared upon end of infusion
[29] 1994	6	Chronic neuropathic pain (central pain, peripheral neuropathy)	+	Single or series of 0.25 mg/kg KET injections vs PBO	5/6 patients had pain relief lasting 2 – 3 h, 1 had 2 weeks effect; 1 patient showed no effect
[34] 1994	8	Postherpetic neuralgia	+	Single 0.15 mg/kg KET injection vs morphine (0.075 mg/kg) or PBO	Pain relief by KET (but not morphine or placebo)
[35] 1994	9	Spinal cord injury	+	KET (0.06 mg/kg bolus + 6 μg/kg/h for 20 min) vs alfentanil vs PBO	Pain relief by KET of 40% (and alfentanil of 20%)

*Number of patients receiving ketamine.

KET: Ketamine; NRS: Numerical rating scale; NS: Not significant; PBO: Placebo; QST: Quantitative sensory testing; SCI: Spinal cord injury; S-KET: S(+)-ketamine; TCI: Target controlled intravenous infusion; VAS: Visual analogue score.

Table 2. Randomized controlled trials on the effect of non-intravenous ketamine on chronic pain (in chronological order).

[Ref.] Year	N*	Chronic pain disease	Cross over	Design and treatment	Results
[30] 2010	101	Chemotherapy-induced neuropathy		Topical. KET–amitriptyline–baclofen cocktail (n = 101) vs PBO (n = 104)	No effect on pain relief greater than placebo
[43] 2010	16	Chronic neuropathic pain		Intranasal S-KET. low dose 0.2 mg/kg, n = 8 and high dose 0.4 mg/kg, n = 8	Pain scores decreased with max. effect at t = 60 min. No effect on QST
[37] 2009	20	Complex regional pain syndrome	+	Topical. KET (10% in organogel) vs PBO	KET caused reduction of allodynia and hyperalgesia
[27] 2008	18	Temporomandibular joint arthralgia	+	Intraarticular.18 patients received 1 injection with KET or saline	No effect on pain or somatosensory end points
[32] 2008	14	Chronic myofascial pain in temporomandibular disorder	+	i.m. injection of KET or PBO in m. masseter	No relief of spontaneous pain
[52] 2005	45	Neuropathic pain patients with allodynia, hyperalgesia or pinprick hyperesthesia		Topical. 4 Groups: PBO (n = 25), 2% amitriptyline (n = 22), 1% KET (n = 22), 1% KET + 2% amitriptyline (n = 23)	Effects no larger than PBO
[61] 2005	22	Central neuropathic pain		Iontophoresis. KET 50 mg (n = 11) vs 75 mg (n = 11) per day for 1 week vs PBO (n = 11)	No effect on pain scores from KET but 75 mg improved quality of life and health status
[31] 2004	20	Breakthrough pain in chronic pain patients (n = 16) and cancer patients (n = 4)	+	Intranasal. KET 10 – 50 mg (1 – 5 sprays) vs PBO (1 – 5 sprays)	KET produced analgesia within 10 min lasting ≥ 1 h. Max effect occurred after 40 min (NRS change = 3.13. vs PBO = 0.8, p = 0.0001)
[51] 2003	20	Chronic neuropathic pain	+	Topical. KET for 2 days: 0.5% KET vs 1% amitriptyline vs 0.5% KET + 1% amitriptyline vs PBO	Effects no larger than PBO
[47] 2002	10	Chronic neuropathic pain		Epidural. KET (0.3 mg/kg/day) + lidocaine (n = 10) vs epidural clonidine (90 μg/day) + lidocaine (n = 13) using PCEA device. Treatment duration 3 weeks	Significant reductions in pain intensity (VAS) in both groups from 9 to 2 cm. Effect persisted for 2 – 5 weeks following epidural catheter removal
[38] 2002	8	Chronic neuropathic pain	+	Oral. KET syrup 0.5 mg/kg vs PBO every 6 h for 1 week	KET caused pain relief: VAS from 78 to 49 mm

*Number of patients receiving ketamine.

KET: Ketamine; NRS: Numerical rating scale; NS: Not significant; PBO: Placebo; PCEA: Patient controlled epidural analgesia; QST: Quantitative sensory testing; SCI: Spinal cord injury; S-KET: S(+)-ketamine; VAS: Visual analogue score.

Table 2. Randomized controlled trials on the effect of non-intravenous ketamine on chronic pain (in chronological order) (continued).

[Ref.] Year	N*	Chronic pain disease	Cross over	Design and treatment	Results
[59] 1999	26	Trigeminal neuropathic pain	+	i.m. Study A: KET 0.4 mg/kg vs pethidine 1 mg/kg Oral. Study B: KET 4 mg/kg vs PBO for 3 days	Study A: KET: 9/26 no effect; 9/26 effect 1 h; 8/26 effect > 12 h Study B: 5/26 had an analgesic effect
[42] 1999	21	Chronic neuropathic pain		Oral. n = 1 trial in 9 patients: KET 10 mg once daily for 6 weeks vs PBO	3/21 patients showed a consistent analgesic effect
[55] 1995	34	Acute migraine (n = 17), Chronic episodic migraine (n = 17)	+	s.c. 80 μg/kg in acute sufferers and 80 μg/kg 3 times daily in chronic sufferers for 3 weeks	KET produced significant pain relief. Acute sufferers: 3/17 100% relief, 6/17 90 – 70% relief and 8 45 – 50% relief (duration of effect 4 h). Similar observations for chronic sufferers. Variable effects following infusion
[39] 1992	20	Whiplash, postdiscoidectomy, chronic back-ache		Intra-ligamentous injection with 0.25 mg/kg ketamine vs 2% lidocaine	VAS reduced from 8 to 2 after KET with increased functionality (no effect of lidocaine)

*Number of patients receiving ketamine.

KET: Ketamine; NRS: Numerical rating scale; NS: Not significant; PBO: Placebo; PCEA: Patient controlled epidural analgesia; QST: Quantitative sensory testing; SCI: Spinal cord injury; S-KET: S(+)-ketamine; VAS: Visual analogue score.

moderate (most studies do not present the method of randomization, refrained from stating how dropouts and withdrawals were taken into account, and did not present information on allocation concealment). Furthermore, various studies did not give quantitative data on the ketamine analgesic effect and some studies were ended prematurely. The number of studies that we graded as good [10,11] were insufficient to perform a meta-analysis. Hence we decided to perform a semi-quantitative analysis on the effect of intravenous infusion duration on treatment effect (magnitude and duration).

We included studies that tested the effect of ≥ 0.15 mg/kg ketamine on chronic pain intensity (**Figure 2**). The results show that the majority of studies demonstrate a > 50% reduction of pain intensity, but the effect did not persist beyond the 48 h following infusion. The infusion duration of these studies ranged from 30 min to 2 h. Only four studies reported an analgesic effect persisting beyond the 48 h following infusion, three of which (all published after 2008) employed long-term infusion schemes (4.2 days continuous to daily 4-h infusions for 10 days, with a dose range of 16 – 25 mg/h) [10-12]. Our analysis indicates that at an infusion duration > 10 h the probability of an effect lasting > 48 h approaches 95%, while at durations > 30 h the probability approaches 99% (**Figure 2**). Note, however, that following infusion analgesia slowly dissipates over time (see, for example, **Figure 3**) [10,11]. This indicates that these infusion paradigms were insufficient to cause a permanent reduction of pain. Possibly other infusion regimens (e.g., regular 10-h infusions, daily 1- to 2-h infusions) may have a more permanent effect. None of the published RCTs addressed this issue.

5.2 Randomized clinical trials on long-term intravenous infusion: 2009 – 2010

Three RCTs on i.v. ketamine published after 2008 were identified [10-12]; all used a multiple day infusion scheme. The most recent study by Amr is on the effect of ketamine in spinal cord injury-related chronic pain [11]. Group 1 (n = 20) received 80 mg intravenous ketamine over 5 h daily for 1 week plus 300 mg gabapentin three times daily; Group 2 (n = 20) received a 5-h placebo infusion once daily plus 300 mg gabapentin three times daily. Pain relief was significantly greater in Group 1 relative to Group 2 during infusion and during the first 2 weeks following infusion. Thereafter, there were no more differences between treatment groups in pain scores, although pain scores remained decreased versus baseline for ≥ 4 weeks following the end of treatment in both groups. Ketamine-related side effects occurred in 3/20 patients (short-lasting delusions). None of the side effects required intervention. We consider this a qualitatively good study that may lead the way to out-patient treatment of chronic pain patients with intravenous ketamine.

Schwartzman and colleagues assessed the effect of daily 4-h i.v. ketamine infusions (max. dose 0.35 mg/kg/h) for 10 days in complex regional pain syndrome (CRPS) chronic pain patients [12]. Subjects in both arms of the study received clonidine and midazolam. The subjects receiving ketamine had consistent decreases for all pain-related parameters that lasted for the 12-week post-treatment evaluation period (total McGill pain score pretreatment = 23.1, post treatment weeks 1 – 2 = 16.2, post weeks 3 – 4 = 13.4 and post weeks 9 – 12 = 15.4). Ketamine-related side effects included nausea, headache, tiredness and dysphoria. This study was criticized for reasons of early termination, small sample size, and relatively limited analgesic effect [62]. While powered to study 20 patients per arm, the study was stopped after 9 patients were enrolled in the ketamine arm and 10 in the placebo arm. The reasons given for the premature end of the trial were that the authors had seen greater pain relief with a higher dose of ketamine than allowed in the protocol (max. dose 25 mg/h) and the absence of a placebo effect. Note, however, that these greater analgesic responses were based on an open-label study [62].

Sigtermans and co-workers studied the effect of i.v. ketamine in CRPS patients with moderate to severe chronic pain [10]. Thirty patients (disease duration: mean 7.4 years, range 0.1 – 32 years; mean baseline pain score 7.2 on a scale of 0 – 10) were treated with a 4.2-day continuous infusion of ketamine's S(+) enantiomer with a mean dose of 20 mg/h. Significant analgesic effects were observed in the 4.2-day treatment phase of the study (pain score 2.7 vs 5.5). Over the 12-week duration of the study, ketamine modulated the course of chronic pain more favorably than placebo (**Figure 3**). Ketamine-related side effects included nausea/vomiting and psychotropic effects. Although this study is considered qualitatively 'good', points of criticism include the absence of improvement of function and the cost of the intensive and long-term in-house treatment [62,63]. Twenty patients who initially received placebo were allowed to receive the identical ketamine treatment, but now in an open-label fashion. As expected, their analgesic responses were larger by ≥ 1 NRS point at 2 weeks and pain relief > 50% lasted for > 3 weeks (**Figure 3**). This suggests that a large proportion of the response seen in this patient group is expectancy-related.

6. Safety and tolerability

Ketamine causes a variety of dose-dependent side effects ranging from nausea/vomiting, sedation, vertigo, tachycardia and hypertension to increased cardiac output [7,10,15,64]. Recent discussions indicate that three important issues regarding safety and tolerability of ketamine are of concern [62]: the occurrence of psychotropic side effects; possible neurotoxicity; and the abuse potential of repeated or long-term ketamine use.

6.1 Cardiovascular side effects

The effects of ketamine on the cardiovascular system are related to activation of the sympathetic system (ketamine causes the systemic release of catecholamines and inhibition

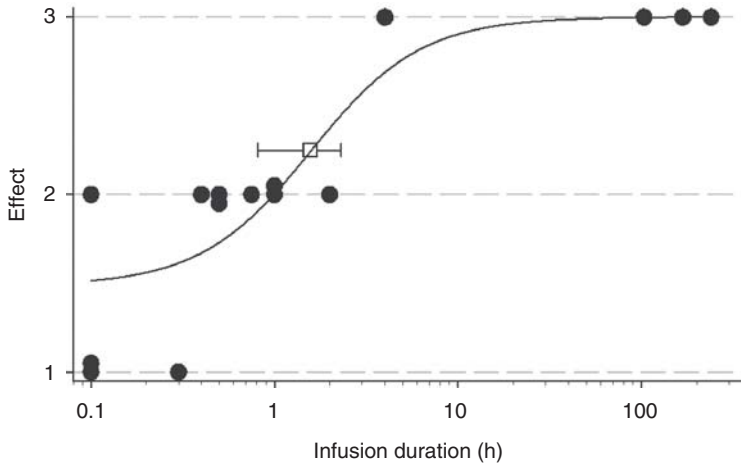

Figure 2. Semi-quantitative analysis on the effect of infusion duration on intravenous ketamine analgesic efficacy. Randomized controlled trials that infused ≥ 0.15 mg/kg were included in the analysis. On the *x*-axis infusion duration in hours, on the *y*-axis effect defined as follows: no analgesic effect (effect = 0), a reduction in pain intensity ≤ 50% of pretreatment pain during infusion (effect = 1), a reduction in pain intensity > 50% of pretreatment pain during infusion (effect = 2) and a significant reduction in pain intensity with pain relief persisting for ≥ 48 h following the termination of infusion (effect = 3). Each filled circle is one study. The continuous line is the result of a logistic regression analysis. The open square is the ID_{50} or infusion duration causing a median analgesic effect (in the current set of studies a median effect = 2.25 was estimated). ID_{50} = 1.7 ± 0.8 h (median ± SE) in a dose range of 0.15 – 0.5 mg/kg. At infusion duration > 10 h, the probability of an effect lasting > 48 h approaches 95%, while at durations > 30 h the probability approaches 99%.

of norepinephrine re-uptake at peripheral nerves and non-neuronal tissues such as the myocardium) [64]. At the doses used in the treatment of chronic pain, effects on the cardiovascular system seem moderate and well-tolerated. However, care is always required in patients with cardiovascular disease (e.g., patients with ischemic heart disease and hypertension).

6.2 Psychotropic side effects and abuse potential

After intravenous dosing, psychotropic side effects are common, ranging from 'drug high' to de-realization/depersonalization, hallucinations and fear/panic attacks. These symptoms resemble psychotic episodes in schizophrenia, but disappear rapidly upon termination of the infusion [10,65]. These effects are dose-dependent [66]. Patient compliance with psychotropic symptoms is variable. When unacceptable psychotropic effects occur, the ketamine infusion rate may be lowered or a benzodiazepine or α_2-adrenergic receptor agonist (clonidine, dexmedetomidine, neuroleptics, antiepileptics) may be added [67]. During prolonged infusions, the occurrence and severity of psychotropic effects seems to decline over time. However, the psychotropic effects may cause the patient to abandon further treatment [10]. In our experience, there are no differences in occurrence of psychotropic side effects during treatment with the racemic mixture or the S(+) enantiomer.

Ketamine is a drug of abuse and increasingly used for recreational use (mostly by sniffing ketamine powder, known as 'Special K' or 'Vitamin K') [68]. Side effects related to the chronic use of ketamine are cognitive dysfunction (memory deficits) and mild psychotic attacks (e.g., flashbacks) occurring up to weeks after the intake [69]. In animals, regular ketamine use has been associated with typical addictive behavior [70].

6.3 Neurotoxicity

Animal studies show that under specific circumstances and in specific areas of the brain, NMDAR antagonists – including (high-dose) ketamine – have neuroprotective effects, while under other circumstances these same agents are neurotoxic [67,71,72]. Neuronal injury (vacuolization in neurons and apoptotic neurodegeneration) is caused by loss of inhibition of inhibitory pathways, leading to the enhancement of excitatory neuronal activity. Several drugs are able to prevent neuronal injury from NMDAR antagonists, including benzodiazepines and α_2-agonists [73]. Despite the observation in animals, ketamine is still widely used in humans, partly because no data in humans are available that cause concern about neurotoxicity ('no hint of a suggested association between ketamine and brain damage or learning delay, the presumed sequelae of neuroapoptosis, has been reported' [74]) and the fact that most infusions are combined with either a benzodiazepine or an α_2-agonist.

7. Summary and conclusions

Worldwide, the number of patients affected by chronic pain is growing and conventional treatment is often insufficient [1].

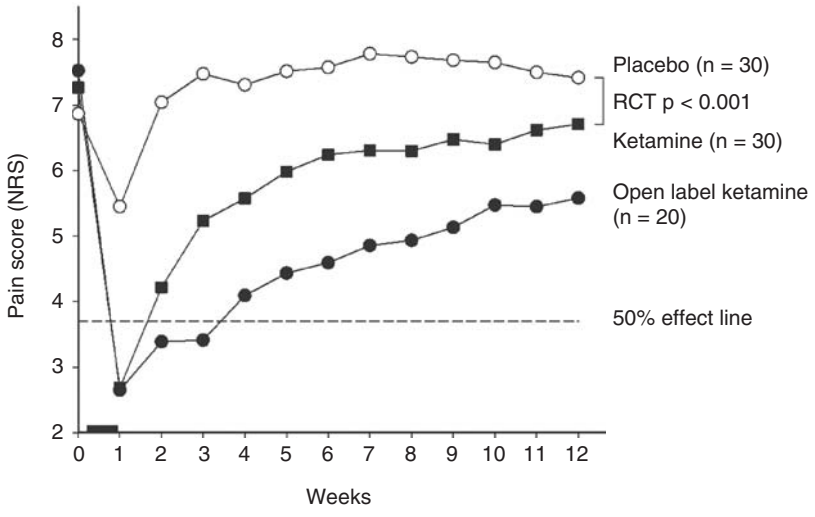

Figure 3. Results of trial on a 4.2-day continuous intravenous ketamine infusion in 60 patients with complex regional pain syndrome chronic pain [10]. The results of the randomized trial are given (squares: ketamine data, open circles: placebo data) showing a 12-week significant effect on pain intensity scores ($p < 0.001$). Twenty subjects initially receiving placebo returned to receive open-label ketamine (closed circles). The black bar indicates the infusion period.
Adapted from [10].
NRS: Numerical rating scale.

Recently, the importance of the NMDAR in the etiology and maintenance of chronic pain has been established. Of all available NMDAR antagonists, ketamine is the most potent and consequently has been applied in the treatment of various chronic pain syndromes. Most frequently studied is the intravenous route of administration, followed by topical, oral and intranasal routes.

The majority of RCTs on intravenous ketamine published since 1992 indicate that when applying short-term infusions (< 4 h), chronic pain is reduced by about 50% irrespective of the dose given; but the effect dissipates rapidly upon termination of the infusion. Three recent studies [10-12] (published in 2009 and 2010) on long-term (days to weeks) ketamine administration (mean infusion rate 20 mg/h) show that the duration of effect lasts multiple weeks, although a slow return to pretreatment pain scores is observed in all studies. In none of the studies has a full effect of ketamine on pain or any effect on function or quality of life been detected, possibly due to the fact that none of the studies was properly powered to study these latter end points. Evidently, further RCTs of good quality are required before any conclusion can be drawn on the efficacy of ketamine, specifically long-term ketamine infusions, on long-term pain relief in chronic pain patients.

In most RCTs, various side effects were noted. The most worrisome side effects for the patients are psychotropic in nature (ranging from 'drug high' to panic/fear and hallucinations); these may be prevented/treated by co-administration of benzodiazepines and/or α_2-adrenergic receptor agonists. Other side effects include nausea/vomiting, sedation and hypertension/tachycardia. The latter symptoms are related to ketamine's activation of the sympathetic system, and seem of minor importance at low infusion rates. Finally, there is concern for the possibility of neurotoxicity and potential for abuse through long-term or repetitive ketamine use. Although indications for these concerns were derived from animal studies at relatively high ketamine doses, these issues remain understudied in humans.

8. Expert opinion

Ketamine's use as an anesthetic and analgesic in the treatment of acute pain is driven by its pharmacokinetics (i.e., upon termination of infusion, anesthesia and analgesia dissipate rapidly) [12,14]. In contrast, long-term (days to weeks) continuous or repetitive infusion of low-dose ketamine results in pain relief persisting for weeks following treatment [9,24,58]. This suggests that ketamine has a disease-modulatory role and initiates a cascade of events, of which the first step is probably desensitization in instances where NMDAR sensitization is an important factor in the process of the development and chronification of pain. This effect of ketamine in the chronic pain process is exceptional and different from most other analgesic agents that do not have the ability to interfere with the process of central sensitization. Despite these promising results, ketamine is not (yet) viable as a routine treatment for chronic pain.

Several important issues have to be resolved. First, safety/toxicity studies in humans aimed at cognitive (e.g.,

memory deficits) and long-term effects of ketamine, as well as studies on ketamine's abuse liability, are needed. Second, administration modes allowing out-patient treatment need to be developed and tested. This will not only be less costly compared with multiple-day in-patient treatment, but will also allow the patient to be treated in their own surroundings. Finally, safe dosing schemes must be developed that ensure persistent relief of pain. When these issues have been resolved satisfactorily, ketamine may gain a prominent place in the treatment of chronic pain.

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Declaration of interest

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