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HOT TOPIC

The Use of Ketamine in Neuropathic Pain

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Abstract Hyperactivity of *N*-methyl-D-aspartate (NMDA) receptors may be one of the factors in the genesis of neuropathic pain (NP). Ketamine is a dissociative anesthetic and analgesic that is the most potent NMDA receptor antagonist currently available for human use. There is a growing body of literature for three decades suggesting efficacy of subanaesthetic doses of ketamine in the treatment of NP, particularly the pain in complex regional pain syndromes. The primary limitations of ketamine use are secondary to psychotomimetic and, to a lesser extent, sympathetic activation. The purpose of this article is to review the history, pharmacology, pharmacodynamics, clinical benefits, and limitations of ketamine for treatment of NP. Methods of administration and management of adverse effects are highlighted based on the clinical experience of the authors.

Keywords Ketamine · Neuropathic pain · NMDA receptors · Hyperalgesia · Allodynia · Central sensitization · Complex regional pain syndromes

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Introduction

Neuropathic pain (NP) is defined as a pain state arising from a lesion or disease of the somatosensory system [1]. Conditions associated with NP include infections, trauma, metabolic abnormalities, chemotherapy, surgery, irradiation, neurotoxins, inherited neurodegeneration, nerve compression, inflammation, autoimmune disease, and tumor infiltration [2]. While etiologically heterogeneous, NP syndromes share the primary characteristics of ongoing pain, dysesthesias, and hyperalgesia in the absence of an identifiable stimulus.

There are multiple mechanisms responsible for NP. These maladaptive responses in the nociceptive pathway drive persistently altered processing of both nociceptive and innocuous afferent inputs. Mechanisms underlying NP include altered gene expression, changes in gene regulation within the CNS, changes in ion channels that lead to ectopic activity, and synaptic facilitation of the neural axis producing central amplification [3]. The activation and upregulation of dorsal horn excitatory glutamatergic *N*-methyl-D-aspartate (NMDA) receptors is believed to play a central role in NP, allodynia, and hyperalgesia [4, 5].

First-line treatment options for NP have included tricyclic antidepressants, serotonin/norepinephrine reuptake inhibitors such as duloxetine and venlafaxine, and calcium channel $\alpha_2\delta$ agonists such as gabapentin and pregabalin [6]. Yet, NP syndromes have been characteristically resistant to these standard pharmacologic therapies and effective treatments remain a major clinical challenge.

In 1990, the first reports of subanesthetic uses of ketamine were described for cancer pain, with low doses showing efficacy for opioid-resistant pain in cancer patients [7]. Since then, there has been increasing clinical use of low-dose ketamine to provide analgesic effects in a

wide range of acute and chronic pain conditions [8•]. There is a growing body of literature from experimental animal models, human volunteer studies, and small clinical trials that have suggested the efficacy of subanesthetic doses of ketamine in the treatment of various neuropathic conditions [8•, 9••, 10, 11, 12••, 13]. However, the psychotomimetic actions of ketamine and its clinical risk–benefit ratio have precluded ketamine's use as a first-line treatment [14]. This selective review of ketamine use in NP is derived from English-language published papers, from 1966 to October 2013, identified through PubMed using the search terms 'ketamine' and 'NP' as well as the clinical experience of the authors. Due to space limitations, it does not provide a comprehensive review, but instead focuses on selected areas of importance. The purpose of this article is to review the history, pharmacology, pharmacodynamics, clinical benefits, and limitations of ketamine for NP.

History of Ketamine

Ketamine hydrochloride was first synthesized in 1962 by Parke-Davis scientists searching for the ideal anesthetic agent [15]. The scientists were experimenting with chemical derivatives of phencyclidine (PCP) to find a drug with the same anesthetic effect of PCP but with a shorter duration of action and less propensity for hallucinations, prolonged emergence delirium, and other unpleasant psychotic side effects [16]. Clinically approved for human use since 1970 [17], ketamine is well established as a reliable anesthetic agent for induction and maintenance of elective surgery, in emergency out-of hospital medicine, and as an aid in human anesthetic applications, especially trauma, burn, and pediatric patients [11, 18••, 19]. In anesthetic practice, high plasma and brain concentrations of ketamine result in dissociative anesthesia, amnesia, a raised arterial pressure, increased heart rate and cardiac output with relative preservation of airway reflexes and respiration [20].

While the initial interest in ketamine was its use as a sole anesthetic or induction agent, Sadove et al. [21] were the first to explore the analgesic properties of low-dose ketamine in 1971. Their double-blind clinical study in postoperative patients comparing change in pain threshold from low-dose ketamine to that produced by meperidine and placebo suggested the useful clinical application of ketamine in subdissociative low doses as an analgesic [21]. Soon after, the discovery of the NMDA receptor in 1987 [22] and its role in pain processing and spinal neural plasticity triggered renewed interest in ketamine as a potential anti-hyperalgesic agent.

Ketamine's Mechanism of Action

The mechanism of action of ketamine remained unknown until the early 1980s, when Lodge et al. [23] discovered that low intravenous doses of ketamine and PCP were able to selectively inhibit firing of spinal neurons evoked by NMDA, the prototypical agonist of the glutamate NMDA receptor [23–25]. Ketamine was later established to act as a noncompetitive NMDA antagonist blocking the receptor by binding to its PCP-specific site when the receptor channel is in the open activated state [25–27].

The role of ketamine specifically in NP treatment is based primarily on its potent antagonistic effect of the NMDA receptor, a well-known primary target for the treatment of NP [10]. Activation of NMDA receptors, especially those located within the dorsal horn of the spinal cord, are critically involved in nociceptive transmission, synaptic plasticity inflammation, and nerve injury-induced central sensitization, all of which play a crucial role in the pathogenesis of neuropathic chronic pain [4, 28]. Ketamine inhibits NMDA receptor-mediated responses in the spinal cord [24] and thalamus [29]. Ketamine has also been found to inhibit the 'wind-up' phenomenon, the frequency-dependent increase in the excitability of spinal cord neurons evoked by electrical stimulation of C-fiber primary afferent nerves [24, 28]. Ketamine equally binds the NMDA subtypes 2A to 2D; therefore, it is proposed to have a more favorable effect in such heterogenic disease as NP, as compared with NMDA receptor antagonists with more discriminative NMDA subtype selectivity [30].

Besides acting on the NMDA receptor, ketamine's analgesic effect in NP may include interactions with μ opioid receptors [31], monoamine transporters [32], toll-like receptor 3 (TLR-3) [33], microglial calcium-activated K+ channels [34], and dopamine receptors, as well as other cholinergic, purinergic and adenosine receptor systems [25, 35]. The ability of ketamine to block conductance of specific ion channels may be the reason it has local anesthetic properties after topical administration [36]. Ketamine's high affinity to D2 receptors is also suggested as the cause for typical psychotropic effects observed in humans [37].

Recent studies have also shown ketamine to induce rapid, potent, and prolonged antidepressant effects [38–43]. These growing studies are of particular interest in understanding the efficacy of ketamine in NP treatment given the integral component of mood in the affective component of pain. The biological mechanisms underlying ketamine's antidepressant activity are not fully understood but may involve inhibition of NMDA and upregulation in α-amino-3-hydroxy-5 methylisoxazole-4-propionic acid (AMPA) receptor expression [44], subsequent activation of the mammalian target of rapamycin (mTOR) intracellular

cascade [45], and stimulation of neuroplasticity marker brain-derived neurotrophic factor (BDNF) activity [46].

Pharmacology and Pharmocodynamics

Ketamine is a PCP derivative with a chiral center on the C-2 atom of the ketamine cyclohexane ring. It gives rise to two sterioisomers, S(+) and R(−) ketamine. Because of its greater affinity and selectivity for the PCP binding site of the NMDA-receptor, the S(+) enantiomer parenterally is about 4 times more potent an analgesic than the R-enantiomer [47, 48], and twice as potent as the racemic mixture [14, 49]. In equianalgesic doses, S(+) ketamine produces fewer psychic disturbances and less agitation than R(−) ketamine [50].

When used for pain management, ketamine is commonly administered intravenously. However, analgesia has also been delivered via subcutaneous, intramuscular, epidural, intrathecal, intraarticular, oral, topical, intranasal, and sublingual routes [51]. Ketamine rapidly passes the blood–brain barrier which allows for its rapid analgesic effect with a blood-effect site equilibration half-life of 1–10 min [52]. Ketamine peak plasma concentration is reached within 1 min, has a redistribution half-life of 7–15 min, and clearance of 15 mL/kg/min [53]. Traditionally, IV elimination half-life is reported as 2–3 h [52], although when used in long-term treatment of chronic pain, the analgesic onset/offset half-life of ketamine has been reported as high as 11 days when treated with continuous IV infusion [54].

Oral administration of ketamine undergoes extensive first-pass metabolism in the liver with bioavailability of oral ketamine ranging from 16 to 24 % depending on dosage used [11, 14, 51, 55]. Peak plasma concentrations after oral ingestion are achieved in ~30 min [14]. Ketamine is primarily metabolized by CYP3A4, CYP2B6, and CYP2C9 to form norketamine, its pharmacologically active metabolite, which is renally excreted [11]. The T1/2 of oral ketamine has been reported to be 5–6 h with elimination half-life of 2–3 h for ketamine and ~4 h for norketamine [11, 51]. Oral ketamine is associated with higher serum levels of norketamine as compared to IV and other routes of administration, and, in chronic use, norketamine is thought to be the primary analgesic agent [11, 14].

Evidence for the Use of Ketamine in Neuropathic Pain

Systematic Reviews on Use of Ketamine in Neuropathic Pain

The first published review on the effectiveness of ketamine in chronic pain management by Hocking and Cousins [12••] in 2003 found 11 controlled trials, 2 uncontrolled trials, 9 case reports and 2 case series from 1966 to 2002. The majority of conditions studied were in the NP category including central pain, phantom and ischemic limb pain, post-herpetic neuralgia, orofacial pain, complex regional pain syndrome (CRPS), and fibromyalgia. Based on the reviewed data, the authors report, "ketamine may be used most effectively to reduce the symptoms of allodynia, hyperalgesia, and hyperpathia rather than acting as a traditional analgesic" [12••]. Due to the limited number of randomized controlled trials, heterogeneity of data, and commonly reported psychotomimetic side effects, the review concludes that "the evidence for efficacy of ketamine for treatment of chronic pain is moderate to weak" [12••]. The authors do support a ketamine trial for patients with severe chronic pain that is incapacitating and refractory to other first- and second-line pharmacological therapies.

Six years later, Bell [56] published a topical review on ketamine use in chronic noncancer pain which included another 18 controlled trials investigating its efficacy in primarily chronic NP. The review concludes while ketamine can provide short-term relief of refractory NP in some patients, data supporting the efficacy and tolerability of ketamine in the long-term treatment of chronic pain is extremely limited [56]. The review cautions that ketamine can be a drug of addiction with neurotoxic effects, unpleasant adverse effects, and long-term safety issues which indicate the need for future carefully controlled clinical trials focusing on optimal dose, route of administration, and duration of treatment.

A year later, in 2009, Blonk and colleagues reviewed the literature on the efficacy of specifically oral ketamine use in chronic pain from 1950 to 2009 [11]. They found that, of the 22 studies acceptable for review, 16 were non-comparative observational studies or anecdotal reports. The review concludes that as there are a very limited number of high quality studies available for review and efficacy and long-term adverse effects are insufficiently studied, oral ketamine may have a limited role as add-on therapy in complex chronic pain patients with severe pain refractory to routine therapeutic options.

In 2012, a Cochrane review [57] assessed the effectiveness and adverse effects of ketamine in the treatment of refractory NP in cancer. The review found 32 case reports or open label uncontrolled studies describing improvement of opioid analgesia with ketamine; however, only 2 RCTs with a total of merely 30 patients met the reviewers' inclusion criteria. With insufficient data to enable any evidence-based conclusions or recommendations about the benefit and harm of adjuvant ketamine, the authors conclude that ketamine may be a treatment option in patients who appear to have a problem tolerating opioids or when

there are problems with opioid responsiveness. The review highlights the need in future ketamine research for larger, higher quality trials with clearly defined outcomes which are clinically useful, such as relief of NP, reduction of tolerance or reduction of opioid consumption, specific route of administration, which dose is effective, and what are the costs to the patient in terms of adverse events [57].

A summary of the randomized, double-blind controlled studies investigating ketamine use in NP from 1995 to 2013 is included in Table 1.

Literature on Ketamine Use in Central Neuropathic Pain

The efficacy of intravenous, subcutaneous, oral, and transdermal ketamine has been studied in neuropathic central pain primarily in spinal cord injury (SCI) and post-stroke patient populations. Fisher and Hagan [58] describe the sustained benefit of oral ketamine 25 mg three times daily in a patient with post-cauda equina NP. To date, there are three randomized, double-blind, placebo-controlled studies which have focused specifically on ketamine's efficacy in chronic NP of spinal origin [59–61]. All three studies demonstrated IV ketamine's efficacy over placebo in decreasing pain pre- and post-treatment, including the intensity of continuous pain [59–61] evoked pain [59], and allodynia [59] in post-traumatic SCI patients. Side effects were minimal in two [62] [61] of the three randomized controlled studies.

Regarding the duration of analgesia from ketamine in spine-mediated NP, Amr [61] studied 40 SCI patients with NP given either placebo, normal saline, or ketamine 80 mg IV. Patients underwent infusion 5 h daily for 1 week with significant pain improvement found in the ketamine group that lasted up to 2 weeks post-infusion. More recently, Kim et al. [63] found an even greater duration of pain relief in the first study of ketamine's efficacy during the acute phase of NP. Patients were followed for a mean 14.3 months and at the termination of ketamine treatment, VAS pain scores had decreased by 74.6 %. At the last clinic visit, ~96.8 % of patients experienced complete pain relief. The authors posit that ketamine treatment started before the establishment of central sensitization may be helpful in reducing pain in the chronic phase.

Although there are no published randomized, double-blind, placebo-controlled studies focused on ketamine use solely in post-stroke patients, Yamomoto et al. [64] found 11 out of 23 patients with central post-stroke pain achieved >40 % pain reduction temporarily after a total dose 25 mg of IV ketamine was administered over 25 min. Backonja et al. [65] found in 6 patients with both central and peripheral NP, the 2 stroke patients with central NP demonstrated a >50 % decrease in pain, allodynia and hyperalgesia for 2–3 h after single injection of ketamine 250 mcg/kg delivered over 5 min.

Administration of S(+) ketamine has twice the analgesic potency of racemic R(−) ketamine and in equianalgesic doses produces fewer psychic disturbances and less agiation than R(−) ketamine [50]. The efficacy of S(+) ketamine via iontophoresis-assisted transdermal delivery at 50 and 75 mg doses was studied in 33 patients with central NP secondary to stroke, spinal cord lesion, thalamus lesion, brainstem infarct, multiple sclerosis, and Parkinson's disease [50]. Although there was no improvement in pain after 1 week with either 50 or 75 mg S(+) ketamine doses, there were significant improvements in scores evaluating health status and quality of life after 1 week of 75 mg S(+) ketamine administration via without adverse effects.

Literature on Ketamine Use in Peripheral Neuropathic Pain

The efficacy of intravenous, subcutaneous, oral, topical, and intranasal ketamine has been studied in peripheral NP. There are at least 9 randomized, double-blind trials demonstrating the efficacy of ketamine in NP [66–75]. In patients with post-nerve injury NP, ketamine administered IV has shown significant reduction in pain and allodynia as compared to placebo [66–70, 73, 74] as well as compared to morphine [73]. Niesters et al. [73] report the duration of analgesia after IV ketamine infusion in peripheral NP was reported as >6 h in 2 out of 10 patients and >12 h in 8 out of 10 patients.

Intranasal use of the more potent enatiomer (S) ketamine at doses of 0.2 and 0.4 mg/kg was studied in 16 patients with NP and showed a significant reduction in NP that was dose-dependent, lasting 2–3 h with maximum pain reduction of 30–40 % at 50 min after application [72]. The two randomized, double-blind, placebo-controlled studies on topical administration of ketamine did not show efficacy in the treatment of peripheral NP with no effect from ketamine 1 % topical cream applied three times daily for 3 weeks in 92 patients with peripheral NP [76] or when ketamine 5 % topical cream was applied for 1 month in 17 patients with diabetic peripheral neuropathy [75].

Literature on Ketamine Use in Postherpetic Neuralgia

The use of IV ketamine as a single bolus of 0.15 mg/kg over 10 min showed significant reduction in pain including wind-up-like pain as compared to both placebo and morphine in 8 patients with postherpetic neuralgia (PHN) [62]. However, the topical administration of S-Ketamine 1 % applied either four times daily for 15 days [77] or R-ketamine 1 % applied three times daily for 3 weeks [76] did not demonstrate any benefit over placebo in patients with PHN.

Table 1 Summary of randomized, double-blind, controlled studies on ketamine use in NP from 1995 to 2013

Pain type category	Admin/duration	Study	Patients no. and type	Study design	Regimen intervention	Outcome	Withdrawals/side effects
Central pain: SCI	IV/17–22 min	Eide et al. [59]	9 SCI pts with central dysthesias for median 28 months	R, DB, PLC, CO	IV inf. of K 60 μg/kg bolus + inf. @ 6 μg/kg/min (median: 110 ng/mL) versus ALF 7 μg/kg bolus + inf. 0.6 μg/kg/min versus PL inf. of NS over 17–22 min. 2 h WOP then CO	Intensity of continuous pain and evoked pain ↓ in both K and ALF; K group: Allodynia ↓, wind-up pain ⇄, Heat pain threshold ⇄	K group: "bothersome dizziness" in 1 pt
Central pain: SCI	IV/40 min	Kvarnstrom et al. [60]	10 SCI pts with NP below level of injury	R, DB, PLC, CO	40 min IV inf. of K 0.4 mg/kg vs. L 2.5 mg/kg vs. PL(NS)	>50 % ↓ in VAS during inf. in 5/10 in K group vs. 1/10 in L group vs. 0/10 in PL group Neither K nor L changed temperature thresholds nor sensory function	K group: SE in 9/10 and total 39 SE registered with 3 most common of somnolence, dizziness, change in vision L group: SE in 5/10 with 13 SE, half with somnolence and perioral paresthesia (2) SEPL group: SE in 1/10 with somnolence (1) and dizziness (1)
Central pain: SCI	IV/35 h	Amr [61]	40 SCI pts with chronic NP	R, DB, PLC	Group I: K 80 mg IV inf. in 500 mL NS over 5 h/ days × 1 week + G 300 mg TID. Group II: PL NS inf. + 300 mg of G TID after 300 mg of G TID. All received V 2–5 mg prior to inf. to avoid hypertensive response and muscle pain	Both groups: pain ↓ pre and post-tx. Group 1 K: pain improved over Group II at all measurements during inf. 2 weeks after inf. termination No difference between groups at 3 and 4 weeks after inf. termination ($P = 0.54$ and $P = 0.25$)	Both groups tolerated drugs well w/no SE requiring intervention.K group: short-lasting delusions (3); 15 % ↑ in baseline HR during inf. (2); tired (2). G SE of dizziness occurred right after ingestion (2 pts, 1 in each group) Group 2: tiredness and lack of coordination
Central pain: post-stroke	IV/5 min	Backonja et al. [65]	6 pts total, 3 central pain pts (2 CVA +1 brachial plexus avulsion)	R, DB, PLC, CO after 4 h	Single injection of K 250 mcg/ kg IV slow push over 5 min vs. P(NS) with min 4 h WOP then CO.All pts premedicated (lorazepam/midazolam) prior to injections	2/2 CVA pts with >50 % ↓pain, allodynia and hyperalgesia for 2–3 h. 1 brachial plexus pt.: no relief from pain but ↓allodynia, hyperalgesia	SE in 5/6 pts; sedation 'funny in her head', transient increase in BP, HR, nystagmus
Central NP	Iontophoresis/ 1 week	Vranken et al. [50]	33 pts with central NP: stroke (24 %), MS (3 %), Parkinson's (3 %), thalamus lesion (9 %), brainstem infarct (12 %), spinal cord lesion (49 %)	R, DB, PLC	50–75 mg S(+)-K transdermal iontophoresis qd vs. PL × 1 week	After 1 week, 50 mg S(+)-K daily no effect After 1 week, 75 mg S(+)-K daily improved health status and QOL but no change in VAS pain.	Mild and spontaneous resolving SE. Only 1 SE of nausea with 75 mg S + K dose

Table 1 continued

Pain type category	Admin/duration	Study	Patients no. and type	Study design	Regimen intervention	Outcome	Withdrawals/side effects
Peripheral NP	IV/5 min	Backonja et al. [65]	6 pts total with NP: 3 central + 3 peripheral	R, DB, PLC CO after 4 h	Single injection of K 250 mcg/kg IV slow push over 5 min vs. P(NS) with min 4 h WOP then CO. All pts premedicated (lorazepam/midazolam) prior to injections	3/3 PNS pain pts >50 % ↓pain, allodynia and hyperalgesia for 2–3 h 2 pts with PNS-related NP showed K effective in dose-related fashion.	5/6 pts with SE; Sedation most common; 'spacey, wacky', nystagmus, diplopia. Bright colors, dream-like, nightmares 'felt weird'. Continuous. SC inf. of K in 1 pt.: intolerable cognitive and memory SE
Peripheral NP	IV/2 h	Max et al. [66]	8 pts with post-traumatic NP with widespread allodynia	R, DB, PLC, CO	K. IV 0.75 mg/kg/h vs. AL 1.5 μg/kg/min vs. PL for 2 h—doubled at 60 min and 90 min if no benefit or minimal SE—halved if SE.	K sig. ↓ pain and allodynia. AL sig. ↓ allodynia but not background pain	SE always preceded analgesia and persisted beyond return of pain after stopping inf.
Peripheral NP	IV/1 h	Felsby et al. [67]	10 pts with peripheral NP	R, DB, PLC	3 sessions with 24 h WOP. K 0.2 mg/kg vs. MgCl 0.16 mmol/kg vs. PL(NS) IV over 10 min then continuous inf. K 0.3 mg/kg, MgCl 0.16 mmol/kg or PL	K sig. ↓ pain (57 %) and ↓ allodynia (33 %) MgCl non-sig ↓ pain (29 %) and ↓ allodynia (18 %)	HR and BP within ±20 % of baseline 7/10 with psychotomimetic SE after K. Heat and pain at injection site from MgCL
Chronic NP	PO/6 weeks	Haines and Gaines [112]	21 pts with chronic NP (2 post-stroke, 7 back pain, 5 PHN, 1 post-traumatic, 1 myelopathy, 2 spinal cord surgery, 1 phantom pain, 1 MS, 1 burning feet)	*n-of-1* trial, DB, PLC, CO	K PO qd 20 mg dose ↑ by 10 mg qd until analgesic effect, adverse effects occurred, or until max100 mg (avg 45 mg) Pts responding to K PO then entered into *n of 1* randomized trial of 3 treatment/placebo 1 week pairs for total 6 weeks	12/21 did not progress to *n-of-1* trial due to no benefit and/or intolerable adverse effects. 9/21 entered *n* of *1* K vs. PL trial: 6 pts no diff between K and PL and consistent analgesia in 3/9 or overall 3/21 pts (14 %)	10/21 withdrew due to intolerable SE. 17/21 had SE: most common light headedness (4), dizziness (4), tiredness (4) headache (3) 'nervous, floating feeling' (3) bad dreams (1)
Peripheral NP	IV/20 min	Leung et al. [68]	12 pts with post-nerve injury allodynia and hyperalgesia (RSD 6; Causalgia, 1; PHN, 4; SCI, 1)	R, DB, PLC	20 min IV infusion of K vs. ALF vs. PL (diphenhydramine) given 1 WOP to target plasma levels of ALF at 25, 50 and 75 ng/mL and K at 50, 100 and 150 ng/mL	Dose-dependent ↑in cold and cold pain thresholds, and ↓ in stroking pain scores with ALF and K. Sig ↓ in hyperalgesia with K. Dose-dependent↓ in both spontaneous and von Frey pain scores with ALF.	3 most common SE: lightheadedness, sedation, dry mouth. No sig CNS side effects and changes noted.
Chronic NP	PO/1 week	Furuhashi-Yonaha et al. [113]	8 pts with chronic NP previously responsive to K IV	R, PLC	K oral syrup (0.5 mg/kg) or PL syrup given 6 h × 1 week	K ↓ VAS pain severity and allodynia after 15 min and improvement lasted 6–8 h. K plasma concentrations below levels of detection (0.05 μg/mL) in all pts despite good pain relief	2/8 with headache relieved by loxoprofen. 1/8 with nightmares reduced by diazepam and slight dizziness that required no treatment

Table 1 continued

Pain type category	Admin/duration	Study	Patients no. and type	Study design	Regimen intervention	Outcome	Withdrawals/side effects
Peripheral NP	IV/20 min	Jorum et al. [69]	12 pts (11 with posttraumatic neuralgia +1 PHN)	R, DB, PLC, CO	On 3 separate test sessions, WOP 2 h, each pt given ALF or K or PL (NS) K 60 mg/kg bolus then inf. 6 mg/kg/min for 20 min.	K and ALF↓ spontaneous pain, ↓ hyperalgesia to cold pain, but no change in threshold for cold pain detection.	K most common SE: feeling intoxicated (8), dizziness (7), fatigue (6)
Chronic peripheral NP	IV/40 min	Kvarnstrom et al. [70]	12 pts with chronic (avg 5.5 year) traumatic NP	R, PLC, CO	40 min IV infusion with K 2.5 mg/kg vs. L 1.0–1.5 mg/kg vs. PL (NS)	Mean ↓ in VAS 55 % K, 34 % L, 22 % PL. 50 % ↓in 7/12 in K, 4/12 L, 2/12 PL	K group: 12/12 somnolence, 10/12 paresthesias, 9/12 dizziness, 8/12 out-of-body sensation, 6/12 vision changes, 6/12 unpleasant experience, 5/12 hearing changes. No correlation between max drug concentration and # of SE
Chronic peripheral NP	Topical/3 weeks	Lynch et al. [76]	92 pts with peripheral NP (20 diabetic neuropathy + 14 PHN + 58 post-surgical/post-trauma)	R, DB, PLC Study	3-week study on efficacy of 4 topical creams 4 mL applied TID × 3 weeks (PL, 2 % Am, 1 % K, or 2 % Am–1 % K combined)	↓ in pain scores of 1.1–1.5 units in all groups from baseline week to final week but no sig difference between groups from PL. Blood concentrations revealed no significant systemic absorption.	SE in 30 % of entire 92 pts evenly distributed across treatments (Am, 26 %; K, 30 %; K–Am, 35 %; placebo, 27 %) Most common SE: minor and temporary skin irritation at site of application (4 on PL, 1 on K, 1 on Am). Sedation in 5 pts (3 on Am, 2 on combo cream)
Chronic NP	Intranasal/single dose	Huge et al. [72]	16 pts with NP	R, DB	16 pts split into 2 groups receiving intranasally (S)-ketamine 0.2 mg/kg (group 1); (S)-ketamine 0.4 mg/kg (group 2) as 2 × 5 sprays in each nostril. No placebo group in study.	Ongoing NP sig ↓ and dose-dependently ↓ for ~2–3 h with max pain reduction ~30 and 40 % at 60 min after (S)-K application. Time course of pain ↓ correlated with plasma concentrations of (S) norketamine and (S)-ketamine. ⇄ on thermal or mechanical detection and pain thresholds in normal or symptomatic skin areas.	Vertigo, sedation and subjective difficulties to concentrate most common.SE approximately doubled in higher dose group (weighted scores: 14 vs. 32; $P < 0.05$).

Table 1 continued

Pain type category	Admin/duration	Study	Patients no. and type	Study design	Regimen intervention	Outcome	Withdrawals/side effects
Peripheral NP	IV/1 h	Niesters et al. [73]	10 pts with NP	R, DB, PLC, CO	Each pt tested on 3 days with 2 weeks WOP between each session and received either 1 h IV infusion of PL(NS), M 0.05 mg/kg bolus + 0.015 mg/kg or S(+)Ketamine 0.57 mg/kg	Pain relief greatest after K followed by M and then PL. K duration of effects lasting >12 h in 8/10 subjects and >6 h in other 2 subjects M effects lasting >12 h in 0/10, >6 h in 8/10 and <6 h in other 2. After PL, all analgesic effects dissipated within 6 h	Minor SE in K infusion: nausea (4), emesis (2) vs. M infusion: nausea (7), emesis (4)
Nerve injury pain	IV/30 min	Gottrup et al. [74]	20 pts with nerve injury pain	R, DB, PLC, CO	On 4 different days, 30-min IV inf. of K (0.24 mg/kg), L (5 mg/kg), or saline given	K ↓ ongoing pain and evoked pain to brush and pinprick vs. L only ↓ evoked pain to repetitive pinprick stimuli. No correlation between pain-relieving L or K on ongoing or mechanically evoked pains	All SE graded mild-moderate and no serious SE. Most common SE in K group tiredness (5) paresthesias (4), dizziness (4). 16/19 (84 %) with SE in L group vs. 2/19 (11 %) in PL group. 16/19 (84 %) with SE from K vs. 3/19 (16 %) in PL group. 1 pt excluded due to hallucination and aggressive behavior.
Peripheral NP	Topical/ 1 month	Mahoney et al. [75]	17 pts with diabetic peripheral neuropathy	R, DB, PLC	Either 1 mL K 5 % topical or PL cream used for 1 month.	No tx main effect with pain ↓ over time in both groups	None reported
Post-herpetic neuralgia	IV/10 min	Eide et al. [62]	8 Pts with PHN at various sites	R, DB, CO, PLC	Single IV bolus K (0.15 mg/kg vs. M 0.075 mg/kg vs. PL over 10 min. 7 day WOP. No analgesics used in 48 h prior to test	Threshold for warm, cold, heat, pain or tactile sensation ⇄. K normalized abnormal heat pain in 4 pts. K but not M caused significant relief in pain. Wind-up like pain inhibited by K but aggravated by M	8/8 K pts had SE: dizziness (5), fatigue (4), unreality (3), altered vision (3) auditory acuity (1). 6/8 M and 1/8 PL had SE: none distressing
Post-herpetic neuralgia	Topical/15 days	Barros et al. [77]	12 pts with PHN	R, DB, PLC, CO	S-ketamine 1 % topical or PL topical ointment applied 4×/ days for 15 days then 7 day WOP and crossover	No diff in pain reduction between S–K and PL after 15 and 30 days marks	Mild allergic skin reaction (local pruritic erythematous plaques) with ointment in 2/12 but did not prevent continuation in study
Orofacial Pain	PO/ 2 days × 10	Eide and Stubhaug [78]	1 pt with glossopharyngeal neuralgia	N of 1, DB, PLC	K 60 mg PO given 6×/day – observed in open dose escalating trial. N of 1 trial: K PO or PL on 10 2-day periods	K sig. ↓pain including marked ↓ pain intensity with swallowing	SE: fatigue, dizziness, "well tolerated"

Table 1 continued

Pain type category	Admin/duration	Study	Patients no. and type	Study design	Regimen intervention	Outcome	Withdrawals/side effects
Orofacial Pain	IV/120 min	Baad-Hansen et al. [80]	20 pts: 10 with atypical odontalgia + 10 controls	R, DB, CO, PLC	30 min S-Ketamine vs. Fentanyl vs. PL	No effect of S-Ketamine on spontaneous AO pain or capsaicin-evoked pain	SE from S-Ketamine : dizziness 10/20 (6 AO pts, 4 controls), nausea (3 AO pts, 5 controls)
Trigeminal pain	IM and PO/ 3 days	Rabben et al. [114] and Rabben and Oye [79]	30 pts. (26 pts PO trial) with secondary trigeminal neuralgia	DB, PLC, CO	Pethidine 1 mg/kg or K 0.4 mg/kg with midazolam 0.05 mg/kg IM single dose	IM injections: 9/30 no relief from either drug; 8/30 prolonged analgesia from both drugs but ↑ relief with K; 9/30 transient relief with K but min. relief with pethidine.	Most common SE: dizziness, sedation, dry mouth. 6 K pts: sensory disturbances of blurred vision, altered hearing, general feeling of insobriety
							Psychotomimetic SE more marked after PO: only reported if unable to sleep w/in 30 min
					1 week after IM challenge, remaining 26 pts received K 4 mg/kg PO or PL for 3 nights then CO after 1 WOP	PO: 5/8 with prolonged analgesia from K IM had sig. analgesia. 0/9 with transient K IM effect with K PO analgesia and non-responders to K IM → no response to K PO	No reported hangover effect next day
Phantom limb pain	IV/45 min	Nikoljsen et al. [83]	11 pts with residual limb and phantom pain	R, DB, PLC, CO	K 0.1 mg/kg IV over 5 min then inf. 7 μg/kg/min for 45 min or PL. CO after 3 days WOP	↓ residual limb and phantom pain by ↓ VAS and MPQ scores. K sig. ↑pressure threshold and ↓hyperpathia	9/11 SE of insobriety or discomfort
Phantom limb pain	IV/1 h	Eichenberger et al. [84]	20 pts with phantom limb pain	R, DB, CO	K 0.4 mg/kg IV vs. Calcitonin IV vs. K + Calcitonin vs. PL IV	K but not Calcitonin ↓ phantom limb pain	K group: Sedation most common with 1 K infusion held 5 min because pt fell asleep
							Other K SE light/visual hallucination, hearing impairment, impaired position feeling. Combo tx: mild sedation (11), dizziness (9), nausea (4)
Ischemic limb pain	IV/5 min	Persson et al. [81]	8 pts with arteriosclerosis obliterans with rest pain in the lower extremity	R, DB, CO	5 min inf of K 0.15, 0.3, 0.45 mg/kg IV or M 10 mg IV on 4 study days with min 24 h WOP.	Dose-dependent analgesic effect of K with transient complete pain relief in 8/8 at highest dose of 0.45 mg/kg. 5/8 with complete relief with M; 3 with little or no relief to M had high baseline pain scores	Dose-dependent SE: mainly disturbed cognition and perception

Table 1 continued

Pain type category	Admin/duration	Study	Patients no. and type	Study design	Regimen intervention	Outcome	Withdrawals/side effects
Ischemic limb pain	IV	Mitchell and Fallon [82]	35 pts with allodynia, hyperalgesia, hyperpathia secondary to critical limb ischemia	R, DB, PLC	Opioids + K IV single infusion (0.6 mg/kg) vs. Opioids + PL	K ↓ pain 50 % immediately pre-infusion to 65 % 24 h post-infusion and 69 % 5 days post-infusion. K group showed sig. difference 24 h post-infusion of effect of pain on their general activity ($P = 0.03$) and on their enjoyment of life ($P = 0.004$)	All pts also received haloperidol 1.5 mg PO evening of infusion to decrease SE K group :−33 % (6) "feeling more emotional than usual 24 h after the infusion" vs. only 6 % ($n = 1$) PL group. No sig. diff between 2 groups in vivid dreams, hallucinations, or dissociation.
Fibromyalgia	IV/30 min	Sorensen et al. [87]	18 pts with fibromyalgia muscle pain	R, DB, CO, PLC	IV/30 min of K 0.3 mg/kg vs. M 0.3 mg/kg vs. lidocaine 5 mg/kg vs. PL NS	K ↓pain intensity during and after test period, decreased tenderness at tender points and increased endurance. Physical functioning ability score (FIQ) sig. improved after K inf.	SE? cannot find actual paper to download on Pubmed
Fibromyalgia	IV/30 min	Graven-Nielsen et al. [88]	29 pts with fibromyalgia; 15 fibromyalgia K responder pts	R, DB PLC	K 0.3 mg/kg IV or PL over 30 min on 2 days. Active drug >50 % ↓ pain intensity at rest on 2 occasions id'ed 17 K responders. 15 received DB inf. of K or PL on 2 sessions separated by 1 week WOP.	IV infusion identified 17 responders. 12 failed to respond initially. In K responders, K ↓ pain at rest, ↓ referred pain, ↓ temporal summation, ↓ muscular hyperalgesia	2 withdrew for unrelated reasons. SE not documented
Fibromyalgia	IV/30 min	Noppers et al. [85]	24 pts with fibromyalgia	R, DB, PLC	Received either 30-min IV infusion with S(+) ketamine 0.5 mg/kg or PL(V) 5 mg .	No. of pts >50 % reduction in VAS pain K(8) vs. V (3) ($P < 0.05$) at 15 min. correlating with K plasma conc. No sig difference between groups at 180 min, 1 or 8 weeks post-tx. No difference in ADLs	Sig. tx effect in S(+) K group vs. PLC for alterations in reality, surroundings, time, thoughts and feeling high, at t = 45 min ($P < 0.05$)

Table 1 continued

Pain type category	Admin/duration	Study	Patients no. and type	Study design	Regimen intervention	Outcome	Withdrawals/side effects
Cancer pain	SC/3–5 days	Hardy et al. [115]	185 pts with chronic refractory pain (nociceptive and neuropathic) due to cancer or its tx	R, DC, PLC	SC inf. of PL(NS) or K at 3 dose levels (100, 300, or 500 mg) in a 5-day schedule, starting at 1st dose level(100 mg/24 h Any psychotomimetic toxicity taxed with haloperidol or midazolam	No $\rightleftarrows$ in positive in PLC or K group. Pain type (nociceptive vs. neuropathic) not a predictor of response. No. of pts needed to tx for 1 additional pt to have positive outcome from K was 25 (95 % CI 6-infinity). No. needed to harm, because of toxicity-related withdrawal, was 6 (95 % CI 4–13)	2 × incidence of adverse evens worse than baseline in K group after day 1 and throughout study. 7 serious adverse events were reported, 2 of which (bradyarrhythmia and cardiac arrest occured in K pts). Most common SE: light-headedness (5), hypoxia (5), somnolence (9)
CRPS	Topical/30 min	Finch et al. [95]	20 pts (18 CRPS 1 + 2 CRPS II)	R, DB, PLC, CO	0.5 mL of K 10 % cream vs. PL cream applied to symptomatic and contralateral limb and forehead on 2 occasions separated by at least 1 week	No significant pain reduction overall 30 min after application. K significantly ↓ allodynia and punctate hyperalgesia in symptomatic limb without systematic effect detectable in blood	No adverse SE reported
CRPS	IV/ 4 h × 10 days	Schwartzman et al. [91]	19 pts with CRPS	R, DB, PLC	PL(NS) or K IV for 4 h daily × 10 days, max dose 0.35 mg/kg/h vs. clonidine given to both groups	27 % ↓ pain in K group vs. 2 % in PL group	6/19 pts with nausea, headache, dysphoria
CRPS	IV/4.2 days (100 h)	Sigtermans et al. [54]	60 pts with CRPS I	R, DB, PLC	60 pts admitted to short stay ward for 5 days given either K IV (5–30 mg/h) or NS for total 4.2 days (100 h) of continuous infusion with 3 month follow-up	↓ pain in K group after infusion up to 11 weeks even though plasma concentration of K and its metabolites ↓ rapidly after termination of infusion. $\rightleftarrows$ functional improvement	Nausea 63 % K vs. 17 % PL group vomiting 47 vs. 10 % in PL, psychotomimetic effects 93 vs. 17 % PL, headache 37 vs. 33 % PL. Liver function, blood pressure unaffected by K

↑Significantly increased, ↓significantly decreased, $\rightleftarrows$ no significant change, *ALF* alfentanil, *Am* amitriptyline, *BP* blood pressure, *Cl* clonidine, *CNS* central nervous system, *CO* crossover, *CR* case report, *CRPS* complex regional pain syndrome, *CS* case series, *d* days, *DB* double-blind, *FU* follow-up, *G* gabapentin, *GI* gastrointestinal, *HR* heart rate, *h* hours, *inf.* infusion, *IM* intramuscular, *IV* intravenous, *K* ketamine, *L* lidocaine, *Mg* magnesium, *M* morphine, *min* minutes, *NP* neuropathic pain, *NS* normal saline, *O* observational, *PHN* postherpetic neuralgia, *PL* placebo, *PLC* placebo controlled, *PNS* peripheral nervous system, *PO* oral, *pts* patients, *R* randomized, *SC* subcutaneous, *SE* side effects, *SCI* spinal cord injury, *tx* treatment, *U* unblind, *WOP* washout period, *V* versed (midazolam), *VAS* visual analogue scale, *vs.* versus

Literature on Ketamine Use in Orofacial Pain

Eide and Stubhaug [78]. reported significant pain reduction with swallowing as compared to placebo in a *n* of 1 study in which oral ketamine 60 mg was given six times daily in a patient with glossopharyngeal neuralgia. Rabben and Oye [79] evaluated both intramuscular and oral efficacy of ketamine in 30 patients with secondary trigeminal neuralgia in a double-blind, placebo-controlled crossover study and found of the 26 patients who proceeded to the oral trial of ketamine 4 mg/kg for 3 nights, 5 of the 8 patients with prolonged analgesia from IM ketamine demonstrated significant pain relief as compared to placebo. However, there was no significant benefit on spontaneous or capsaicin-evoked pain in a study of 10 patients with atypical odontalgia when S-ketamine was given IV over 120 min [80].

Literature on Ketamine Use in Ischemic Limb Pain and Phantom Limb Pain

Ketamine administered IV has shown efficacy in 2 randomized, double-blind studies in patients with ischemic limb pain [81, 82]. Persson et al. [81] found a dose-dependent analgesic effect with ketamine infusions at 0.15, 0.3, and 0.45 mg/kg IV with transient complete pain relief in all 8 patients at the highest dose of 0.45 mg/kg. Side effects were reported as dose-dependent and mainly experienced as disturbed cognition and perception. Mitchell and Fallon [82] also found that a single ketamine infusion-administered 0.5 mg/kg IV provided reduction in pain at 24 h and 5 days post-infusion over placebo in 35 patients with allodynia, hyperalgesia, and hyperpathia secondary to critical limb ischemia. There was also significant improvement 24 h post-infusion of the effect of pain on their general activity and enjoyment of life over the placebo group. Ketamine administered intravenously in doses ranging from 7 mcg/kg/min to 0.4 mg/kg for 45–60 min also showed efficacy in decreasing residual limb and phantom pain in two randomized, double-blind crossover studies [83, 84].

Literature on Ketamine Use in Fibromyalgia

Although there is ongoing debate whether fibromyalgia is neuropathic in origin [85], fibromyalgia pain has been associated with central sensitization and malfunctioning sensory processing within the central nervous system [86]. Three randomized, double-blind studies have been published on the use of ketamine in fibromyalgia pain [85, 87, 88]. Sorensen et al. [87] found that ketamine IV 0.3 mg/kg administered over 30 min resulted in a significant decrease in pain intensity during and after the test period, decreased tenderness at tender points, and increased endurance in 18 patients with fibromyalgia. Most notably, physical functioning ability scores improved significantly in the fibromyalgia patients after ketamine infusion. Graven-Nielsen et al. [88] studied the use of ketamine 0.3 mg/kg IV over 30 min versus placebo in 29 patients with fibromyalgia and found that of the 17 of 29 identified as ketamine responders, those patients experienced significant decrease in pain at rest, referred pain, temporal summation, and muscular hyperalgesia. Noppers et al. [85] studied the use of S(+)ketamine 0.5 mg/kg IV over 30 min and found >50 % reduction in pain relief in the ketamine group versus placebo group at 15 min but no improvements were found in activities of daily living scores at 180 min, 1 or 8 weeks post-treatment.

Literature on Ketamine Use in Complex Regional Pain Syndrome

The basic features of CRPS include pain disproportionate to the injury, allodynia and hyperalgesia, and autonomic abnormalities [9••]. One of the hallmarks of CRPS is that of central sensitization caused by a reduction in the firing threshold of Aδ and C fibers leading to the ongoing release of neurotransmitters and peptide neuromodulators from peripheral afferent terminals [89]. As the most potent clinically available NMDA receptor antagonist, ketamine is an ideal candidate in the treatment of CRPS because of its potential to reverse central sensitization, alter neural plasticity and reduce neuroinflammation [90].

A comprehensive systematic review of literature up to May 2011 evaluating the efficacy of ketamine in CRPS treatment by Azari et al. [9••] found three randomized, placebo-controlled trials, seven observational studies, and nine case reports/series. The authors conclude, "ketamine has both acute efficacy and long-term implications in the management of complex regional pain." A recent 5-year retrospective analysis by Patil and Anitescu [13] investigating the efficacy of outpatient ketamine infusions in patients with severe refractory pain of multiple etiologies also demonstrated significant reduction in VAS pain scores in patients with CRPS.

The Scwartzman et al. [91] randomized, placebo-controlled trial studied the efficacy of ketamine IV infusions at 25 mL/h for 4 h daily for 10 days versus placebo infusions in 19 CPRS patients. At 12 weeks post-treatment, significant decreases in pain in most affected area, burning pain, pain when touched or lightly touched or brushed lightly, overall pain level, as well as decreased nighttime awakening were found in the ketamine group. Although the study showed that ketamine infusions significantly reduced the affective component of pain by 50 % for 3 months, no changes in quality of life measures were found.

The Sigtermans et al. [54] randomized, double-blind, placebo-controlled, parallel-group trial in 60 CRPS patients found that after a 4.2 days/100 h continuous IV ketamine

infusion, pain scores were lower in the ketamine group over a 12-week period with the lowest pain scores seen 1 week after ketamine treatment completion. No functional improvement in the ketamine group was initially found despite pain relief; however, a follow-up secondary analysis [92] of time-dependent data between pain and motor function found pain intensity was significantly inversely related to motor function, irrespective of whether patients had received ketamine or placebo. The authors suggest that, because patients were unaware of possible effects of ketamine on motor function, motor function changes could be mediated by, or occur simultaneously with, changes in pain intensity [92].

Dahan et al. [93] also performed a randomized, placebo-controlled trial of 60 CRPS-1 patients allocated to receive either 100-h IV infusion of S(+) ketamine or placebo with drug infusion rate increased from 5 mg/h/70 kg to 20 mg/h based on the effect/side effect profile. The study also demonstrated IV ketamine's prolonged duration of pain relief with significant pain relief in the ketamine group with analgesia outlasting the treatment period by 50 days [93].

Correll et al. [94] demonstrated the potential benefit of follow-up repeat ketamine infusions in their retrospective study in which 12 of 33 CPRS patients who received a second treatment of intravenous ketamine infusion (doses from 10 to 50 mg/h for a mean of 4.7 days) achieved a longer duration of pain relief after the first treatment [94]: 54 % of 33 patients were pain-free at 3 months and 31 % remained pain-free at 6 months after a single ketamine infusion. Following a repeat ketamine infusion, 58 % of 12 patients had pain relief at 1 year and ~33 % remained pain- free for more than 3 years.

While the majority of ketamine use in CRPS research has studied intravenous administration, Finch et al. [95] studied the use of topical 10 % ketamine in patients with CRPS in a randomized, crossover, placebo-controlled study of 20 CPRS patients. There was no significant pain reduction in the topical ketamine group. However, a significant reduction in allodynia and hyperalgesia to punctate stimuli in the affected extremity was demonstrated, which the authors report is likely due to ketamine's effect at cutaneous NMDA receptors given systemic ketamine levels were not detectable.

Discussion

Route of Administration

Of the various routes of administration including subcutaneous, intravenous, intranasal, oral, and topical applications, studies with ketamine administered intravenously have provided the greatest treatment efficacy in NP. Topical administration of ketamine at any concentration has not shown any significant benefit in the reduction of neuropathic resting pain in lower concentrations of 1–5 %, although at concentrations of 10 %, it has demonstrated efficacy in the treatment of allodynia. Although the literature has demonstrated some efficacy for oral and intranasal applications in the treatment of NP, therapeutic use is highly limited by difficulties in controlling and monitoring its administration and possible adverse effects. It is our opinion that the potential risks of diversion, abuse as a recreational drug [89] as well as its reported potential to facilitate date-rape [96, 97], unfortunately far outweigh oral ketamine's potential therapeutic benefit in clinical practice.

Optimal Dose and Duration

There is no consensus in the literature regarding the optimal dose or duration of treatment of ketamine in NP. Ketamine doses have varied greatly among different studies with effective oral doses ranging from 45 to 1,000 mg, and duration of oral ketamine treatment has ranged from several months up to a maximum of more than 1 year [11]. Intravenous infusion dosages in the literature have ranged from 0.35 to a high of 7 mg/kg/h [98, 99]. The titration of ketamine infusions has also differed with some studies titrating in set intervals while others titrating to analgesia or feelings of inebriation [54]. Reported durations of intravenous ketamine infusions have also varied from minutes to hours to infusions up to 10 days [11, 91].

Adverse Effects and Complications of Therapy

Given that NMDA receptor-mediated transmission is involved in the processing of sensory information in the brain [48], it is expected that administration of antagonists at this receptor will lead to a number of side effects. Confusion, delirium, vivid dreams, hallucinations, and feelings of detachment from the body are associated with ketamine use and are particularly prominent on emergence from ketamine [19]. The most common major side effects in outpatient ketamine infusion protocols utilizing midazolam and clonidine report nausea, headache, tiredness, or dysphoria [54]. In studies such as Sigtermans et al. [54] which used infusion protocols without clonidine or midazolam premedication, there was a 93 % incidence of psychotomimetic effects with nausea noted in 63 %, vomiting in 47 %, and headache in 37 %.

Similar to PCP, ketamine has also been a drug of abuse, taken recreationally for its hallucinogenic and euphoric action [89]. Although ketamine has been safely used for over 35 years in clinical anesthesia, concerns have been raised regarding NMDA antagonist-induced neurotoxicity

[100]. Olney et al. [101, 102] have described these neurotoxic effects of ketamine and other NMDA antagonists in neurodegenerative changes seen in corticolimbic regions of adult rat brains; however, these neurotoxic effects have not been reported in humans [100]. Subanesthetic doses of ketamine have been associated with impaired attention, memory, and judgment, and ketamine has even been used as a pharmacological model for acute schizophrenia [14].

Although cardiac and neurologic toxicities have also been reported from the use of ketamine including tachycardia and intracranial hypertension [14], ketamine's deleterious effect on liver and urinary tract function has been noted most frequently. Kiefer et al. [98] reported evidence of liver dysfunction in 16 out of 20 patients receiving ketamine infusions with transient elevations in liver enzymes, creatine kinase, and CK-myocardiac band during treatment. All levels returned to reference ranges at 10–14 days after the infusion. Noppers et al. [103] also report 3 cases of drug-induced liver injury following repeated courses of S(+) ketamine treatment for CRPS 1 in 6 patients with elevated liver enzymes, all $\geq$3 times the upper limit of normal and modestly increased eosinophilic leukocytes. All 3 affected patients received 2 ketamine exposures within 4 weeks' time, while 3 patients receiving ketamine at a wider time interval of 12 weeks had no signs of liver injury. The authors suggest there may be an increased risk for ketamine-induced liver injury when infusions are prolonged or repeated within a short time frame.

The use of ketamine can cause urinary tract symptoms, including frequency, urgency, urge incontinence, dysuria, and hematuria [104, 105]. Urinary dysfunction was found in more than 25 % of recreational users of ketamine, with a dose and frequency response relationship established [106]. Although the causal agent has not been determined, direct irritation by ketamine and its metabolites is a possibility [14]. Investigations have revealed interstitial cystitis, detrusor overactivity, decreased bladder capacity, vesicoureteric reflux, hydronephrosis, papillary necrosis, and renal impairment [52, 104–108].

Clinical Experience

We believe in the significant benefits of ketamine intravenous infusions in the treatment and management of a specific subgroup patients with CRPS. We have had very limited success with non CRPS neuropathic pain. Collectively, we have performed over 700 ketamine infusions since 2006 in our clinical practice. It is our personal clinical experience that ketamine infusions have the greatest success in the treatment of NP with a sympathetic component responsive to pure sympathetic blockade. Of note, in patients with NP and concomitant clinical depression, we have observed a marked improvement in depression after ketamine infusions, which is in concordance with the robust expanding evidence of ketamine's rapid and potent antidepressant effects [38–43]. The effect on clinical depression has been noted before the effect on the pain. We find that ketamine infusions in NP treatment are particularly effective given the clustering of chronic pain with depression occurs at such a high prevalence, ranging from 30 to 60 % [109–111].

The key to achieving success with ketamine involves safeguarding from adverse events by premedicating patients appropriately, individualizing therapy, and strict monitoring of vital signs. Cardiorespiratory monitoring is an essential component of risk management. No single protocol has predicted success as some patients have found benefit with two or three infusions, whereas others have required 10 days of treatment. In our practice, we find it important to try to wean off opiates as much as possible prior to ketamine infusion because of the higher risk of opioids in combination with midazolam of developing respiratory depression. All patients must receive medical clearance prior to prolonged ketamine infusion treatments. Prior to administering ketamine IV infusion, we recommend premedicating patients with clonidine, ondansetron, and midazolam. We use clonidine for its neuroprotective effects from NMDA antagonists [102], and have also seen its benefit in controlling increased blood pressures and assistance in minimizing dissociative effects. We premedicate with ondansetron to help prevent the otherwise common adverse effect of nausea and emesis with high doses of ketamine. We use midazolam and titrate effect to achieve amnesia to keep patients peaceful before starting the ketamine infusions. In rare cases when patients are refractory to midazolam, we may use pre-infusion doses of oral diazepam. Occasional use of intramuscular anti-psychotic medication is necessary when patients are refractory to benzodiazepines.

In our clinical experience, for logistical issues, we perform a trial of 3 infusions in an outpatient surgical center prior to administering any prolonged daily treatment of ketamine infusions to assess for responsiveness, efficacy, and tolerability of side effects. In ketamine naïve patients, we administer between 100 and 200 mg during a 4-h intravenous infusion starting at low doses. We then schedule patients to receive ketamine infusions in the outpatient surgery center with IV infusions for up to 4 h daily for up to 10 days with duration dependent on response to treatment. Patients' vital signs are monitored continuously throughout the infusions. If the patient has tolerated previous treatments successfully, then consideration is given for increasing the infusion rate, though this may increase the number of side effects. Labetalol and intravenous fluids are rarely administered to maintain blood pressure at appropriate levels. The

highest dosing that has been used clinically has been titrated to by the authors is 1,800 mg/day in one patient who was tolerant to ketamine effect and side effects.

Of the adverse effects most commonly encountered, we have seen nausea and very rarely vomiting and have treated this effectively with ondansetron or, if severe, with granisetron intravenously and subsequently orally. Meclizine is beneficial post-infusion to assist with nystagmus and related nausea. We have seen a small percentage of patients who are prone to tension headaches prior to ketamine use re-experience headache during ketamine infusions that are responsive to ketorolac. All our patients are also treated with clonazepam 0.5 mg 1–2 tab orally nightly starting the first night of infusion to reduce the incidence of emergent phenomena. Only if necessary, olanzapine 25 mg qhs or other antipsychotics have been used if these symptoms are not responsive to benzodiazepines.

We have seen the majority of our patients benefit with >50 % pain relief after 10-day infusions treatment which lasts on average up to 3 months (some requiring no subsequent infusions) before patients may return for "booster infusions" which are typically 3 infusions. We have observed rapid resolution of flagrant edema post-infusion. In patients with movement disorders, we usually observe marked resolution of these symptoms prior to achieving pain relief. We have also seen more benefit when patients with CRPS who are treated earlier and typically require lower doses to titrate to effect.

Conclusions

Based on the review of current literature, we have found efficacy for ketamine infusions in a variety of NP etiologies. In our experience in treating NP with ketamine, we note a safe margin of tolerability evidenced by the low degree of severity for the documented side effects. A thorough review of our recording and management of side effects is in process. Identifying the patients who may benefit as ketamine responders is ongoing with clinical trials and research that suggest there are certain individuals and etiology subtypes whose NP may or may not respond to ketamine [5]. We find that CRPS patients with refractory pain have demonstrated the greatest benefit from ketamine via IV infusions. The literature suggests that prolonged or repetitive infusions may be required to ensure prolonged pain relief in chronic NP. We recognize that there are several limitations for ketamine intravenous use in NP. The recent reports of urologic and hepatotoxic effects from therapeutic use of ketamine dictate an extremely cautious and prudent approach to its use in the clinical practice of NP management. Yet, the studies on the efficacy of ketamine in treatment of refractory NP demonstrate there is clearly a definite population of patients with NP, for whom the benefits of ketamine intravenous infusion treatment considerably outweigh the risks and other available alternatives.

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Compliance with Ethics Guidelines

Conflict of Interest S. L. O'Brien declares no conflicts of interest. S. Pangarkar declares no conflicts of interest. J. Prager declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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