Intravenous Ketamine Infusions for Neuropathic Pain Management: A Promising Therapy in Need of Optimization

Dermot P Maher, MD, MS, Lucy Chen, MD, and Jianren Mao, MD, PhD

Intravenous ketamine infusions have been used extensively to treat often-intractable neuropathic pain conditions. Because there are many widely divergent ketamine infusion protocols described in the literature, the variation in these protocols presents a challenge for direct comparison of one protocol with another and in discerning an optimal protocol. Careful examination of the published literature suggests that ketamine infusions can be useful to treat neuropathic pain and that certain characteristics of ketamine infusions may be associated with better clinical outcomes. Increased duration of relief from neuropathic pain is associated with (1) higher total infused doses of ketamine; (2) prolonged infusion durations, although the rate of infusion does not appear to be a factor; and (3) coadministration of adjunct medications such as midazolam and/or clonidine that mitigate some of the unpleasant psychomimetic side effects. However, there are few studies designed to optimize ketamine infusion protocols by defining what an effective infusion protocol entails with regard to a respective neuropathic pain condition. Therefore, despite common clinical practice, the current state of the literature leaves the use of ketamine infusions without meaningful guidance from high-quality comparative evidence. The objectives of this topical review are to (1) analyze the available clinical evidence related to ketamine infusion protocols and (2) call for clinical studies to identify optimal ketamine infusion protocols tailored for individual neuropathic pain conditions. The Oxford Center for Evidence-Based Medicine classification for levels of evidence was used to stratify the grades of clinical recommendation for each infusion variable studied. (Anesth Analg 2017;124:661–74)

Ketamine was first synthesized in the 1960s as a safer dissociative analgesic and amnestic alternative to phencyclidine.[1] Initial evidence for the treatment of neuropathic pain with ketamine was derived from clinical case reports on the management of nerve injury in the setting of oncologic disease.[2] Moving forward, ketamine infusions have been studied in the treatment of complex regional pain syndrome (CRPS),[3–7] spinal cord injury,[8–10] phantom limb pain,[11] postherpetic neuralgia,[12,13] fibromyalgia,[14–16] and oncologically mediated neuropathic pain.[17–19] Additional prospective studies also suggest a role for ketamine infusion therapy in the treatment of trigeminal neuropathic pain, acute and chronic migraines, and temporomandibular pain.[20–23] Moreover, several retrospective studies further contribute meaningful data regarding the clinical use of ketamine infusions.[24–27]

As a noncompetitive antagonist of the *N*-methyl-D-aspartic acid receptor, ketamine produces profound modulatory effects on ascending nociceptive transmission.[28,29] As is the case with many neuropathic pain agents, transient antagonism at the receptor level may not fully explain the mechanism of neuropathic pain alleviation observed with ketamine therapy as the relief seems to significantly outlast the plasma half-life in many reports. Ketamine also modulates descending inhibitory pathways through activation of areas involved in regulation of pain, including the anterior cingulate cortex, orbital frontal cortex, insula, and brainstem in healthy volunteers receiving low-dose ketamine infusions.[30]

Ketamine binds noncompetitively to or otherwise influences multiple receptors and ion channels, mainly *N*-methyl-D-aspartic acid receptor antagonism, but also pharmacologic effects on α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors, kainite receptors, and γ-aminobutyric acid receptors, L-type calcium channels, μ-opioid receptors, and muscarinic and monoaminergic receptors.[31,32] The analgesic effects of ketamine may also be derived from inhibition of inducible nitric oxide synthase.[32] Ketamine has documented efficacy at subanesthetic doses (<1 mg/kg or alternately defined as doses that will cause minimal acceptable levels of sedation) for the amelioration of postoperative pain, decreasing postoperative opioid analgesic requirements and decreasing nausea and vomiting while adding only a mild side effect profile.[33] After single bolus administration, its redistribution half-life is 7 to 15 minutes and elimination is 2 to 3 hours.[34] Ketamine also has rapid passage through the blood-brain barrier with blood-effect site equilibration in 1 to 10 minutes.[35,36] After a 100-hour duration administration of *S*-ketamine at 20 to 30 mg/h in CRPS-1 patients, the analgesic half-life was 11 days.[3,34] Ketamine is metabolized by CYP3A4, CYP2B6, and CPY2C9 to norketamine via *N*-demethylation.[34] The plasma concentration of norketamine may exceed ketamine after prolonged infusions, possibly contributing to the analgesic profile.[1,3,35]

Despite the extensive utilization in various clinical arenas, there is no consensus on an optimal intravenous (IV) ketamine

From the Division of Pain Medicine, Massachusetts General Hospital, Harvard School of Medicine, Boston, Massachusetts.

Accepted for publication October 31, 2016.

Funding: This work is partially supported by NIH R01 grant DA036564.

Conflicts of Interest: See Disclosures at the end of the article.

Address correspondence to Dermot P Maher, MD, MS, Division of Pain Medicine, Massachusetts General Hospital, Center for Pain Medicine, Suite 340, 15 Parkman St, Boston, MA 02114. Address e-mail to dpmaher@mgh.harvard.edu.

DOI: 10.1213/ANE.0000000000001787

infusion protocol for the treatment of neuropathic pain conditions.[37] At this point, the numerous described ketamine infusion protocols and their indications prohibit a meta-analysis. Therefore, the objectives of this topical review are to (1) examine which common components of ketamine infusion protocols are associated with prolonged duration of relief, minimal side effects, and increased pain relief for the treatment of neuropathic pain and (2) call for clinical studies to identify optimal ketamine infusion protocols tailored for individual neuropathic pain conditions. Many studies failed to report changes in functional status, and this metric could not be appropriately incorporated in our analysis. The purpose of this study is not to either make or stratify the strength of recommendations for the use of ketamine infusions, because the existing literature does not allow for such analysis.

METHODS

An electronic literature search was conducted using the National Library of Medicine's MEDLINE database, PubMed, and Google Scholar to identify relevant peer-reviewed articles discussing the use of IV ketamine infusions for the treatment of neurologic pain. The detailed search strategy included the following subject headings: "ketamine infusion" and "neuropathic pain." Our search included doses of ketamine infusions in both the subanesthetic and the sedative range, but excluded studies for the use of ketamine in the perioperative phase of care. Search was limited to human subjects, English language, and articles with available full text. The references of articles found in the initial search were then iteratively searched for additional relevant citations. Both prospective and large retrospective studies were included in final analysis. This review excluded case reports and small retrospective studies (<5 subjects). The search yielded a total of 26 articles, including 16 prospective randomized placebo-controlled trials,[3,4,8–11,13–17,19–23] 4 prospective, observational nonrandomized studies providing,[5–7,18,38] 4 retrospective studies,[24–27] and 1 prospective randomized non–placebo-controlled study.[12]

The majority of the evidence for the treatment of neuropathic pain with ketamine infusions comes from case reports or case series. Although case reports and small cohort analyses are scientifically intriguing and medically encouraging, we excluded case reports and smaller retrospective cohort analyses of fewer than 5 patients from this review to focus on higher-quality evidence, with an emphasis on the reported infusion protocol, duration, and degree of measured benefits and side effects. In addition, we excluded studies addressing the utilization of ketamine for perioperative pain because of the lack of clarity with regard to the nature of postoperative pain. A PRISMA flow diagram (Figure) details the search strategy for this review.

The level of evidence for the treatment of neuropathic pain conditions with ketamine infusions was stratified based on the Oxford University Center for Evidence-Based Medicine (CEBM) criteria, which are presented in Table 1.[39]

RESULTS

Ketamine Infusion Protocols

As summarized in Table 2, the majority of ketamine infusion protocols included in this review demonstrated a decrease in self-reported pain. Direct comparisons of protocols with regard to the degree of pain relief may be inaccurate because of the various outcome metrics and pain scales reported. In addition, the different time points at which pain was measured further confound interpretation. Studies used heterogeneous inclusion and exclusion criteria. As numerous protocols with significant variation have been described, no definitive recommendations or even gradation of the strengths of recommendations are provided in this review.[40] However, certain infusion parameters are suggested to have a more profound effect particularly on the duration of clinical effects. If a purified isomer of ketamine, such as *S*(+)-ketamine, was used in a study, it was indicated in Table 2. Two studies used *S*(+)-ketamine.[3,16] All other studies apparently used a racemic mixture.

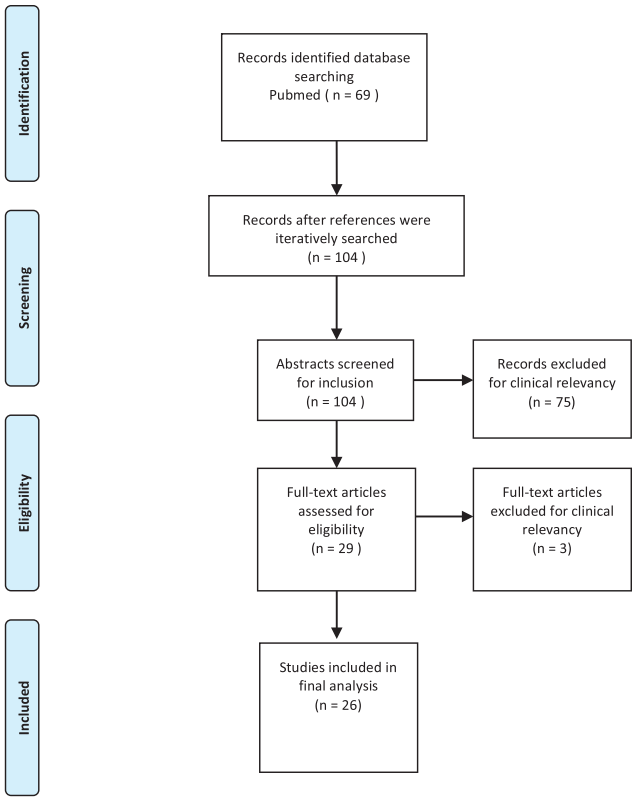

Figure. PRISMA flow diagram.

Duration of Infusion

1. Studies utilizing infusions lasting 1 hour or less reported a decrease in visual analog scale (VAS) or 11-point numerical rating scale only for 3 hours or less.[15–17] An exception is a retrospective study indicating that, after an infusion of less than 1 hour, most patients, including a large percentage diagnosed with CRPS, reported an average of 1 to 2 days of relief in the total study cohort and over one-third of subjects reported relief lasting more than 3 weeks.[27] Although several studies utilizing infusions of 1 hour or less did not report the exact times at which pain and symptom outcomes were measured, it was presumably measured near the completion of the infusion.[9,13,14,22,23]

Table 1. Oxford University Center for Evidence-Based Medicine (CEBM) Levels of Evidence

	Level 1	Level 2	Level 3	Level 4	Level 5
Treatment benefits	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Nonrandomized controlled cohort/ follow-up study	Case series, case-control studies, or historically controlled studies	Mechanism-based reasoning
Treatment harms	Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Nonrandomized controlled cohort/ follow-up study	Case series, case-control, or historically controlled studies	Mechanism-based reasoning

Source: http://www.cebm.net/ocebm-levels-of-evidence/.

2. A study of 3 consecutive infusions lasting 1 hour administered in sequence every other day demonstrated a decrease in VAS compared with placebo that persisted for 2 weeks.[12] A protocol utilizing ketamine infused over 1 hour only demonstrated a sustained decrease in VAS at 48 hours if the ketamine infusion was combined with a calcitonin infusion.[11]
3. One study only gave a single 2-hour infusion and reported an equivalent decrease in VAS compared with alfentanil administered over the same time period.[21] An infusion protocol of 5 hours' duration reported decreased pain scores at 2 weeks but not at 3 and 4 weeks.[10] Another protocol utilizing ketamine infusions over 4 hours given for 10 days resulted in reduced burning pain at 4 weeks, decreased hyperesthesia at 8 weeks, and decreased responses to components of the McGill Pain Questionnaire (MPQ) at 12 weeks.[4] This study's outcomes seem to suggest that the duration of pain relief of individual protocols could be dependent on the measured outcome variable with some, such as the MPQ, more susceptible to pronounced improvements with ketamine therapy.
4. Finally, studies involving the use of 4- to 5-day infusion protocols in subanesthetic inpatient or intentionally sedating patients in intensive care unit (ICU) settings demonstrate pain relief lasting from 6 weeks to 6 months.[3,5–7,18] Two retrospective studies did not report the duration of pain relief after a multiday infusion.[24,25] In general, however, patients experienced side effects at the same rate regardless of the duration of the ketamine infusion.

Total Infusion Dose

Differences in reported measurements of pain make it challenging to compare pain relief achieved by different doses of ketamine over a similar period. Furthermore, it is not possible to attribute the duration of pain relief mostly to either the duration of infusion or the dose based on weight of infused ketamine.

1. In several studies, a total infused dose of ketamine ranging from 324 to 6800 mg administered over several days normalized to a 70-kg patient resulted in reductions in reported pain lasting between 4 weeks and 6 months, depending on the measurement tool used to evaluate pain reduction.[3–7] The range of ketamine doses was administered in both the inpatient and the outpatient setting. In contrast, 2 studies with infusions at this dose did not report the duration with regard to pain relief.[24,25] It should be noted that to achieve some of the noted anesthetic doses of ketamine, patients were often placed in inpatient and ICU settings. However, one of these studies was able to achieve a cumulative dose of 1000 mg normalized to a 70-kg patient of ketamine infused at a subanesthetic rate over 10 days in the outpatient setting resulting in decreased burning pain for 4 weeks and decreased MPQ for 12 weeks.[4] Presumably, this would also result in a decrease in the cost of the infusion protocol by sparing use of ICU or inpatient resources. It should be noted that high-dose infusions have only been studied in CRPS patients.
2. One study comparing an infused ketamine dose of either 17.5 or 35 mg normalized to a 70-kg patient given over 30 minutes in patients with oncologically induced pain resulted in a decrease in pain lasting 3 hours.[17] A larger total dose of ketamine was reported to decrease pain to a greater extent. This is one of the few studies directly comparing different amounts of ketamine and demonstrates that increased doses will result in more profound, but not more lasting, pain relief when administered over the same period. In another study, 80 mg IV ketamine for the treatment of traumatic spinal cord injury resulted in 2 weeks of relief, which was not detectable at 3 or 4 weeks.[10] Smaller total doses of infused ketamine did not result in continued pain relief beyond the immediate postinfusion period.[15,21,22]
3. Of significance to note is that, in the previously discussed studies, unpleasant psychomimetic side effects occurred at approximately the same rate regardless of the infused dose. This observation might be confounded by the use of coadministered medications, such as midazolam, in the cases with higher-dose ketamine infusions. Nonetheless, unpleasant psychomimetic side effects were described even at low total doses of ketamine in the above studies.[17,21,22]

Infusion Rate

The majority of described protocols use an infusion rate between 0.1 and 0.5 mg/kg/h.[3,4,7,9–17,19,38] Three protocols describe the use of infusion rates of greater than 0.1 mg/kg/h, 2 of which required admission to an ICU setting for supportive care and monitoring, and 1 that was conducted as an outpatient also with appropriate monitoring.[5,6,27]

Table 2. Summary of Reported Ketamine Infusion Protocols

Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
Sigtermans et al[3]	CRPS-1	60	PRCT parallel	100 h continuously	IP	22.2 mg/h normalized to a 70-kg patient. 0.43 mg/kg/h maximum. S(+)-ketamine used.	None	Decreased NRS-11 compared with placebo until 11 wk.	No difference in:	1. Ketamine increased the incidence of nausea, vomiting, psychomimetic effects.
									1. RASQ and WAQ. 2. AROM. 3. Threshold for touch. 4. Skin temperature. 5. Volumetric measurement of limb.	2. No difference in headaches.
Schwartzman et al[4]	CRPS	19	PRCT parallel	4 h for 10 nonconsecutive days	OP	100 mg over 4 h. 0.35 mg/kg/h maximum.	0.1 mg PO clonidine and 4 mg IV midazolam at the start of each daily infusion	1. Decrease in sensory and affective components of the MPQ at 12 wk.	No difference in 2 quality of life questionnaires.	1. Four ketamine patients and 2 placebo patients experienced side effects, including nausea, headache, and tiredness.
								2. Reduction in hyperesthesia at 8 wk.		2. No patient reported hallucinations or dysphoria.
								3. Reduction in burning pain and pain in the most affect limb at 4 wk.		
Koffler et al[5]	CRPS-1	9	PONRT	4.5 d continuously in an inpatient ICU setting	IP	3–7 mg/kg/h target serum level of 250–300 μg/dL resulting in medically induced coma.	Supportive ICU care	1. Decrease in acute pain measured by MPQ at 6 wk.	1. All patients successfully weaned from opioid therapy at 6 wk.	Weakness, dizziness, fatigue, hyperhidrosis, sensation of warmth, and slight anxiety reported at 2 wk. No side effects reported at 6 wk.
								2. Decrease in overall pain measured by PRI at 6 wk.	2. No change in attention measured by CCPT. 3. No change in learning or memory measured by HVLT.	

(*Continued*)

Table 2. Continued

Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
									3. No change in depression or anxiety measured by BDI.	
Kiefer et al[6]	CRPS-1	20	PONRT	5 d continuously in an inpatient ICU setting.	IP	Bolus of 1–1.5 mg/kg, then 3 mg/kg/h and increased to 7 mg/kg/h.	1. Bolus of 2.5–7.5 mg midazolam, followed by infusion at 0.15–0.4 mg/kg/h. 2. Clonidine 0.2–0.85 μg/kg/h. 3. Supportive ICU care.	1. Pain relief at 1 wk, 1 mo, 3 mo, and 6 mo. 2. Recrudescence of CRPS symptoms in 6/20 patients at 6 mo and at lower intensities.	Improved quality of life measured by WHYMPI.	None.
Goldberg et al[7]	CRPS-1	16	PONRT	5 d continuously in an inpatient setting.	IP	10 mg/h increased to a maximum rate of 40 mg/h.	1. Midazolam 2–4 mg Q4h PRN. 2. Clonidine 0.1 mg/d transdermal. 3. Inpatient supportive care.	1. Pain relief starting at 3 d. 2. Sixty percent of patients reported pain relief lasting for 4 mo. 3. Forty percent of patients reported pain relief lasting for 6 mo. 4. Inpatient supportive care.	None.	None.
Correll et al[26]	CRPS-1 and 2	31 CRPS-1 and 2 CPRS-2	RS	Continued for as long as patient-tolerated infusion. Ten patients received a second infusion and 2 received a third infusion.	IP	10 mg/h. Increased as tolerated. Average maximum tolerated infusion rate 23.4 mg/h.	None.	1. After first infusion, average duration of relief 9.44 mo. 2. After second infusion, average duration of pain relief 25 mo.	None.	1. Sensation of inebriation was used as the end point for titration and universally noted. 2. No patient experienced sedation. 3. Six patients experienced hallucinations.

(*Continued*)

Table 2. Continued

Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
										4. Four patients experienced elevated transaminases.
Eide et al[8]	Traumatic spinal cord injury	9	PRCT crossover	17–21 min	IP	60 μg/kg bolus infusion of 6 μg/kg.	None.	Decreased continuous VAS pain intensity and allodynia. compared with placebo immediately after infusion.	1. No change in heat pain threshold.	Five patients reported side effects with modest dizziness being most common.
									2. No change in wind up-like pain.	
Kvarnström et al[9]	Traumatic spinal cord injury	10	PRCT crossover	40 min	Not reported	0.4 mg/kg of ketamine.	None.	Five of 10 had a 50% reduction in VAS immediately.	Quantitative sensory testing, vibratory testing, thermal threshold testing were equivalent between the placebo and the ketamine group.	Nine of 10 patients reported adverse side effects after ketamine infusions with somnolence, dizziness, and changes in vision being the most common.
Amr[10]	Traumatic spinal cord injury	40	PRCT crossover active placebo	5 h	IP	80 mg ketamine.	1. 2–5 mg IV midazolam.	1. Reduction of pain immediately after and 2 wk after infusion.	None.	None.
							2. 300 mg gabapentin.	2. No difference in pain at 3 and 4 wk after infusion.		
Eichenberger et al[11]	Phantom limb pain	10	PRCT Crossover	1 h	OP	0.4 mg/kg ketamine.	One arm of study combined ketamine infusion with a 200 IU calcitonin infusion over 1 h.	1. Six of 10 patients reported a 50% reduction in VAS.	Study not powered to detect changes in pain threshold or pain tolerance.	1. Five patients experienced visual hallucinations, hearing impairments.
								2. Only combination of calcitonin and ketamine produced 50% reduction in VAS at 48 h.		2. Three patients experienced sedation during the ketamine infusion.
Kim et al[12]	PHN	30	PRNCT 15 ketamine 15 $MgSO_4$	1 h every other day for 3 d	IP	0.1 mg/kg ketamine or 30 mg/kg of $MgSO_4$.	0.1 mg/kg midazolam to render patients unconscious.	1. Decreased mean VAS at 2 wk for both ketamine and $MgSO_4$ from baseline but no group difference.	1. Ketamine group had improved allodynia and electrical pain.	The most common complications reported in both infusion groups included somnolence and dizziness.

(*Continued*)

Table 2. Continued

Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
							2. Inpatient supportive care.	2. No difference in DN4 scale at 2 wk.	2. Painful cold and tingling sense improved in $MgSO_4$ group.	
Eide et al[13]	PHN	8	PRCT crossover	10 min	IP	0.15 mg/kg ketamine.	None.	1. Reduced pain immediately after infusion. 2. Reduced experimentally induced allodynia and wind up-like pain. 3. Normalization of abnormal thermal pain sensations.	1. No changes in thresholds for cold, warm, heat pain, or tactile sensations.	All patients experienced some degree of nonspecified unpleasant side effects.
Graven-Nielsen et al (Part 1)[14]	Fibromyalgia	29	PRCT crossover	30 min	OP	0.3 mg/kg ketamine.	None.	1. Seventeen patients reported at least a 50% reduction in VAS. 2. Seven patients did not report a 50% reduction in VAS. 3. Five patients reported at least a 50% reduction in VAS in response to saline placebo.	None.	None.
Graven-Nielsen et al (Part 2)[14]	Fibromyalgia	15	PRCT crossover	30 min	OP	0.3 mg/kg ketamine.	None.	1. No change in VAS duration.	1. Reduced IM saline induced VAS pain area and peak. 2. Reduced local pain area and referred pain area. 3. Attenuation of temporal summation after cutaneous and muscular electrical stimulation. 4. No change in electrical pain threshold.	None.
Sörensen et al[15]	Fibromyalgia	11	PRCT crossover	10 min	Not reported	0.3 mg/kg ketamine.	None.	1. Reduced VAS at 20 and 80 min after infusion.	1. Increased pressure pain threshold at 20 and 80 min.	None.

(*Continued*)

Table 2. Continued

Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
									2. Increased pain tolerance at tender points, control points, and muscle endurance at 20 and 80 min.	
Noppers et al[16]	Fibromyalgia	24	PRCT parallel active placebo	30 min	OP	0.5 mg/kg of S(+)-ketamine or 5 mg IV midazolam.	None.	1. Both groups reduced NRS-11 pain at 90 and 180 min. 2. No reduction in pain was observed at 8 wk in either group measured by FIQ.	None.	No difference in psychedelic effects measured by Bowdle questionnaire.
Mercadante et al[17]	Cancer-induced neuropathy	8	PRCT parallel	30 min	OP	0.25 mg/kg of ketamine or 0.5 mg/kg ketamine.	None.	1. All patients reported decreased pain after both doses at 3 h. 2. Larger dose was associated with larger decrease in pain at 3 h. 3. One patient continued to report decreased pain at 12 h.	None.	1. Four patients reported visual hallucinations after the 0.5-mg/kg infusion and 1 after the 0.25-mg/kg infusion. 2. No changes in MMSE.
Jackson et al[18]	Cancer pain	29	PONRT	3–5 d	IP	100 mg/24 h for day 1, 300 mg/24 for day 2, and 500 mg/24 h thereafter.	All patients were taking concurrent opioids.	1. Five of 29 initial responders had pain within 24 h of cessation of infusion. 2. Maximum duration of relief was 8 wk.	None.	12 patients reported psychomimetic effects with increased incidence at higher doses.
Salas et al[19]	Cancer pain refractory to opioids	20	PRCT	48 h	IP	0.5 mg/kg for 24 h, increased to 1 mg/kg if NPIS >1.	All patients received 1 mg/kg MSO_4 if opioid naive. Equivalent opioid dose if not naive.	1. NPIS equivalent between the 2 groups at 2 h, 24 h, and 48 h postinfusion.	1. No differences in MSO_4 utilization were noted. 2. No differences in patient satisfaction were noted. 3. No difference in ESAS.	No difference in ESS.

(*Continued*)

Table 2. Continued

Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
Tawfic et al[24]	Sickle cell crisis	9	RS	2–5 d	IP	0.25 mg/kg ketamine bolus. 0.2–0.25 mg/kg/h.	1 mg midazolam bolus followed by 0.5–1 mg/h. 2. Supportive ICU care.	1. Improved pain scores compared with baseline on first day.	1. Lower MSO_4 requirement compared with baseline. 2. Patients reported durable improved sleep.	1. One patient had psychomimetic effects. 2. Five patients had pre-existing nausea, which continued during the study period.
Kang et al[38]	Mixed neuropathic pain diagnoses	103	PONRT	2 h for 3 sessions every other day	IP	0.2 mg/kg bolus 0.5 mg/kg ketamine.	0.1 mg/kg midazolam loading dose followed by 0.025 mg/kg midazolam.	Decreased VAS compared with baseline 2 wk after treatment.	None.	50% of patients reported adverse events either during or after infusions, including snoring, muscle movement, decreased HR, decreased BP, and increased BP. No patient reported dysphoria.
Leung et al[20]	Mixed neuropathic pain diagnoses	12	PRCT parallel	20 min	OP	Target plasma level of 50, 100, and 150 ng/mL.	Compared with alfentanil with a target plasma concentration of 25, 50, 75 ng/mL or a diphenhydramine placebo control.	1. Concentration-dependent reduction in stroking pain immediately after the infusion.	1. Both ketamine and alfentanil decreased the stroking-evoked and cold allodynia areas. 2. Only ketamine decreased the Von Frey-evoked allodynia area.	1. A third of patients receiving ketamine developed lightheadedness. 2. Three subjects developed mild sedation.
Max et al[21]	Mixed neuropathic pain diagnoses	8	PRCT parallel	2 h	OP	0.75 mg/kg/h, doubled at 60 and 90 min if no analgesic benefit.	One study arm combined with alfentanil at of 1.5 μg/kg/mL.	1. Equivalent decrease in pain after the infusion. 2. Equivalent decreased allodynia after infusion.	Side effects occurred before the onset of pain relief.	Three patients experienced dissociative reactions. Two patients each experienced muteness, nausea, and dizziness.
Felsby et al[22]	Mixed neuropathic pain diagnoses	10	PRCT, crossover	Up to 1 h	OP	0.84 μg/kg over 10 min; 1.3 μg/kg/h infusion.	None.	1. VAS and reduced area of allodynia were related after infusion.	1. Ketamine reduced VAS scores.	1. No significant hemodynamic changes.

(*Continued*)

Table 2. Continued

Reference	Clinical Indication	Study Size	Study Design	Duration of Infusion	Study Setting	Dose Range	Combination Therapy	Duration of Pain Relief	Secondary Outcomes	Side Effects
									2. Ketamine reduced area of allodynia.	2. Psychomimetic effects were common after ketamine infusions.
Jørum et al[23]	Mixed neuropathic pain diagnoses	10	PRCT, crossover, active control	25 min	OP	60 μg/kg over 5 min, 6 μg/kg/h infusion.	None.	Decreased VAS for spontaneous pain immediately after infusion.	1. Reduced hyperalgesia to cold pain without alteration in cold pain threshold. 2. Decreased radiation from the site of cold pain. 3. Attenuation of mechanoallodynia.	1. Dizziness was more common in patients who received ketamine. 2. Other side effects were similar in frequency when compared with alfentanil.
Patil and Anitescu[27]	18 CRPS, 8 chronic headache and 7 LBP, 16 mixed neuropathic pain diagnoses	49 patients 369 infusions	RS	CRPS average 43.5 min every 30.8 d. Non-CRPS average 34.7 min every 34 d	OP	Average CRPS dose 1.0 mg/kg. Average non-CRPS dose 0.9 mg/kg.	None.	27% report relief lasting several hours, 73% report relief lasting more than 1–2 d, 38% report relief lasting more than 3 wk.	1. CRPS average VAS change was 7.7. 2. Non-CRPS average VAS change was 6.	1. Minimal side effects reported in all patients. 2. Hypertension and sedation were the most common side effects. 3. Higher incidence of hallucination and confusion in patients without CRPS.
Polomano et al[25]	Neuropathic pain after combat limb injury	19	RS	3 d	IP	120 μg/kg/h ketamine.	None.	1. Reduced PPI over the study period. 2. Improved GPR over the study period.	1. No change in opioid use during infusion.	1. Four patients reported feeling drowsy on days 1 and 2. 2. One patient reported hallucinations. 3. One patient reported nausea.

Abbreviations: AROM, active range of motion; BDI, Beck Depression Inventory; BP, blood pressure; CCPT, Connor's Continuous Performance Test; CRPS, complex regional pain syndrome; DN4, Douleur Neuropathique 4 Score; ESAS, Edmonton Symptom Assessment Scale; ESS, Epworth Sleep Scale; FIQ, Fibromyalgia Impact Questionnaire; GPR, Global Pain Relief; HP, habitual pain; HVLT, Hopkins Verbal Learning Test; HR, heart rate; ICU, intensive care unit; IU, international units; IM, intramuscular; IP, inpatient; $MgSO_4$, magnesium sulfate; MSO_4, morphine sulfate; MMSE, Mini-Mental Status Examination; MPQ, Short-form McGill Pain Questionnaire; NRS-11, 11-point numerical rating scale; NPIS, Numeric Pain Intensity Scale; OP, outpatient; PHN, postherpetic neuralgia; PO, oral; PONRT, prospective observational nonrandomized trial; PPI, present pain intensity; PPT, pressure point pain measured at the infraspinatus; PRCT, prospective; randomized control trial; PRI, Pain Rating Index; Prn, pro re nata; PRNCT, prospective randomized noncontrolled trial; RASQ, Radboud Skills Questionnaire; RS, repeated stimulation; WAQ, Walking Ability Questionnaire; WHYMPI, West Haven-Yale multidimensional pain inventory; VAS, visual analog scale.

When described, the reason for choosing a certain rate is attributed to the authors' clinical experiences or a desire to avoid unpleasant side effects. The high infusion rates in ICU settings did result in increased duration of pain relief. However, similar durations of pain relief were reported with comparably lower infusion rates given for a prolonged period of time in an inpatient and outpatient setting.[3,4] The percentage of patients experiencing unpleasant side effects is reported to be comparable between different infusion rates.

Combination Drug Protocols

Several studies have examined the use of coadministered medications for either reduction of side effects or improvement of analgesia. Several of the reviewed studies gave adjuvant medications as a standing component of a ketamine infusion protocol.[4,6,10–12,18,19,24,38]

1. One protocol gave midazolam on "*pro re nata*" (PRN) basis.[7] Other studies describe ICU or inpatient supportive care without significant elaboration with regard to the use of adjunct medications.[5,6] Several protocols used coadministration of midazolam as preinfusion IV boluses of 2 to 7.5 mg, 2 to 4 mg IV PRN doses, or simultaneous infusions at rates of 0.1 to 0.4 mg/kg/h.[4,6,7,10,12] Combination protocols resulted in decreases in reported pain ranging from 2 weeks to 6 months of duration. Larger cumulative doses of midazolam were used to provide sedation in an effort to keep patients comfortable during an infusion, and the dose did not seem to correlate with the duration of pain relief. One study used 5 mg IV midazolam as an active placebo and demonstrated decreased pain at 1½ and 3 hours but no decreases in pain at 8 weeks, which was equivalent in both groups.[16] The authors suggest that midazolam's muscle relaxation properties may have contributed to the equivalence between the 2 groups. The muscle-relaxing effects of midazolam may have also contributed to the observed duration of pain reduction in the previously referenced protocols. The use of midazolam is associated with a decrease in hallucinations and dysphoria. However, ketamine-infused patients who additionally received midazolam did not have a reduction in the incidence of headaches, nausea, somnolence, and dizziness. It is not possible to clearly attribute the observed effects to ketamine, midazolam, or a combination.
2. Three protocols utilized 0.1 mg oral clonidine, 0.1 mg/d clonidine patch, or 0.2 to 0.85 μg/kg/h infused clonidine to decrease side effects when coadministered with ketamine and midazolam.[4,6,7] One of these studies reported nausea, headaches, and tiredness in 4 of 9 ketamine-infused patients in the outpatient setting.[4] Another protocol coadministered ketamine with 200 IU calcitonin, and only the combination protocol resulted in decreased pain at 48 hours.[11] Several studies coadministered opioids as study treatment group or as part of standard continued patient therapy.[18–21] Comparisons of short infusions of ketamine with short-acting opioids, such as alfentanil, resulted in equivalent and relatively short-lived duration of pain relief.[20,21] Finally, in one study 300 mg oral gabapentin was combined with 2 to 5 mg of midazolam and 80 mg ketamine, which resulted in decreased pain both immediately after and 2 weeks after the infusion.[10]

Results for Specific Pain Conditions

Complex Regional Pain Syndrome

Six studies focused exclusively on the use of ketamine infusions for the treatment of CRPS.[3–7,26] In addition, a majority of patients analyzed in a retrospective study were diagnosed with CRPS.[27] The majority of these articles report pain relief of several weeks after an infusion in an inpatient setting over 4 to 5 days. However, outpatient infusion protocols requiring multiple serial infusions also reported pain relief lasting several months in some cases.[26,27] Although the general trend when all studies are considered is that longer durations provide increased duration of pain relief, there may be an optimal infusion duration of several hours beyond which no benefit is derived but the potential for side effects increases. The effective treatment of management of CRPS pain did not seem to be related to the actual dose of ketamine or the rate of infusion, with subanesthetic doses in the outpatient setting providing comparable duration of pain relief compared with higher-dose infusion protocols designed to be performed in ICU settings. The cost and required resource allocation for inpatient and ICU care are presumably greater than for outpatient management.

Fibromyalgia

Three studies focused on the use of ketamine infusions for the treatment of fibromyalgia.[14–16] All 3 studies utilized a relatively low dose of ketamine between 0.3 and 0.5 mg/kg administered over 10 to 30 minutes. No study reported benefits beyond the first few hours after the infusion. It is not certain whether this is because of a lack of responsiveness of fibromyalgia pain to ketamine infusions or whether a higher dose is required to produce longer lasting analgesia. The changes in pain scores after the infusion in 2 studies are encouraging and suggest that further optimization of dose and duration may provide some degree of relief.

Traumatic Spinal Cord Injury

The studies focused on the utilization of ketamine infusions to treat pain after traumatic spinal cord injury.[8–10] Two of the studies utilized a relatively low dose of ketamine between 6 μg/kg and 0.4 mg/kg over 17 to 40 minutes.[8,9] One protocol utilized approximately 0.2 mg/kg (based on 70 kg) over 5 hours for a total dose of 80 mg a ketamine.[10] In keeping with the general trend, shorter infusion times and lower total doses of ketamine provided relief only in the immediate postinfusion phase, whereas higher doses provided relief that lasted 2 weeks.

Several other pain pathologies have been studied in well-conducted studies. However, the small number of available studies for discreet pain diagnoses does not allow for meaningful comparison.

DISCUSSION

Because of the diversity of infusion protocols and the lack of direct protocol comparisons, conducting a formal meta-analysis is not possible at this time. Definite recommendations cannot be made based on available literature.

However, several relationships do emerge from inspection of the available data. These trends may provide guidance for clinicians initiating ketamine infusion therapy in their practice and to guide future optimization research.

1. CEBM level 2 evidence for treatment suggests that longer-duration infusions of ketamine provide longer lasting pain relief for patients with chronic neuropathic pain. Although admitting patients to ICUs may be prohibitively expensive, multihour outpatient treatments over the course of several days may provide more longer-lasting benefit than single- or short-duration infusions. This may also be a more logistically and financially feasible situation.
2. Although the rate of infusion does not appear to be related to either the duration or the degree of pain relief offered by different ketamine infusion protocols, increases in the total dose of ketamine administered result in a higher degree of pain relief and possibly greater duration of pain relief. The later observation could possibly be attributed to either the extended duration of infusions or the higher delivered doses of ketamine. This is also CEBM level 2 evidence for treatment with ketamine infusions. However, a lack of comparative effectiveness studies and different primary end points does not allow for direct comparison and optimization of protocols.
3. There is level 2 evidence for treatment that patients subject to almost all infusion protocols experience side effects regardless of infusion rate, infusion duration, or total ketamine infused. The use of coadministered medications, such as midazolam, reduces the incidences of side effects and may also provide additional analgesic benefit. Other serious side effects may still occur and should be monitored.

On the basis of the available evidence, a successful ketamine infusion protocol for the treatment of chronic neuropathic pain would include several components: (1) applying the longest possible infusion duration that is logistically feasible using multiple outpatient clinic visits if necessary; (2) using a dose of ketamine between 0.1 and 0.5 mg/kg/h to avoid excessive sedation in the majority of patients; and (3) utilizing adjunct medications such as midazolam to decrease the incidence of psychomimetic side effects and possibly improve the degree of pain relief. All infusions should be done in a monitored setting with standard American Society of Anesthesiology monitors under physician supervision. Although a dose of ketamine between 0.1 and 0.5 mg/kg/h does not eliminate the need for monitoring of the risk of sedation, safe and effective use of this range has been reported in the monitored outpatient, non-ICU setting. Potential adverse outcomes, such as excessive sedation, dysphoria, and cardiovascular complications, should be monitored during and after the infusion.

Caveats of Current Ketamine Infusion Protocols

There are several important caveats regarding the protocols used in prospective studies for discrete chronic neuropathic pain conditions.

1. Although many of the published protocols for ketamine infusions are prospective, placebo-controlled, observational studies, or retrospective studies, there is a lack of comparative effectiveness trials analyzing different infusion protocols. In addition, there is overlap between inpatient and outpatient ketamine infusion protocols with regard to overall dosing and duration of treatment. Although several of the protocols compared a single ketamine infusion protocol with another therapy,[9,11–13,15,16,20,21] only 1 study directly compared 2 different doses of ketamine.[17] To our knowledge, no studies have compared the impact of different infusion durations, infusion frequency, and use of different adjunct medications on pain relief. There have also been sparse studies that compared ketamine infusions with other forms of neuropathic pain treatment modalities, such as spinal cord stimulators or transcranial electrical stimulation.
2. Although empirical experience is an important aspect of clinical practice, the lack of clarification of ketamine infusion protocols in the literature calls for comparative effectiveness trials to optimize the degree and duration of pain relief by using a practical and cost-effective protocol. Without such comparative trials, it is difficult to assess the failure or success of a particular protocol with regard to a particular infusion variable, such as ketamine dose or infusion duration.
3. It is yet to be established whether different protocols are best suited for different neuropathic pain diagnoses or different levels of severity. For example, will a patient with traumatic spinal cord injury for 25 years find therapeutic benefit with the same ketamine infusion protocol as a patient with fibromyalgia for 3 years?
4. Currently, the mitigation of unpleasant psychomimetic side effects is potentially achieved by coadministration of medications, such as midazolam or clonidine. Other nonpsychomimetic side effects may be intrinsic to the use of ketamine infusions and require further investigation, particularly in cases that utilize high doses and long duration of ketamine infusions. In this regard, hepatotoxicity has been reported after ketamine infusions.[41]

SUMMARY AND FUTURE DIRECTIONS

Given a relative paucity of evidence in the current literature to guide ketamine infusion therapy for the treatment of various neuropathic pain conditions, such as CRPS, postherpetic neuralgia, traumatic spinal cord injury, and phantom limb pain, further well-conducted prospective comparative effectiveness studies are needed to analyze different ketamine infusion protocols in discreet neuropathic pain states. The goal of this study is to identify factors associated with better outcomes for the treatment of neuropathic pain with ketamine infusion therapy and to underscore the need for optimization through further clinical trials.

DISCLOSURES

Name: Dermot P Maher, MD, MS.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Conflicts of Interest: Dermot P Maher reported no conflicts of interest.

Name: Lucy Chen, MD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Conflicts of Interest: Lucy Chen reported no conflicts of interest.
Name: Jianren Mao, MD, PhD.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Conflicts of Interest: Jianren Mao reported no conflicts of interest.
His work is funded by NIH R01 grant DA036564.
This manuscript was handled by: Honorio T. Benzon, MD.

REFERENCES

1. Domino EF. Taming the ketamine tiger. 1965. *Anesthesiology*. 2010;113:678–684.
2. Kronenberg RH. Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. *J Pain Palliat Care Pharmacother.* 2002;16:27–35.
3. Sigtermans MJ, van Hilten JJ, Bauer MC, et al. Ketamine produces effective and long-term pain relief in patients with Complex Regional Pain Syndrome Type 1. *Pain.* 2009;145:304–311.
4. Schwartzman RJ, Alexander GM, Grothusen JR, et al. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain.* 2009;147:107–115.
5. Koffler SP, Hampstead BM, Irani F, et al. The neurocognitive effects of 5 day anesthetic ketamine for the treatment of refractory complex regional pain syndrome. *Arch Clin Neuropsychol.* 2007;22:719–729.
6. Kiefer RT, Rohr P, Ploppa A, et al. Efficacy of ketamine in anesthetic dosage for the treatment of refractory complex regional pain syndrome: an open-label phase II study. *Pain Med*. 2008;9:1173–1201.
7. Goldberg ME, Torjman MC, Schwartzman RJ, et al. Pharmacodynamic profiles of ketamine ®- and (S)- with 5-day inpatient infusion for the treatment of complex regional pain syndrome. *Pain Physician.* 2010;13:379–387.
8. Eide PK, Stubhaug A, Stenehjem AE. Central dysesthesia pain after traumatic spinal cord injury is dependent on N-methyl-D-aspartate receptor activation. *Neurosurgery.* 1995;37:1080–1087.
9. Kvarnström A, Karlsten R, Quiding H, et al. The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury. *Acta Anaesthesiol Scand*. 2004;48:498–506.
10. Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: a prospective, randomized, double blind trial. *Pain Physician.* 2010;13:245–249.
11. Eichenberger U, Neff F, Sveticic G, et al. Chronic phantom limb pain: the effects of calcitonin, ketamine, and their combination on pain and sensory thresholds. *Anesth Analg.* 2008;106:1265–1273.
12. Kim YH, Lee PB, Oh TK. Is magnesium sulfate effective for pain in chronic postherpetic neuralgia patients comparing with ketamine infusion therapy? *J Clin Anesth.* 2015;27:296–300.
13. Eide PK, Jørum E, Stubhaug A, et al. Relief of post-herpetic neuralgia with the N-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain.* 1994;58:347–354.
14. Graven-Nielsen T, Aspegren Kendall S, Henriksson KG, et al. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. *Pain*. 2000;85:483–491.
15. Sörensen J, Bengtsson A, Bäckman E, et al. Pain analysis in patients with fibromyalgia. Effects of intravenous morphine, lidocaine, and ketamine. *Scand J Rheumatol*. 1995;24:360–365.
16. Noppers I, Niesters M, Swartjes M, et al. Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial. *Eur J Pain*. 2011;15:942–949.
17. Mercadante S, Arcuri E, Tirelli W, et al. Analgesic effect of intravenous ketamine in cancer patients on morphine therapy: a randomized, controlled, double-blind, crossover, double-dose study. *J Pain Symptom Manage*. 2000;20:246–252.
18. Jackson K, Ashby M, Martin P, et al. "Burst" ketamine for refractory cancer pain: an open-label audit of 39 patients. *J Pain Symptom Manage*. 2001;22:834–842.
19. Salas S, Frasca M, Planchet-Barraud B, et al. Ketamine analgesic effect by continuous intravenous infusion in refractory cancer pain: considerations about the clinical research in palliative care. *J Palliat Med*. 2012;15:287–293.
20. Leung A, Wallace MS, Ridgeway B, et al. Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. *Pain*. 2001;91:177–187.
21. Max MB, Byas-Smith MG, Gracely RH, et al. Intravenous infusion of the NMDA antagonist, ketamine, in chronic posttraumatic pain with allodynia: a double-blind comparison to alfentanil and placebo. *Clin Neuropharmacol*. 1995;18:360–368.
22. Felsby S, Nielsen J, Arendt-Nielsen L, et al. NMDA receptor blockade in chronic neuropathic pain: a comparison of ketamine and magnesium chloride. *Pain*. 1996;64:283–291.
23. Jørum E, Warncke T, Stubhaug A. Cold allodynia and hyperalgesia in neuropathic pain: the effect of N-methyl-D-aspartate (NMDA) receptor antagonist ketamine—a double-blind, cross-over comparison with alfentanil and placebo. *Pain.* 2003;101:229–235.
24. Tawfic QA, Faris AS, Kausalya R. The role of a low-dose ketamine-midazolam regimen in the management of severe painful crisis in patients with sickle cell disease. *J Pain Symptom Manage*. 2014;47:334–340.
25. Polomano RC, Buckenmaier CC III, Kwon KH, et al. Effects of low-dose IV ketamine on peripheral and central pain from major limb injuries sustained in combat. *Pain Med.* 2013;14:1088–1100.
26. Correll GE, Maleki J, Gracely EJ, et al. Subanesthetic ketamine infusion therapy: a retrospective analysis of a novel therapeutic approach to complex regional pain syndrome. *Pain Med.* 2004;5:263–275.
27. Patil S, Anitescu M. Efficacy of outpatient ketamine infusions in refractory chronic pain syndromes: a 5-year retrospective analysis. *Pain Med*. 2012;13:263–269.
28. Schwartzman RJ, Grothusen J, Kiefer TR, et al. Neuropathic central pain: epidemiology, etiology, and treatment options. *Arch Neurol*. 2001;58:1547–1550.
29. Zhou QQ, Imbe H, Zou S, et al. Selective upregulation of the flip-flop splice variants of AMPA receptor subunits in the rat spinal cord after hindpaw inflammation. *Brain Res Mol Brain Res*. 2001;88:186–193.
30. Niesters M, Khalili-Mahani N, Martini C, et al. Effect of subanesthetic ketamine on intrinsic functional brain connectivity: a placebo-controlled functional magnetic resonance imaging study in healthy male volunteers. *Anesthesiology*. 2012;117:868–877.
31. Hocking G, Cousins MJ. Ketamine in chronic pain management: an evidence-based review. *Anesth Analg*. 2003;97:1730–1739.
32. Himmelseher S, Durieux ME. Ketamine for perioperative pain management. *Anesthesiology*. 2005;102:211–220.
33. Bell RF, Dahl JB, Moore RA, et al. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review (Cochrane review). *Acta Anaesthesiol Scand.* 2005;49:1405–1428.
34. Dahan A, Olofsen E, Sigtermans M, et al. Population pharmacokinetic-pharmacodynamic modeling of ketamine-induced pain relief of chronic pain. *Eur J Pain*. 2011;15:258–267.
35. Sigtermans M, Dahan A, Mooren R, et al. S(+)-ketamine effect on experimental pain and cardiac output: a population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers. *Anesthesiology*. 2009;111:892–903.
36. Herd DW, Anderson BJ, Keene NA, et al. Investigating the pharmacodynamics of ketamine in children. *Paediatr Anaesth.* 2008;18:36–42.
37. Niesters M, Martini C, Dahan A. Ketamine for chronic pain: risks and benefits. *Br J Clin Pharmacol*. 2014;77:357–367.
38. Kang JG, Lee CJ, Kim TH, et al. Analgesic effects of ketamine infusion therapy in Korean patients with neuropathic pain: a 2-week, open-label, uncontrolled study. *Curr Ther Res Clin Exp*. 2010;71:93–104.
39. Oxford Centre for Evidence-Based Medicine–Levels of Evidence. March 2009. http://www.cebm.net/ocebm-levels-of-evidence/. Oxford University Center for Evidence Based Medicine.

40. Eagle KA, Berger PB, Calkins H, et al; American College of Cardiology; American Heart Association. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery–executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol*. 2002;39:542–553.
41. Noppers IM, Niesters M, Aarts LP, et al. Drug-induced liver injury following a repeated course of ketamine treatment for chronic pain in CRPS type 1 patients: a report of 3 cases. *Pain*. 2011;152:2173–2178.