Ketamine Infusions for Chronic Pain: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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BACKGROUND: IV ketamine is widely used to treat patients with chronic pain, yet the long-term impact remains uncertain. We synthesized evidence from randomized control trials to investigate the effectiveness of IV ketamine infusions for pain relief in chronic conditions and to determine whether any pain classifications or treatment regimens are associated with greater benefit.
METHODS: We searched Medline, Embase, and Google Scholar, as well as the clinicaltrials.gov website from inception through December 16, 2017 for randomized control trials comparing IV ketamine to placebo infusions for chronic pain that reported outcomes for ≥48 hours after the intervention. Three authors independently screened the studies, pooled the data, and appraised risk of bias. Random-effects model was used to calculate weighted mean differences for pain scores and secondary outcomes. Our primary outcome was the lowest recorded pain score ≥48 hours after cessation of treatment. Secondary outcomes included responder rate and adverse effects.
RESULTS: Among 696 studies assessed for eligibility, 7 met inclusion criteria. All studies except one were at high risk of bias. These studies randomly assigned 211 patients with neuropathic (n = 2), mixed (n = 2), and nonneuropathic (nociplastic or nociceptive) (n = 3) pain. Three studies reported significant analgesic benefit favoring ketamine, with the meta-analysis revealing a small effect up to 2 weeks after the infusion (mean difference in pain scores, −1.83 points on a 0–10 numerical rating scale; 95% CI, −2.35 to −1.31 points; $P < .0001$). In the 3 studies that reported responder rates, the proportion with a positive outcome was greater in the ketamine than in the placebo group (51.3% vs 19.4%; relative risk, 2.43; 95% CI, 1.10–5.40; $P = .029$; $I^2 = 0.0\%$). No differences were noted based on pain classification or condition. Compared to low-dose ketamine studies and investigations that evaluated non–complex regional pain syndrome conditions, a small but nonsignificant greater reduction in pain scores was found among studies that either utilized high-dose ketamine therapy ($P = .213$) or enrolled complex regional pain syndrome patients ($P = .079$).
CONCLUSIONS: Evidence suggests that IV ketamine provides significant short-term analgesic benefit in patients with refractory chronic pain, with some evidence of a dose–response relationship. Larger, multicenter studies with longer follow-ups are needed to better select patients and determine the optimal treatment protocol. (Anesth Analg 2019;129:241–54)

KEY POINTS

- **Question:** What is the duration of analgesic benefit with the use of IV ketamine in patients with chronic pain?
- **Findings:** A meta-analysis revealed analgesic benefit for up to 2 weeks after the use of IV ketamine.
- **Meaning:** The use of IV ketamine in chronic pain patients provides short-term benefit with no strong evidence of long-term benefit.

Ketamine is classified by the Food and Drug Administration as an anesthetic induction agent in doses ranging from 1 to 4.5 mg·kg^{-1}.[1] Consequently, there is an absence of regulatory guidance on subanesthetic dosing regimens for chronic pain and depression. Yet, in the past decade, the use of ketamine for these conditions has

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skyrocketed. "Ketamine clinics" have sprouted up worldwide with little oversight on myriad issues such as indications, contraindications, and safety such that its unbridled use has been compared to the "Wild West."[2]

The progression of analgesic drug development typically follows a pattern whereby animal studies precede human experimental studies, which eventually lead to clinical trials establishing efficacy and safety in disease-based populations. Human studies designed to seek a new indication or that involve increased risk may be subject to Investigational New Drug application requirements, which can be cumbersome for individual investigators. Because ketamine is available as a generic formulation and has been in clinical use since 1970, the typical model has been upended.

Although several reviews have been published on ketamine for chronic pain, these are flawed or do not address pertinent questions, as outlined in consensus guidelines based on a collaborative effort of 3 pain societies.[3] For example, the meta-analysis by Michelet et al[4] for non–cancer pain considered routes of administration other than IV, which negatively skewed the results. The decision to include other routes of administration is questionable because the mechanism(s) of action may be different and the question payers, patients, regulators, and clinicians are struggling with is whether IV administration is effective.[3] Unlike other routes of administration with poor bioavailability that use administration of ketamine "as needed," IV infusions block *N*-methyl-D-aspartate (NMDA) receptors in the central nervous system (CNS), a target intricately involved in neuroplasticity. In addition, because they are utilized in a controlled setting as a long-term treatment (ie, not for pain exacerbations), they are less likely to negatively impact patients on a day-to-day basis (eg, ability to operate a motor vehicle). Although ketamine acts via a multitude of different receptors that may contribute to analgesia, parenteral administration, particularly via continuous infusion, is postulated to work primarily by reversing central sensitization (ie, reducing the hyperexcitability of the CNS and amplification of noxious and non-noxious stimuli).

The recently published guidelines for the use of IV ketamine to relieve chronic pain[3] provide a framework for this systematic review but are based on subjective evaluation of the available evidence, and do not estimate an effect size, or examine relevant subgroup comparisons (eg, neuropathic versus mixed versus nociceptive versus nociplastic pain, high-dose versus low-dose infusion regimens). Still other systematic reviews have focused on the use of ketamine in specific contexts, such as in the emergency department or as a tool to preventive chronic postsurgical pain.[5,6] These lacunae in knowledge formed the underpinnings for our rationale to include only studies evaluating IV administration with intermediate-term follow-up. In this study, we examined pain scores and complication profiles of chronic pain patients who received either IV ketamine or "placebo." The objectives of our systematic review and meta-analysis of clinical trials evaluating the analgesic effects of ketamine for chronic pain were as follows: (1) to quantify the magnitude of analgesic effect of ketamine infusions, and to determine response rate; (2) to quantify the rate and types of adverse effects; and (3) to identify which pain conditions and patients are most likely to respond to treatment with ketamine and whether there is a dose–response relationship.

METHODS

This systematic review and meta-analysis was conducted according to the recommendations of the Cochrane Collaboration[7] and is reported per Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.[8] It was registered with an international prospective register of systematic reviews (PROSPERO) on October 17, 2017 with the identifying code CRD42017075521.

Search Strategy and Study Selection

We systematically searched and screened titles and abstracts from MEDLINE, Embase, and Google Scholar, as well as a clinical trials website (http://www.clinicaltrials.com) from inception to December 16, 2017. For Embase and MEDLINE, both controlled vocabulary terms (EMBASE-Emtree; MEDLINE-MeSH) and text word searches were conducted for the following search segments: "ketamine," "N-methylketamine," "Norketamine," "S-ketamine," "N-Methyl-D-Aspartate or NMDA antagonist," "CRPS," "complex regional pain syndrome," "fibromyalgia," "pain syndrome," "neuropathic pain," "neuropathy," "pain," "chronic pain," "cancer," "neuralgia," and "analgesia," without language restrictions (Supplemental Digital Content, Table 1, http://links.lww.com/AA/C794). We then reviewed the full articles and applied our selection criteria. We complemented our search by reviewing the bibliographies of selected articles to identify additional articles that were missed in our initial search (Supplemental Digital Content, Table 1, http://links.lww.com/AA/C794). Two authors (V.O. and M.S.O.) independently evaluated titles, abstracts, and full texts. All instances of discordance were discussed between the investigators and the senior author (S.P.C.) to reach consensus.

Criteria for Considering Trials

Type of Study. The search was limited to randomized controlled trials comparing the effect of IV ketamine infusions to a placebo for relieving chronic pain. Animal studies, case series, use of non-IV formulations of ketamine, uncontrolled trials, and review articles were excluded.

Follow-up for Outcomes. Only trials with a follow-up period of ≥48 hours after the cessation of the ketamine infusion were included.

Participants. Only trials performed on human subjects ≥18 years of age who had chronic pain[9–12] for ≥3 months were included in this review. The intensity of pain had to be moderate
or severe (≥4/10 on a numerical rating scale or ≥40/100 on a visual analog scale).

Interventions and Comparators. The intervention was defined as the IV administration of a bolus and/or infusion of ketamine. The comparators were placebo with or without conventional medical management which could include pharmacological, physical, psychological, or interventional therapies. We included studies that allowed for preinfusion

pain management regimens to be continued and those that included the same cointerventions for both groups.

Outcomes. The primary outcome was the lowest intensity pain score recorded ≥48 hours after completion of treatment expressed on a 0–10 scale. Intensity scores reported on a visual analog scale were transformed to a 0–10 numerical rating scale because these scales have high correlation.[13,14] Given the paucity of well-designed trials, we chose to include studies that assessed the primary outcome at a wide range of time intervals (48 hours to 12 weeks after administration of ketamine).[15] The following were considered as secondary outcomes: positive response, defined as reduction in pain scores by ≥30% or ≥50% from baseline 48 hours or longer after the intervention, and the incidence of adverse effects. Although ≥50% pain relief is the most common threshold for designating a treatment response as positive,[16] studies have found that ≥30% relief constitutes clinically meaningful improvement.[17] The 48-hour cutoff was chosen because of the need to choose a time point remote from the infusion that would simultaneously be inclusive, and allow us to control for short-term anesthetic effects.

Risk of Bias Assessment

Two authors (V.O. and M.S.O.) independently assessed risk of bias using the Cochrane Collaboration's instrument, which assesses the following domains: generation of the allocation sequence, allocation concealment, blinding of investigators and participants, blinding of outcome assessors, incomplete outcome data, selective reporting, and other possible sources that contain less empirical evidence but collectively may be important (eg, unequal distribution of prognostic factors, industry participation, trial termination).[7] Each item was classified as having low, unclear, or high risk of bias. A decision to classify "overall bias" as low, unclear, or high was made using the following criteria: "High," any trial with a high risk of bias on ≥1 key domains; "Unclear," any trial with an unclear risk of bias on ≥1 key domains; and "Low," any trial without a high risk of bias on any key domain and without significant methodological concerns. We used visual inspection of the funnel plot to assess for publication bias and small study effects, with Begg rank correlation and Egger regression asymmetry tests used to confirm these results if asymmetry was detected provided a sufficient number of studies (≥10) was available.[18]

Data Extraction

Reference data, populations, and outcomes were extracted from articles into prespecified tables using a standardized data extraction form. The data-collection form was pilot-tested before use. We extracted information on studies' general characteristics (publication year, design, number of arms, and outcomes), participants (demographic characteristics and sample size), clinical information (diagnosis, duration, and pain intensity), and experimental intervention (doses and administration regimen). For continuous data, means and SDs were extracted from tables or graphs. If not reported, SDs were obtained from CIs relating to the difference between means. Median values and interquartile ranges were converted to mean and SD if data were normally distributed.[7] We contacted authors when information required about their analysis or results was not reported. In situations where numeric pain scores were not reported, we obtained their estimated values from graphs and figures.

Data Analysis

DerSimonian and Laird random-effects meta-analysis method was used due to expected heterogeneity from diverse populations, diagnoses, and ketamine dosages.[7] Heterogeneity was assessed by inspection of the forest plot and the Q test, and Higgins I^2 statistic was used to quantify it.[7] We used meta-regression to evaluate potential sources of heterogeneity. Investigation of sources of heterogeneity was based on analysis of prespecified subgroups for the primary outcome including types of pain syndromes (complex regional pain syndrome versus non–complex regional pain syndrome), mixed or neuropathic versus nonneuropathic (nociceptive or nociplastic) pain, high- versus low-dose ketamine, inpatient versus outpatient setting, studies with >60% females versus those with less, and studies with a median age >46 years of age versus those with a median age under 46 years of age. The rationale for stratifying studies based on age and sex is the effect of these variables on pain processing and neuroplasticity.[19,20] Due to the small number of studies in each subgroup, a meta-regression analysis was used to determine the level of significance between the aforementioned subgroups.

Studies were categorized as either "high-dose" or "low-dose" based on the cumulative amount of ketamine administered in each study. Assuming a 70-kg patient, we calculated the cumulative amount of ketamine from each infusion regimen by multiplying the amount of the assumed weight by the infusion rate (mg/kg/min) and duration of infusion. Cumulative ketamine dose ≥400 mg was defined as "high-dose group," while cumulative dose <400 mg was defined as "low-dose group."

The weighted mean difference in pain scores was calculated with its 95% CI at 48 hours or later after the infusion. A P value of <.05 was considered significant for the primary outcome. The DerSimonian and Laird method was used for calculating the pooled relative risk with corresponding 95% CI for the rate of positive analgesic response and incidence of adverse effects. For adverse effects, proportions of patients with adverse outcomes were pooled. To avoid inducing bias toward a higher event rate from using a fixed continuity correction for studies with a zero-event rate, proportions were transformed via the Freeman–Tukey Double ArcSine method without continuity correction. Pooled estimates were then calculated based on the transformed values using a random-effects model.[7] CIs for pooled estimates were based on the Wald method. Finally, back-transformed pooled proportions were calculated by using Miller inverse transformation with the harmonic mean of the sample size.[21]

A sample size calculation was performed to estimate the number of patients required to detect a difference of 1 or 1.5 point(s) between the ketamine and comparator groups with an SD of 2.0. Sample sizes of 40 or 86 subjects per group, respectively, were required to obtain results with a probability of type I error of 5% and type II error of 10%. We

performed a sensitivity analysis by excluding studies one-by-one in a stepwise fashion and reassessing how the new estimate differed. Analyses were performed using STATA version 13 (StataCorp, College Station, TX).

Quality of Evidence

The quality of evidence was classified using Guidelines of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology as high, moderate, low, or very low for each outcome based on the risk of bias, inconsistency, indirectness, imprecision, and publication bias. A summary table was constructed with the GRADEpro guideline development tool (http://www.guidelinedevelopment.org/; Evidence Prime Inc, Hamilton, ON, Canada).[22]

RESULTS

Search Results

From the initial 696 records identified through searching databases and other sources, we removed duplicate records and then screened the remaining 467 relevant publications. Among these, 437 were excluded because the publications focused on the perioperative period or failed to report our primary outcome. Thirty full-text articles were assessed for eligibility, with 23 of these excluded because they did not meet inclusion criteria (Figure 1). Seven randomized control trials[23–29] consisting of 211 patients (108 in the IV ketamine groups and 103 in comparator groups; 1 trial had a crossover design with the subjects receiving each of the trial infusions sequentially after the washout period) were included for the systematic review (Table 1), and data from all of these were subjected to meta-analysis.

Participants and Interventions

The median (range) sample size of the 7 randomized control trials was 24 participants (range, 19–60). The median (range) age of participants in the 7 randomized control trials was 48 years (range, 41.9–71 years). All trials evaluated chronic pain syndromes, but there was wide variation in type of pain, distribution, and etiology. Two studies (on phantom limb pain[26] and post–spinal cord injury pain[27]) enrolled patients with predominantly neuropathic pain according to the International Association for the Study of Pain definition.[11] Two studies enrolled patients with pain syndromes considered to have a mix of neuropathic and nociceptive characteristics[30,31] (ie, complex regional pain syndrome types I and II[24] and cancer-related pain[25]), and 3 studies[23,28,29] enrolled patients with nociplastic[23,28] or nociceptive[29] (ie, nonneuropathic) pain. In 2 of these, the conditions treated are believed to derive from disorders involving central pain processing rather than discrete nerve injury (complex regional pain syndrome type I[23] and fibromyalgia[28]), while in the other (limb ischemia[29]), pain is predominantly nociceptive. The exclusion criteria based on participants' age and comorbidities were fairly similar in all studies, although the study on fibromyalgia[28] did not state reasons for exclusion of eligible participants. IV ketamine was used as a primary analgesic in all studies. Two studies included the use of opioids in the intervention and control arms throughout the trial,[25,29] subjects in both arms of another study received gabapentin,[27] and 1 study used midazolam and clonidine in both arms.[24]

Ketamine Infusion Regimens

A wide range of infusion protocols was investigated in the studies included in this review.[23–29] The median (range) duration of ketamine infusion for all 7 studies was 5 hours (range, 0.5–100 hours), and the median number of days over which ketamine was administered, continuously or intermittently, was 1 day (range, 1–10 days). The median (range) dose of ketamine during the infusion using a 70-kg patient as the reference was 0.35 mg·kg^{-1} (0.23–0.6 mg·kg^{-1}). For data available on analgesic effects at the end of the second week after infusion, 3 of 7 studies were included.[23,24,27] One study used the S(+)-isomer of ketamine at an infusion dose range of 0.07–0.43 mg·kg^{-1}·hour^{-1}.[23]

Risk of Bias Assessment

Overall, the risk of bias was considered high in 4 trials[23,27–29] (Figure 2). These trials did not adequately describe the procedures for blinding participants and personnel. The majority of participants in the only 2 studies to assess blinding were able to correctly guess their treatment allocation.[23,28] This suggests that blinding was ineffective in the other trials.[23,24,27–29] Detection bias was high in 2 of the studies.[27,29] Quality of reporting was fair in 6 trials[23–28] and good in 1 trial.[29] There was no difference between the 2 reviewers (V.O. and M.S.O.) for assessment of risk of bias in any study.

Primary Outcome

Pain Scores. Six[23,24,26–29] of the 7 studies reported the lowest pain score between 48 hours and 2 weeks after treatments on a 10-point numerical rating scale, and data from these studies were included in the meta-analysis. The study by Salas et al,[25] which reported no benefit from ketamine in patients with refractory cancer pain, could not be included because it did not provide the variance (SDs) for the mean pain scores. Meta-analysis of the data from these trials revealed a significant reduction in pain scores favoring ketamine over standard or control comparative treatments (mean difference, −1.83 points; 95% CI, −2.35 to −1.31 points; $P < .0001$; $I^2 = 48.5\%$; Figure 3).[23,24,26–29]

Dose–Response. We conducted a subgroup analysis to determine whether the effect on our primary outcome differed depending on the dose of ketamine (high versus low), with the high-dose threshold designated as a cumulative dose exceeding 400 mg. Three studies that reported our primary outcome treated patients with high-dose ketamine,[23,24,27] with 2 of these[23,27] reporting lower pain scores in the ketamine as compared to the control groups. A meta-analysis of data from these high-dose ketamine trials demonstrated a significant reduction in pain scores with ketamine compared to placebo (mean difference, −2.11 points; 95% CI, −2.87 to −1.35 points; $P < .0001$; $I^2 = 69.2\%$). Three of the studies that reported our primary outcome of interest treated patients with low-dose ketamine,[26,28,29] with 1 study reporting benefit.[29] Meta-analysis of data from the low-dose ketamine trials revealed an analgesic benefit for IV ketamine compared to the placebo group (mean

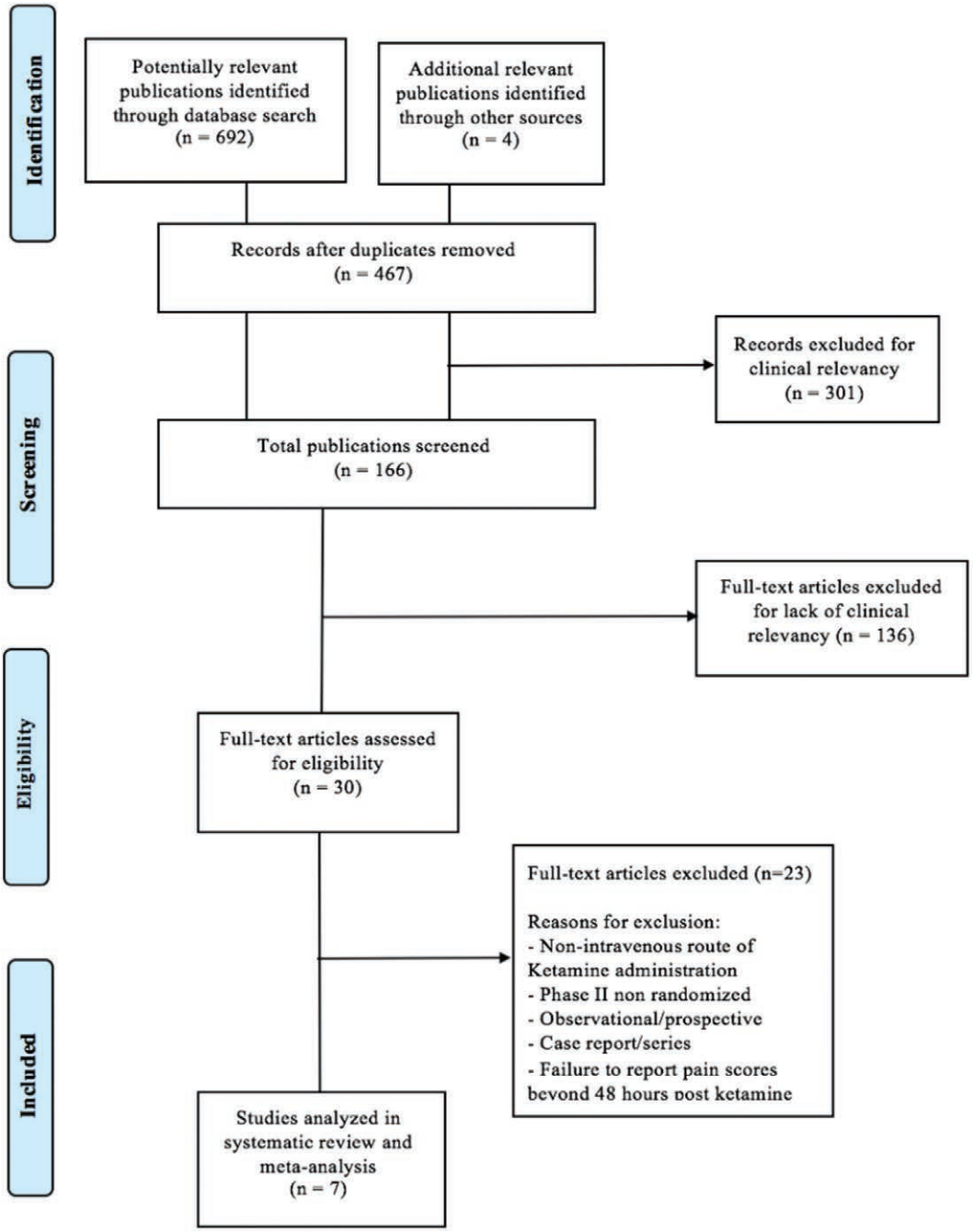


Figure 1. Flow chart demonstrating the identification and selection of articles for the systematic review and meta-analysis.

difference, −1.30 points; 95% CI, −2.01 to −0.59 points; $P = .0001$; $I^2 = 0.0\%$). When the primary outcome for both categories was compared using meta-regression, the use of high-dose ketamine was not significantly different from the use of low-dose ketamine ($P = .213$) (Supplemental Digital Content, Figure 1, http://links.lww.com/AA/C794).

Efficacy in Different Types of Pain. We performed a subgroup analysis comparing analgesic efficacy of ketamine infusions in participants with neuropathic and mixed neuropathic–nociceptive pain syndromes (spinal cord injury, phantom limb pain, and complex regional pain syndrome types I and II)[24,26,27] to primarily nociceptive (ischemic limb pain)[29] or nociplastic pain syndromes (complex regional pain syndrome type I and fibromyalgia).[23,28] Three studies investigated patient populations that had either neuropathic[26,27] or mixed neuropathic–nociceptive pain,[24] with 1 study[27] reporting a significant reduction in pain scores with ketamine infusion. Meta-analyses of these data demonstrated a significant reduction in pain scores with ketamine compared to placebo control groups (mean difference, −1.75 points; 95% CI, −2.08 to −1.43 points; $P < .00001$; $I^2 = 0.0\%$). For the nonneuropathic (nociceptive or nociplastic) pain category, 1[23] of the 3 trials[23,28,29] reported

Table 1. Characteristics of Selected Studies on Ketamine Infusion

Reference	Study Design and Setting	Patient Population	Treatment Group	Ketamine Infusion Duration and Maximum Dose[a]	Control Group
Amr[27]	Double-blind placebo-controlled trial; inpatient	40 subjects with post–spinal cord injury; severe neuropathic pain for over 6 mo	Ketamine infusion + gabapentin 300 mg three times daily (n = 20)	5 h daily for 7 consecutive days (35 h); 0.22 mg/kg/h	Normal saline + gabapentin 300 mg three times daily (n = 20)
Eichenberger et al[26]	Double-blind placebo-controlled crossover trial; inpatient	20 subjects with chronic phantom limb pain	Ketamine infusion (n = 10); ketamine + calcitonin (n = 20)	1-h infusion; 0.4 mg/kg/h	Normal saline (n = 20); calcitonin (n = 20)
Salas et al[25]	Double-blind placebo-controlled trial; inpatient	20 subjects with cancer pain refractory to opioids	Infusions of ketamine and morphine (n = 11)	24-h infusion; 0.5 mg/kg/d in the first 24 h, then 1 mg/kg/d if Numeric Pain Intensity Scale ≥1/10	Infusions of normal saline and morphine (n = 9)
Schwartzman et al[24]	Double-blind placebo-controlled trial; outpatient	19 subjects with complex regional pain syndrome I and II based on International Association for the Study of Pain diagnostic criteria[10]	Ketamine infusion + midazolam + clonidine (n = 9)	4 h/d for 10 consecutive week days (40 h as 5 d on–2 d off–5 d on); 0.35 mg/kg/h (maximum of 25 mg/h)	Normal saline + midazolam + clonidine (n = 10)
Sigtermans et al[23]	Double-blind placebo-controlled trial; inpatient	60 subjects with complex regional pain syndrome I based on International Association for the Study of Pain diagnostic criteria[10,11]	S (+)-ketamine infusion based on stepwise tailoring of dosage based on benefit and adverse effects (range, 0.07–0.43 mg/kg/h) (n = 30)	Continuous for 4.2 d (100 h); 0.43 mg/kg/h with a mean dose of 0.32 mg/kg/h (maximum of 30 mg/h)	Normal saline (n = 30)
Noppers et al[28]	Double-blind placebo-controlled trial; outpatient	24 subjects with fibromyalgia as per American College of Rheumatology 1990 criteria[12]	S (+) ketamine infusion (n = 12)	30 min; 0.5 mg/kg	Midazolam 5 mg (n = 12)
Mitchell and Fallon[29]	Double-blind placebo-controlled trial; inpatient	35 patients with ischemic limb pain	Ketamine infusion + opioids (n = 18)	4 h; 0.6 mg/kg	Normal saline + opioids (n = 17)

Abbreviation: HR, heart rate.
[a]Maximum dose was calculated based on a 70 kg patient.
[b]Time points selected for primary outcome.

lower pain scores favoring IV ketamine. This trial enrolled patients with a nociplastic pain syndrome (complex regional pain syndrome type I).[23] Meta-analysis of these data revealed a significant reduction in pain scores with IV ketamine (mean difference, −1.97 points; 95% CI, −3.04 to −0.90 points; $P < .00001$; $I^2 = 69.5\%$). However, there was no significant difference when the primary outcomes for both groups were compared using meta-regression ($P = .720$) (Supplemental Digital Content, Figure 2, http://links.lww.com/AA/C794).

We also performed a subgroup analysis comparing studies that enrolled participants with complex regional pain syndrome compared to those whose participants did not have complex regional pain syndrome. Two trials investigated patients with complex regional pain syndrome[23,24] with 1[23] revealing lower pain scores with ketamine as compared to placebo control groups. Meta-analysis of these data demonstrated a significant reduction in pain with IV ketamine compared to control (mean difference, −2.38 points; 95% CI, −3.53 to −1.23 points; $P < .0001$; $I^2 = 34.9\%$). Four trials investigated patients without complex regional pain syndrome.[26–29] Two[27,29] of these studies, which enrolled patients with neuropathic pain after spinal cord injury[27] and ischemic limb,[29] reported lower pain scores favoring IV ketamine compared to placebo control group, with the studies performed for phantom limb[26] and fibromyalgia[28] pain reporting a lack of efficacy. Meta-analysis of these data demonstrated a significant reduction in pain scores with

Table 1. Continued

Outcomes Assessed	Pain Assessment Time Points	Analgesic Outcomes	Adverse Effects
Visual analog scale pain scores (0–10)	-Baseline -Daily during the infusion week -End of week 1[b] -Weekly for 3 wk after the infusion	Maximum pain relief 1 wk after the ketamine infusion (ketamine group had lower pain scores than comparator for up to 2 wk after treatments)	Ketamine group: short-duration delusions (n = 3) and increase in HR (n = 2)
-Visual analog scale pain scores (0–10) -Quantitative sensory testing (pain thresholds for electrical, thermal, pressure stimulation)	-Baseline -During and after the infusion -At 48 h[b] after infusion	Ketamine and the combination treatment, but not calcitonin reduced phantom limb pain. At 48 h after infusion, the difference favoring ketamine was not significant. There was no difference between ketamine and combination treatment. Ketamine elevated electrical sensory thresholds.	Ketamine group: -Deep sedation requiring temporary stoppage (n = 1) -Sedation (n = 2) -Light visual hallucinations, hearing impairment, impairment of proprioception (n = 5)
-Numeric Pain Intensity Scale (0–10) -Edmonton Symptom Assessment Scale -Patient Treatment Satisfaction Scale -Daily morphine dose	-Baseline -2, 24, and 48 h after starting infusions	Numeric Pain Intensity Scale, Edmonton Symptom Assessment Scale, and Patient Treatment Satisfaction Scale scores did not differ significantly between the 2 groups during the 3 evaluation periods.	-None
-Numeric Rating Scale pain scores (0–10) -Short-Form McGill Pain Questionnaire -Quantitative sensory testing -Motor function -Cutaneous temperature Quality of life	-2 wk before infusion -1–2 wk[b], 3–4 wk, 5–8 wk, and 9–12 wk after the infusion -3–4 wk -9–12 wk	Ketamine-treated group demonstrated greater decreases in pain scores that lasted for the 12-wk posttreatment evaluation period on some measures, but not for the primary outcome. Differences in quality of life and quantitative sensory testing did not differ between groups.	-Nausea, headache, tiredness, or dysphoria (n = 6) -Trial terminated early (halfway point) after interim analysis because ketamine dose deemed inadequate.
-Numeric Rating Scale pain scores (0–10)	-Baseline -Weekly during the 12-wk infusion -Outcomes assessed at 1,[b] 3, 6, and 12 wk: functional ability, touch thresholds, cutaneous temperature, volumetric assessments -Daily liver functions during the infusion	Pain scores over the 12-wk study period in ketamine group were significantly lower at the end of week 1 through 8 wk. By week 12, the significance in pain relief between groups was lost; there was no improvement in functional status at any time point.	-Nausea (n = 19) -Vomiting (n = 14) -Headache (n = 13) -Psychotomimetic effects (n = 23)
-Visual analog scale pain scores (0–10) -Fibromyalgia Impact Questionnaire -Quantitative sensory testing	-Baseline -1[b] and 8 wk	Pain scores lower in ketamine group at 15 min after infusion, but there was no difference between groups beyond that time point.	-Distortion in perception of surroundings, thoughts, reality. and time; feeling "high" (quantities not noted)
Brief pain inventory scores (0–10)	-Baseline -24 h and 5[b] d after infusion	Significant reduction in pain and improvement in activity and enjoyment of life in the ketamine compared to the placebo group; maximum analgesic benefit 5 d after infusion.	-Higher incidence of "feeling more emotional than usual" in the ketamine group (n = 6)

ketamine (mean difference, −1.71 points; 95% CI, −2.01 to −1.41 points; P = .001; I^2 = 0.0%). When the primary outcomes for both categories were compared using meta-regression, there was no significant difference between groups (P = .079) (Supplemental Digital Content, Figure 3, http://links.lww.com/AA/C794).

Efficacy With Adjunct Medications Versus Stand-Alone Therapy. We performed a subgroup analysis comparing studies using only ketamine[23,24,28] to studies that used analgesic adjuncts (opioids, gabapentin, and calcitonin) in the group receiving ketamine infusion.[26,27,29] Medications administered with the expressed purpose to prevent adverse effects (eg, midazolam and low-dose clonidine) were not considered analgesics.[24] When the primary outcome for both categories were compared using meta-regression, there were no significant differences (P = .127) (Supplemental Digital Content, Figure 4, http://links.lww.com/AA/C794).

Efficacy of Ketamine at Different Time Points. Three trials reported pain scores at 2 weeks posttreatment.[23,24,27] Two of these found lower pain scores in the ketamine group compared to placebo.[23,27] Meta-analysis of these data revealed a significant reduction in pain scores favoring IV ketamine (mean difference, −2.23 points; 95% CI, −2.59 to −1.87 points; P < .001; I^2 = 0.0%) (Supplemental Digital Content, Figure 5, http://links.lww.com/AA/C794). Three

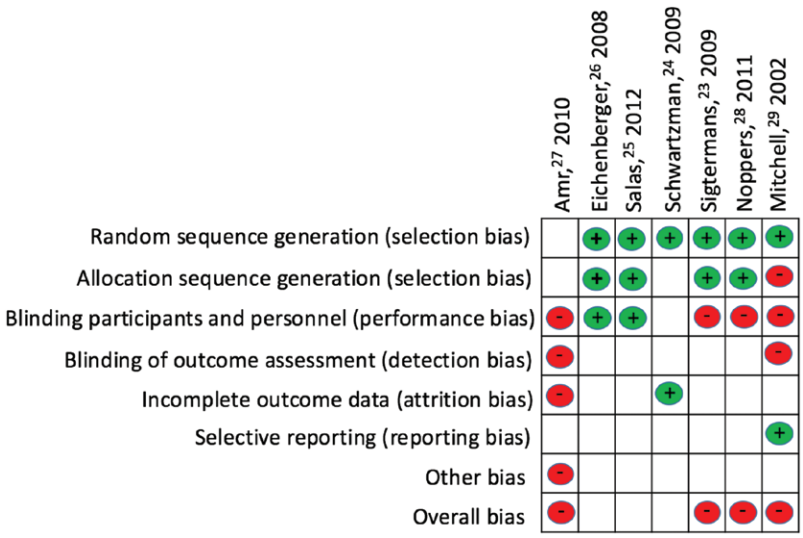
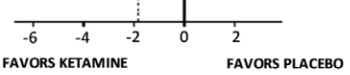


Figure 2. Risk of bias summary. Green circles with "+" sign indicate low risk; red circles with "−" sign indicate high risk; and blank boxes indicate unclear risk.

Author, Year	Ketamine Mean Pain Score[1]	SD	Total	Placebo Mean Pain Score[1]	SD	Total	Weighted Mean Difference D+L, Random, 95% CI	Weighted Mean Difference D+L, Random, 95% CI	Weight (%)
Sigtermans,[23] 2009	2.7	1.3	30	5.4	1.2	30	-2.70 (-3.33, -2.07)		25.48
Eichenberger,[26] 2008	2.5	1.7	10	3.6	1.6	10	-1.10 (2.55, 0.35)		9.78
Schwartzman,[24] 2009	6.3	2.7	9	7.6	1.9	10	-1.30 (-3.42, 0.82)		5.21
Noppers,[28] 2011	0.8	0.3	12	2.0	0.3	12	-1.60 (-3.57, 0.37)		5.93
Amr,[27] 2010	2.5	0.6	20	4.3	0.4	20	-1.80 (-2.13, -1.47)		35.13
Mitchell,[29] 2002	4.5	1.3	16	5.8	1.1	12	-1.31 (-2.21, -0.42)		18.47
Total (95% CI)			**97**			**94**	**-1.83 (-2.35, -1.31)**		**100.00**



Heterogeneity: Tau²=0.17, Chi² =9.71, df=5 (P=0.084): I²=48.5%
Test of Overall effect: Z =6.93, P<0.0001

Figure 3. Forest plot of the effects of ketamine infusion on maximum reduction in mean numeric rating scale (0–10) pain score. df indicates degrees of freedom; D+L, DerSimonian and Laird.

trials[23,24,27] reported pain scores 4 weeks after treatment, with 1[23] finding lower pain scores in the ketamine group. Meta-analysis of these data revealed a nonsignificant reduction in pain scores with IV ketamine compared to placebo (mean difference, −0.74 points; 95% CI, −1.88 to 0.41 points; P = .208; I^2 = 58.6%) (Supplemental Digital Content, Figure 6, http://links.lww.com/AA/C794). Three trials[23,24,28] reported pain scores at 8 weeks (2 months) posttreatment, with 1[23] reporting lower pain scores in the IV ketamine group. Meta-analysis of these data yielded a nonsignificant reduction in pain scores with ketamine compared to placebo (mean difference, −0.68 points; 95% CI, −1.75 to −0.40 points; P = .174; I^2 = 48.2%) (Supplemental Digital Content, Figure 7, http://links.lww.com/AA/C794). Two trials[23,24] reported pain scores 12 weeks (3 months) after treatment, with neither reporting lower pain scores in the IV ketamine group. Meta-analysis of these data revealed a nonsignificant reduction in pain scores with IV ketamine compared to placebo (mean difference, −0.55 points; 95% CI, −1.50 to 0.39 points; P = .251; I^2 = 0.0%) (Supplemental Digital Content, Figure 8, http://links.lww.com/AA/C794). In summary, administration of ketamine resulted in a significant reduction of pain scores when compared to placebo at 2 and 8 weeks (but not 4 weeks) after treatment.

Secondary Outcomes

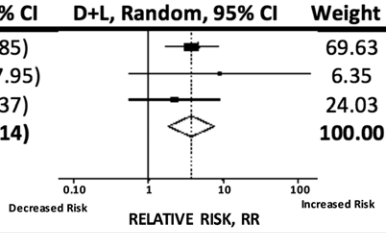
Positive Response. Three of the 7 studies in this review reported the proportion of patients achieving a positive analgesic response (as designated by the authors) with ketamine compared to placebo.[25,26,28] One study used a ≥30% reduction in pain as the criterion for a positive outcome,[25] whereas the other 2 used a ≥50% reduction as the threshold.[26,28] A meta-analysis of these studies demonstrated analgesic superiority for IV ketamine compared to placebo control based on the study-designated definition of success[25,26,28] (19.4% vs 51.3%; relative risk, 2.43; 95% CI, 1.10–5.40; P = .029; I^2 = 0.0%) (Supplemental Digital Content, Figure 9, http://links.lww.com/AA/C794).

Adverse Effects. Common ketamine-related adverse outcomes reported in the trials included nausea, vomiting, psychotomimetic effects, headache, fatigue, and sedation. Compared to placebo, the ketamine group had significantly higher relative risk of nausea (relative risk, 3.52; 95% CI, 1.74–7.14; P < .00001; Figure 4A) and psychotomimetic effects (relative risk, 5.92; 95% CI, 2.95–11.89; P < .00001; Figure 4B). The relative risk of headache (relative risk,

A Nausea

Author, Year	Ketamine Events	Total	Placebo Events	Total	Risk Ratio D+L, Random, 95% CI	Risk Ratio D+L, Random, 95% CI	Weight
Sigtermans,[23] 2009	19	30	5	30	3.80 (1.63, 8.85)		69.63
Eichenberger,[26] 2008	4	10	0	10	9.00 (0.55, 147.95)		6.35
Schwartzman,[24] 2009	4	9	2	10	2.22 (0.53, 9.37)		24.03
Total (95% CI)		**49**		**50**	**3.52 (1.74, 7.14)**		**100.00**

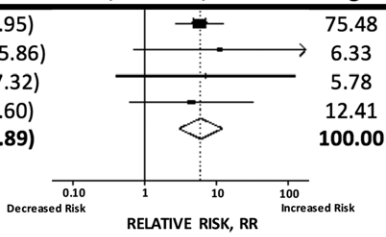
Heterogeneity: $Chi^2 = 0.88$, d.f.=2 (P=0.643): $I^2 = 0.00\%$
Test of Overall effect: Z = 3.50, p<0.00001



B Psychotomimmetic effect

Author, Year	Ketamine Events	Total	Placebo Events	Total	Risk Ratio D+L, Random, 95% CI	Risk Ratio D+L, Random, 95% CI	Weight
Sigtermans,[23] 2009	29	30	5	30	5.80 (2.60, 12.95)		75.48
Eichenberger,[26] 2008	5	10	0	10	11.00 (0.69, 175.86)		6.33
Amr,[27] 2010	3	20	0	20	7.00 (0.39, 127.32)		5.78
Mitchell,[29] 2002	6	16	1	12	4.50 (0.62, 32.60)		12.41
Total (95% CI)		**76**		**72**	**5.92 (2.95, 11.89)**		**100.00**

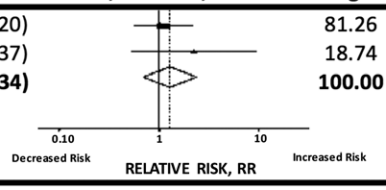
Heterogeneity: $Chi^2 = 0.28$, d.f.=3 (P=0.963): $I^2 = 0.00\%$
Test of Overall effect: Z = 5.00, p<0.00001



C Headache

Author, Year	Ketamine Events	Total	Placebo Events	Total	Risk Ratio D+L, Random, 95% CI	Risk Ratio D+L, Random, 95% CI	Weight
Sigtermans,[23] 2009	11	30	10	30	1.10 (0.55, 2.20)		81.26
Schwartzman,[24] 2009	4	10	2	9	2.22 (0.53, 9.37)		18.74
Total (95% CI)		**40**		**39**	**1.26 (0.67, 2.34)**		**100.00**

Heterogeneity: $Chi^2 = 0.75$, d.f.=1 (P=0.387): $I^2 = 0.00\%$
Test of Overall effect: Z = 0.71, p=0.475



D Tiredness

Author, Year	Ketamine Events	Total	Placebo Events	Total	Risk Ratio D+L, Random, 95% CI	Risk Ratio D+L, Random, 95% CI	Weight
Schwartzman,[24] 2009	4	10	2	9	2.22 (0.53, 9.37)		72.21
Amr,[27] 2010	2	20	1	20	2.00 (0.20, 20.33)		27.79
Total (95% CI)		**30**		**29**	**2.16 (0.64, 7.33)**		**100.00**

Heterogeneity: $Chi^2 = 0.01$, d.f.=1 (P=0.939): $I^2 = 0.00\%$
Test of Overall effect: Z = 1.23, p=0.218

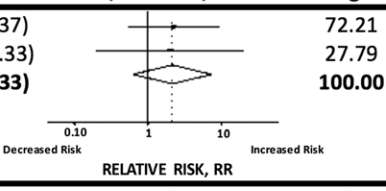


Figure 4. Adverse effects associated with the use of intravenous ketamine. A, Forest plot displaying risk of nausea and 95% CIs with IV ketamine compared to placebo. B, Forest plot displaying risk of psychotomimetic effect and 95% CIs with IV ketamine compared to placebo. C, Forest plot displaying risk of headache and 95% CIs with IV ketamine compared to placebo. D, Forest plot displaying risk of tiredness and 95% CIs with IV ketamine compared to placebo.

1.26; 95% CI, 0.67–2.34; P = .475; Figure 4C) and tiredness (relative risk, 2.16; 95% CI, 0.64–7.33; P = .218; Figure 4D) was higher among the ketamine group, but the differences were not statistically significant. Nausea and vomiting were also higher in the ketamine group, but this was reported by one study. The incidence of these side effect measures is reported in Supplemental Digital Content, Table 2, http://links.lww.com/AA/C794.

Heterogeneity. For the primary outcome, the I^2 statistic was 45.9% for the meta-analysis of IV ketamine use from 6 randomized control trials. These results indicate the presence of a moderate degree of heterogeneity. Several characteristics of these studies may have contributed to heterogeneity including differences in the types of pain conditions and patient populations, time periods for assessing the primary outcome, and variations in the ketamine infusion regimen and comparators explored. To explore the sources of heterogeneity, we conducted subgroup analyses using meta-regression and a sensitivity analysis. We found no significant differences between the following groups: mixed or neuropathic versus nociceptive or nociplastic pain, complex regional pain syndrome versus non–complex regional pain syndrome, inpatient setting (n = 5 studies)[23,25–27,29] versus outpatient setting (n = 2

studies),[23,24] studies with >60% females versus those with less, and studies with a median age >46 years versus those under 46 years. A sensitivity analysis was performed by sequentially removing each individual trial and evaluating how it affected the pooled estimate of the primary outcome, but this process failed to find a significant difference (Supplemental Digital Content, Figure 10, http://links.lww.com/AA/C794).

Publication Bias. To elucidate this possibility, we performed Begg and Egger tests, with the nonsignificant *P* values (*P* = .380 and .423, respectively) suggesting an absence of publication bias. We did not display a funnel plot because the studies in our analysis did not meet the minimum recommended number of studies required for interpreting a funnel plot (usually 10).[18,32]

Grade Evidence. We provided evidence as per GRADE recommendations[22] for the primary outcome, secondary outcomes, and complication profile based on risk of bias, inconsistencies, indirectness, imprecision, magnitude of effect size, evidence of dose–response, and other methodological shortcomings. Based on these considerations, the grade of evidence for the analgesic efficacy of IV ketamine in chronic pain was determined to be low (Table 2). For similar reasons, the grade of evidence for categorical response (≥30% or ≥50% pain relief) and efficacy at 2 weeks after the infusion was also deemed to be low. Our analysis suggests that we have limited confidence in the analgesic effect of IV ketamine in chronic pain patients. However, the true effect with IV ketamine use may be significantly different from the proposed estimates in our study.

DISCUSSION

This systematic review and meta-analysis of 7 randomized control trials evaluated persistent analgesic efficacy from IV ketamine infusions versus placebo for chronic pain. It reveals that IV ketamine is effective for a wide array of chronic pain conditions, although the benefits dissipate with time. Use of IV ketamine resulted in a reduction in pain scores between 48 hours and 2 and 8 weeks after the infusion, but the pooled difference in pain reduction at 4 weeks fell shy of significance. The incidence of nausea and vomiting with IV ketamine was higher than with placebo.

A recently published systematic review and meta-analysis that investigated ketamine for chronic pain included non-IV routes of administration,[4] while another limited the study cohort to participants with complex regional pain syndrome.[33] The review by Michelet et al[4] found no analgesic efficacy with ketamine at 4 weeks, but paradoxically some benefit at 12 weeks, which is a function of methodology that failed to account for differences in follow-up (ie, negative studies at 4 weeks were not considered negative evidence at 12 weeks).[4] It is hypothesized that reversing wind-up and central sensitization require high-concentration bombardment and blockade of NMDA receptors, which are intimately involved in neuroplasticity.[34] Consequently, extremely low-dose transdermal administration or intermittent blockade with "as needed" oral ketamine, which has a very low bioavailability of 8%–24%,[35] is unlikely to accomplish this goal. This fact, along with the widespread interest in IV administration among patients and caregivers, led us to include only studies that examined outcomes after IV administration.

Analgesic Outcomes

The randomized control trials included in our analysis used diverse pain scales that were often presented in ways that made accurate extraction of raw data difficult. Hence, the results in some studies were standardized during quantitative analysis. The challenges imposed by heterogeneity of outcomes in the pain literature[36] have compelled authors of systematic reviews to adopt a "best available evidence approach."[37–39] The conclusions from our meta-analysis examining maximum pain relief should be interpreted with caution because they are based only on 6 small studies. Furthermore, the heterogeneity in time points used for analgesic assessment poses a challenge in evaluating duration of benefit of ketamine infusions.

Analgesic Effect of Ketamine in Different Pain Syndromes

The randomized control trials evaluated in this review included neuropathic, mixed nociceptive and neuropathic pain (eg, spinal cord injury, phantom limb pain, cancer, complex regional pain syndrome types I and II),[24–27] and nociceptive (eg, ischemic limb pain)[29] or nociplastic pain syndromes (eg, complex regional pain syndrome type I and fibromyalgia).[23,28] In subgroup analysis, we found no evidence for superior analgesic benefit from ketamine in neuropathic compared to nociceptive or nociplastic pain syndromes. The same held true for a comparison between non–complex regional pain syndrome and complex regional pain syndrome populations. Some may consider this surprising considering that ketamine has been better studied in neuropathic pain models. It is worth noting that, although not significant, the magnitude of reduction in pain scores was greater among complex regional pain syndrome subgroups, indicating a need for larger and more methodologically robust trials. The International Association for the Study of Pain defines neuropathic pain as "pain caused by a lesion or disease of the somatosensory nervous system."[40] This definition excludes conditions characterized by central sensitization in the absence of a discrete nerve injury, such as complex regional pain syndrome type I and fibromyalgia.[40] More recently, a third pain descriptor, nociplastic, has been introduced to classify conditions associated with altered processing of pain that do not conform to the nociceptive category. Examples of nociplastic pain include fibromyalgia, complex regional pain syndrome, nonspecific chronic low-back pain, irritable bowel syndrome, and other "functional" visceral pain disorders.[41] However, ketamine's primary analgesic effect remains ambiguous because it is purported to work by either dampening of CNS pain amplification via numerous pathways and/or reversal of central sensitization by NMDA receptor blockade.[34] Whereas the preclinical evidence supporting ketamine is strongest for neuropathic pain, there is a growing body of evidence demonstrating antinociceptive and analgesic effects in inflammatory and other nociceptive as

Table 2. Grade Evidence Profile: Ketamine Infusion in Patients With Chronic Pain

Certainty Assessment							No. of Patients		Effect			
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Ketamine Infusion	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Analgesic efficacy of ketamine infusion in chronic pain (assessed with numeric rating scores on 0–10 scale)												
6	Randomized trials	Very serious[a]	Not serious[b]	Serious[b]	Not serious	None	97	94	-	Mean difference, −2.17 (−2.84 to −1.50)	⊕⊕◯◯ LOW	IMPORTANT
Positive response (≥30% or ≥50% pain relief) after ketamine infusion												
3	Randomized trials	Serious[c]	Not serious[d]	Not serious	Serious[e]	None	17/33 (51.3%)	6/31 (19.4%)	Risk ratio, 2.43 (1.10–5.40)	32 more per 100 (from 0 fewer to 100 more)	⊕⊕◯◯ LOW	IMPORTANT
Analgesic efficacy of ketamine infusion at 2 wk after the infusion (assessed with numeric rating scores on 0–10 scale)												
3	Randomized trials	Serious[f]	Serious[g]	Not serious	Not serious	None	59	60	-	Mean difference −2.23 (−2.59 to −1.87)	⊕⊕◯◯ LOW	IMPORTANT
Incidence of nausea among chronic pain patients receiving ketamine infusion												
3	Randomized trials	Serious[f]	Serious[h]	Not serious	Not serious	None	49	50	-	44.3 incidence h igher (39.2 to 71.4)	⊕⊕◯◯ LOW	IMPORTANT

[a]The 4 trials that were deemed to have a high risk of bias did not adequately describe the procedures for randomization, concealment of allocation, and blinding of participants.
[b]Effect estimates of 2 individual studies had nonoverlapping CIs for the lowest reported pain scores after ketamine infusion. There was a moderate degree of heterogeneity between studies (I^2 = 45.9%), which could be explained by the variations in diagnosis, ketamine infusion regimen, or use of adjunct medications.
[c]The 2 trials deemed to have a high risk of bias did not adequately describe blinding of outcome assessment as well as handling of incomplete outcome data.
[d]All 3 trials had inconsistencies with the interventions used for both treatment and control groups.
[e]The selected studies included only 64 patients with 23 events. This raises concerns about the precision of the studies.
[f]One trial with a high risk of bias did not adequately describe the procedures for randomization, concealment of allocation, and blinding of participants.
[g]In addition to nonoverlapping CIs for 2 studies, there was a high degree of heterogeneity between studies (P = .02) which could be explained by variations in interventions.
[h]Both trials had inconsistencies with the interventions used for both treatment and control groups.

well as nociplastic pain conditions, including headaches.[42,43] Whether differences in analgesic effects are due to actual differences in efficacy or a byproduct of methodological differences are areas ripe for further research.

We included studies that evaluated ketamine as add-on therapy for neuropathic and nociceptive or nociplastic pain, which reflects clinical practice. For cancer, the World Health Organization analgesic stepladder recommends adding adjuvants to existing therapy, not as a replacement,[44] and ketamine is not considered a first-line agent for neuropathic pain, but it is typically used as a rescue agent.[45] Reviews have also found that combination therapy is superior to single-agent therapy for chronic pain syndromes.[46] In the recently published guidelines on IV ketamine for acute pain, one of the questions addressed is whether there is any benefit to adding ketamine to opioid therapy, which was answered affirmatively.[47]

Dose–Response Effect of Ketamine

We found evidence for higher dosages to be associated with greater and longer pain relief, which is not surprising because nearly all analgesic medications are associated with a dose–response effect. However, our analysis may not have shown statistical significance because of the small number of studies in our subgroup analysis. We found that IV ketamine is associated with a significantly higher incidence of nausea and vomiting compared to placebo. However, the data were insufficient to determine the cause–effect relationship between adverse effects and discontinuation of IV ketamine. A previous retrospective study found that discontinuation of IV ketamine secondary to side effects was unrelated to maximum infusion rate.[48] This may be a function of the relatively low incidence of certain adverse effects and flaws in surveillance methods. In 1 review,[49]as well as in the consensus guidelines on the use of ketamine in chronic pain,[3] the authors concluded that higher dosages are associated with better analgesia, although studies correlating blood levels with pain relief have yielded mixed results.[24,50–52] Variables that may affect the therapeutic dose range include underlying pathology, previous exposure to ketamine and comedications.

Challenges With Blinding Participants in Studies Evaluating Ketamine

Although all studies included in our review were ostensibly double-blinded, 83% of participants allocated to ketamine correctly guessed treatment in the 2 studies in which blinding was assessed.[24,26] Studies have found that ineffective blinding may augment the treatment effect by between 15% and 25%.[53–55] Although it is challenging to ensure effective blinding when the medication of interest is associated with unique psychotropic effects, the expectations associated with receiving therapy play an integral role in treatment response,[56] and steps can be taken to reduce bias when blinding is not feasible.[57]

Limitations of Current Evidence

There are several limitations to this review including the small number of patients enrolled in trials (median sample size of 24 participants), which may be attributed to the lack of industry funding for a generic medication, and the lack of standardization for infusion regimens, patient selection, and follow-up periods. In general, studies for medications that receive Food and Drug Administration approval go through a well-defined process that includes determining the optimal dose via phase I and II clinical trials, followed by large-scale randomized trials with stringent selection criteria that typically assess participants for 12 weeks. In contrast, the studies in this review treated small number of patients with refractory pain using myriad dose regimens, and often failed to include secondary outcomes or evaluate intermediate-term effects. Clinical heterogeneity in the studies included in this review was a significant challenge we attempted to explore but were unable to identify causes. In addition, the difference in effect size required to detect a statistically significant improvement in pain score may not fully reflect the true clinical effect. For example, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines note, "… in evaluating a new analgesic, if a 2-point decrease on a 0 to 10 numerical rating scale of pain intensity is considered a clinically important improvement for an individual, it should not be inferred that a 2-point difference in pain reduction between the analgesic and placebo must occur before the treatment benefit can be considered clinically important."[58] Due to the subjectivity of reported pain scores among patients, wide variations in response, and high placebo response rates, the clinical relevance of the differences in effect size is hard to determine. Finally, chronic pain management includes not only the reduction of pain but also improved quality of life, which should be measured via validated instruments.[59] Unfortunately, our analysis could not account for these outcomes due to limited availability of outcome data.

Recommendations and Conclusions

Based on the quality of the evidence from studies in this review and the strength of effect, it is recommended that IV ketamine be used, on a case-by-case basis, as a primary analgesic in patients with chronic pain refractory to more conventional treatments (GRADE: weak recommendation; low evidence)[22] (Table 2). However, our confidence in this analgesic effect is limited and the actual effect of IV ketamine among chronic pain patients may vary widely. IV ketamine may be associated with improvement in pain scores observed during the infusion, quantified as early as 48 hours after the infusion, and lasting for ≥2 weeks when high-dose regimens are used. Whereas reductions in pain scores were observed with a range of dosages, more robust analgesic effects were observed with higher dosages. Further research should seek to determine the ideal patients and conditions for this treatment, the optimal dosing regimen, whether combination therapy with ketamine provides superior benefit than stand-alone treatment, the impact of infusions on physical and psychological functioning, and long-term adverse effects.

DISCLOSURES

Name: Vwaire Orhurhu, MD, MPH.
Contribution: This author helped perform the literature search, data extraction, and statistical analysis, draft and critically revise

the manuscript, interpret the results, and perform a critical review of the manuscript for intellectual content.
Name: Mariam Salisu Orhurhu, MD, MPH.
Contribution: This author helped perform the literature search and data extraction, draft the manuscript, critically revise the manuscript, interpret the results, and perform a critical review of the manuscript for intellectual content.
Name: Anuj Bhatia, MD, FRCPC.
Contribution: This author helped draft the manuscript, critically revise the manuscript, interpret the results, and perform a critical review of the manuscript for intellectual content.
Name: Steven P. Cohen, MD.
Contribution: This author helped design the study, draft and critically revise the manuscript, interpret the results, and perform a critical review of the manuscript for intellectual content.
This manuscript was handled by: Honorio T. Benzon, MD.

REFERENCES

1. US Food and Drug Administration. KETALAR (ketamine hydrochloride) Injection. Available at: httpswww.accessdata.fda.govdrugsatfdadocslabelslbl.pdf. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/016812s043lbl.pdf. Published May 2, 2017. Accessed November 30, 2017.
2. Anderson P, ed. Ketamine for chronic pain on the rise. Available at: https://www.medscape.com/viewarticle/878159. Accessed November 30, 2017.
3. Cohen SP, Bhatia A, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia & Pain Medicine (ASRA), the American Academy of Pain Medicine (AAPM) and the American Society of Anesthesiologists (ASA). *Reg Anesth Pain Med*. 2018;43:521–546.
4. Michelet D, Brasher C, Horlin AL, et al. Ketamine for chronic non-cancer pain: a meta-analysis and trial sequential analysis of randomized controlled trials. *Eur J Pain*. 2018;22:632–646.
5. Karlow N, Schlaepfer CH, Stoll CRT, et al. A systematic review and meta-analysis of ketamine as an alternative to opioids for acute pain in the emergency department. *Acad Emerg Med*. 2018;25:1086–1097.
6. Klatt E, Zumbrunn T, Bandschapp O, Girard T, Ruppen W. Intra- and postoperative intravenous ketamine does not prevent chronic pain: a systematic review and meta-analysis. *Scand J Pain*. 2015;7:42–54.
7. Shuster JJ. Review: Cochrane handbook for systematic reviews for interventions, Version 5.1.0, published 3/2011. Julian P.T. Higgins and Sally Green, Editors. *Res Synth Methods*. 2011;2:126–130.
8. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
9. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain Med*. 2007;8:326–331.
10. Bruehl S, Harden RN, Galer BS, et al. External validation of IASP diagnostic criteria for Complex Regional Pain Syndrome and proposed research diagnostic criteria. International Association for the Study of Pain. *Pain*. 1999;81:147–154.
11. Merskey H, Bogduk N. Classification of Chronic Pain, Second Edition, IASP Task Force on Taxonomy. Available at: https://www.iasp-pain.org/Taxonomy. Accessed October 30, 2017.
12. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum*. 1990;33:160–172.
13. Akinpelu AO, Olowe OO. Correlative study of 3 pain rating scales among obstetric patients. *Afr J Med Med Sci*. 2002;31:123–126.
14. Ponce de Leon S, Lara-Muñoz C, Feinstein AR, Wells CK. A comparison of three rating scales for measuring subjective phenomena in clinical research. II. Use of experimentally controlled visual stimuli. *Arch Med Res*. 2004;35:157–162.
15. Noppers I, Niesters M, Aarts L, Smith T, Sarton E, Dahan A. Ketamine for the treatment of chronic non-cancer pain. *Expert Opin Pharmacother*. 2010;11:2417–2429.
16. Mitchell G. An evidence based resource for pain relief. *Evidence-Based Medicine*. 2001;6:136–136.
17. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.
18. Hunter JP, Saratzis A, Sutton AJ, Boucher RH, Sayers RD, Bown MJ. In meta-analyses of proportion studies, funnel plots were found to be an inaccurate method of assessing publication bias. *J Clin Epidemiol*. 2014;67:897–903.
19. Petersen KK, Arendt-Nielsen L, Finocchietti S, et al. Age interactions on pain sensitization in patients with severe knee osteoarthritis and controls. *Clin J Pain*. 2017;33:1081–1087.
20. Hermans L, Van Oosterwijck J, Goubert D, et al. Inventory of personal factors influencing conditioned pain modulation in healthy people: a systematic literature review. *Pain Pract*. 2016;16:758–769.
21. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health*. 2014;72:39.
22. The GRADE Working Group. GRADE. Available at: http://www.gradeworkinggroup.org. Accessed October 10, 2017.
23. 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.
24. Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. Outpatient intravenous ketamine for the treatment of complex regional pain syndrome: a double-blind placebo controlled study. *Pain*. 2009;147:107–115.
25. 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.
26. 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.
27. 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.
28. 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.
29. Mitchell AC, Fallon MT. A single infusion of intravenous ketamine improves pain relief in patients with critical limb ischaemia: results of a double blind randomised controlled trial. *Pain*. 2002;97:275–281.
30. Yoon SY, Oh J. Neuropathic cancer pain: prevalence, pathophysiology, and management. *Korean J Intern Med*. 2018;33:1058–1069.
31. Naleschinski D, Baron R. Complex regional pain syndrome type I: neuropathic or not? *Curr Pain Headache Rep*. 2010;14:196–202.
32. Rothstein HR, Sutton AJ, Borenstein M. Software for publication bias. In: Borenstein M, ed. *Publication Bias in Meta-Analysis. Prevention, Assessment and Adjustments*. Chichester, UK: John Wiley & Sons, Ltd; 2006:193–220.
33. Zhao J, Wang Y, Wang D. The effect of ketamine infusion in the treatment of complex regional pain syndrome: a systemic review and meta-analysis. *Curr Pain Headache Rep*. 2018;22:E257.
34. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain*. 1991;44:293–299.
35. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. *Clin Pharmacokinet*. 2016;55:1059–1077.
36. Carr DB, Goudas LC, Balk EM, Bloch R, Ioannidis JPA, Lau J. Evidence report on the treatment of pain in cancer patients. *J Natl Cancer Inst Monographs*. 2004;2004:23–31.

37. Stanton-Hicks MD, Burton AW, Bruehl SP, et al. An updated interdisciplinary clinical pathway for CRPS: report of an expert panel. *Pain Pract.* 2002;2:1–16.
38. McNicol E, Strassels S, Goudas L, Lau J, Carr D. Nonsteroidal anti-inflammatory drugs, alone or combined with opioids, for cancer pain: a systematic review. *J Clin Oncol.* 2004;22:1975–1992.
39. Mailis A, Furlan A. Sympathectomy for neuropathic pain. Mailis-Gagnon A, ed. *Cochrane Database Syst Rev*. 2003;8:CD002918.
40. Finnerup NB, Haroutounian S, Kamerman P, et al. Neuropathic pain: an updated grading system for research and clinical practice. *Pain*. 2016;157:1599–1606.
41. Kosek E, Cohen M, Baron R, et al. Do we need a third mechanistic descriptor for chronic pain states? *Pain*. 2016;157:1382–1386.
42. Pomeroy JL, Marmura MJ, Nahas SJ, Viscusi ER. Ketamine Infusions for treatment refractory headache. *Headache.* 2017;57:276–282.
43. Schwenk ES, Dayan AC, Rangavajjula A, et al. Ketamine for refractory headache: a retrospective analysis. *Reg Anesth Pain Med.* 2018;43:875–879.
44. Max M. World Health Organization cancer pain relief program: network news. *J Pain Symptom Manage*. 1986;1:53–57.
45. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. *Lancet Neurol.* 2015;14:162–173.
46. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Pain, Palliative and Supportive Care Group, ed. *Cochrane Database Syst Rev*. 2012;83:CD008943.
47. Schwenk ES, Viscusi ER, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. *Reg Anesth Pain Med*. 2018;43:456–466.
48. Schwenk ES, Goldberg SF, Patel RD, et al. Adverse drug effects and preoperative medication factors related to perioperative low-dose Ketamine infusions. *Reg Anesth Pain Med.* 2016;41:482–487.
49. Maher DP, Chen L, Mao J. Intravenous Ketamine infusions for neuropathic pain management: a promising therapy in need of optimization. *Anesth Analg*. 2017;124:661–674.
50. Kvarnström A, Karlsten R, Quiding H, Emanuelsson BM, Gordh T. The effectiveness of intravenous ketamine and lidocaine on peripheral neuropathic pain. *Acta Anaesthesiol Scand.* 2003;47:868–877.
51. Persson J, Hasselström J, Wiklund B, Heller A, Svensson JO, Gustafsson LL. The analgesic effect of racemic ketamine in patients with chronic ischemic pain due to lower extremity arteriosclerosis obliterans. *Acta Anaesthesiol Scand*. 1998;42:750–758.
52. Leung A, Wallace MS, Ridgeway B, Yaksh T. Concentration-effect relationship of intravenous alfentanil and ketamine on peripheral neurosensory thresholds, allodynia and hyperalgesia of neuropathic pain. *Pain*. 2001;91:177–187.
53. Hróbjartsson A, Thomsen AS, Emanuelsson F, et al. Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors. *BMJ*. 2012;344:e1119.
54. Savović J, Jones HE, Altman DG, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. *Ann Intern Med.* 2012;157:429–438.
55. Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *BMJ*. 2008;336:601–605.
56. Holmes RD, Tiwari AK, Kennedy JL. Mechanisms of the placebo effect in pain and psychiatric disorders. *Pharmacogenomics J.* 2016;16:491–500.
57. Kahan BC, Cro S, Doré CJ, et al. Reducing bias in open-label trials where blinded outcome assessment is not feasible: strategies from two randomised trials. *Trials*. 2014;15:456.
58. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9:105–121.
59. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2003;106:337–345.