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Ketamine for Chronic Non-Cancer Pain: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

ACOEM	American College of Occupational and Environmental Medicine
AGREE	Appraisal of Guidelines for Research and Development
AAPM	American Academy of Pain Medicine
AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
ASA	American Society of Anesthesiologists
ASRM	American Society of Regional Anesthesia and Pain Medicine
CRPS	Complex regional pain syndrome
ED	Emergency department
IV	Intravenous
NMDA	*N*-methyl-D-aspartate
RCT	Randomized controlled trial
SR	Systematic review
VAS	Visual analog scale

Context and Policy Issues

In Canada, about one in five adults older than 18 years of age live with chronic pain.[1] Pain can be sub-defined by three main biological mechanisms: 1) Nociceptive pain (from damage to body tissue, as in injury, disease or inflammation); 2) Neuropathic pain (from direct damage of the nervous system); and 3) Nociplastic pain (from a change in sensory neurons function).[1] Chronic pain is associated with significant emotional distress, like anxiety, anger, frustration and depression, and is recognized by the World Health Organization as a disease by itself listed in the International Classification of Disease version 11.[1] Treatment and management of chronic pain are complex and difficult, involving multiple interventions, including pharmacological and psychological interventions.[1] Pharmacological interventions considered for chronic pain include nonopioid analgesics (e.g., nonsteroidal anti-inflammatory drugs, acetaminophen), antidepressants, antiepileptic drugs, other adjuvant medications (e.g., topical agents, cannabis and cannabinoids), opioid, and infusion therapies (e.g., ketamine, lidocaine).[2]

Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, has been approved and primarily used as an anesthetic induction agent in doses ranging between 1 and 4.5 mg/kg.[3] As it also interacts with other receptors, ketamine has been explored for other indications such as depressive disorders, suicidal ideation, substance-use disorders, anxiety disorders, refractory status epilepticus, bronchial asthma exacerbations, and pain management.[4] In hospital and emergency department, ketamine has been used for pain management of acute conditions such as burns, trauma, or post-operative pain.[2] Recently, intravenous (IV) ketamine infusions has been increasingly used as a treatment option for acute pain as well as chronic non-cancer pain such as complex regional pain syndrome

(CRPS), neuropathic pain, and other refractory chronic pain conditions.[2] Despite potential opportunities of ketamine for numerous indications, the use of ketamine is known to be associated with psychotomimetic effects such as euphoria, dysphoria, psychomotor retardation, hallucinations, vivid dreams, and nightmares, as common side effects. Given the availability of ketamine of different formulations and its potential opportunities in pain management, there is a need to determine its benefits and risks in the treatment of chronic pain.

The aim of this report is to review the evidence regarding the clinical effectiveness and cost-effectiveness of ketamine for treating chronic non-cancer pain in adults. This report also aims to review the evidence-based guidelines regarding the use of ketamine for chronic non-cancer pain.

Research Questions

1. What is the clinical effectiveness of ketamine for treating chronic non-cancer pain in adults?
2. What is the cost-effectiveness of ketamine for treating chronic non-cancer pain in adults?
3. What are the evidence-based guidelines for the use of ketamine for chronic non-cancer pain?

Key Findings

This review included two systematic reviews and two randomized controlled trials regarding the clinical effectiveness of ketamine for treating of patients with chronic non-cancer pain, and two guidelines regarding the use of ketamine for this population. No studies regarding the cost-effectiveness of ketamine were identified.

Based on findings of one systematic review compared to placebo, intravenous ketamine infusions significantly reduced pain scores, and had significantly higher positive response rates within two weeks of follow-up, but with significantly higher incidence of nausea, vomiting and psychomimetic effects, including delusion, hallucination and dysphoria. The positive short-term effect of ketamine was independent to dose, types of chronic pain or adjunct medication.

Another systematic review found that topical ketamine and oral ketamine were not efficacious for treatment of neuropathic pain, while IV ketamine was more effective in pain improvement for various conditions of chronic neuropathic pain when compared to placebo.

One included randomized controlled trial found that intravenous ketamine significantly reduced pain compared to placebo in chronic pain patients who experienced acute exacerbation within 60 minutes of treatment, but the ketamine analgesic effect was not observed at 24 to 48 hours of follow-up. Incidence of adverse events was significantly higher in the ketamine group than that in the placebo group.

Another included randomized controlled trial found that intraoperative ketamine infusion significantly reduced immediate postoperative intravenous morphine consumption after spinal fusion surgery in chronic pain patients compared to placebo, with no significant differences between treatment groups regarding acute pain (two to 24 hours postoperative), persistent pain (six months postoperative), and adverse events.

One included guideline does not recommend intravenous ketamine infusion for various chronic pain conditions such as chronic persistent pain, complex regional pain syndrome, fibromyalgia and neuropathic pain due to insufficient evidence. The other guideline also did not find any strong evidence for intravenous ketamine infusion for immediate pain improvement in those pain conditions.

Evidence in this review suggests that intravenous ketamine could only provide short-term pain relief in patients with chronic non-cancer pain, with increased risks of some adverse events such as nausea, vomiting and psychotomimetic effects.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were ketamine and chronic pain. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and April 27, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults (18 years and older) with chronic non-cancer pain conditions (e.g. neuropathic pain, degenerative disc disease, complex regional pain syndrome)
Intervention	Any formulation of ketamine (either as a single ingredient or in combination with other ingredients), used alone or as an add-on to existing pain pharmacotherapy
Comparator	Other pharmacological treatments: • tricyclic antidepressants (e.g., amitriptyline) • serotonin norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine) • any formulation of nonsteroidal anti-inflammatory drugs (e.g., diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin) • opiate agonists (e.g., codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, methadone, morphine, opium, oxycodone, oxymorphone, remifentanil, sufentanil, tapentadol, tramadol) • antiepileptic (e.g. topiramate) • gabapentinoids (e.g. gabapentin, pregabalin) • botulinum toxin • cortisone injections • topical lidocaine

	• topical capsaicin • placebo (i.e., no active treatment)
Outcomes	Q1: Clinical effectiveness (e.g., therapeutic response in signs and symptoms, pain relief, functional status, reduction in the use of opioid analgesics) and safety (e.g., morbidity, mortality, adverse drug reaction) Q2: Cost-effectiveness (e.g., cost per quality adjusted life years, cost per patient adverse event avoided, cost per clinical outcome) Q3: Recommendations on use for chronic non cancer pain and its place in therapy
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, economic evaluations, non-randomized studies, and evidence-based guidelines

RICE = rest, ice, compression, and elevation.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2015. Systematic reviews (SRs) in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included SRs were critically appraised by one reviewer using A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2) checklist[5] The critical appraisal checklist of Downs and Black was used to assess the quality of the included randomized controlled trials (RCTs).[6] The quality of the included evidence-based guideline was assessed using the Appraisal of Guidelines for Research and Development (AGREE) II instrument.[7] Summary scores were not calculated for the included studies; rather, the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 549 citations were identified in the literature search. Following screening of titles and abstracts, 531 citations were excluded and 18 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of the 19 potentially relevant articles, 13 publications were excluded for various reasons, while six publications met the inclusion criteria and were included in this report. These comprised two SRs, two primary studies (both RCTs), and two guidelines. Appendix 1 presents the PRISMA flowchart[8] of the study selection.

Summary of Study Characteristics

The detailed characteristics of the included SRs,[9,10] (Table 2) primary studies[11,12] (Table 3) and the ASRM/AAPM/ASA (American Society of Regional Anesthesia and Pain Medicine, American Academy of Pain Medicine, American Society of Anesthesiologists) and the ACOEM (American College of Occupational and Environmental Medicine) guidelines[13,14] (Table 4) are presented in Appendix 2.

Study Design

Both included SRs[9,10] were comprised of only RCTs. One SR[9] performed literature searches from multiple databases from database inception to December 16, 2017, and used the Cochrane risk of bias instrument to assess the methodological quality of the included RCTs. The other SR[10] only searched the PubMed database for its literature search from 1966 to April 2017, and did not assess the methodological quality of the included RCTs. One SR[9] synthesized data using meta-analysis, while the other SR[10] narratively described the findings of its included studies.

Both included primary studies[11,12] were single-centre, blinded, parallel RCTs, with sample size calculated *a priori*. Data were analyzed using the modified intention-to-treat approach in both RCTs.

Both included guidelines[13,14] were developed by multidisciplinary guideline committees in USA. The committees included healthcare professionals who were directly or indirectly involved in the care of patients with chronic pain. The guidelines used systematic methods to search for, select, and synthesize evidence. The recommendations were evidence-based, and consensus based. The ASRM/AAPM/ASA guideline[13] graded its recommendations from A (strongly recommended) to D (not recommended) or as I (for insufficient), with the level of evidence rated as high, moderate or low. The ACOEM guideline[14] categorized its recommendations from “strongly recommended” to “strongly not recommended” based on the confidence levels of study design.

Country of Origin

Both included SRs were conducted by authors from USA.[9,10] The included RCTs were conducted by authors from USA[11] and Denmark.[12] Both included guidelines were conducted by authors from USA.[13,14]

Patient Population

One SR[9] included seven RCTs (N = 211; ranging from 19 to 60 participants) having adult patients with chronic pain for more than three months, including phantom limb pain, post-spinal cord injury pain, complex regional pain syndrome (CRPS) types I and II, cancer related pain, fibromyalgia, and ischemic limb pain. The SR[9] did not include data of the trial involving cancer related pain in the meta-analysis of primary endpoint due to lack of standard deviation. The other SR[10] included 21 RCTs (N = 456; ranging from 8 to 92 participants) evaluating ketamine treatment in adult patients with neuropathic pain. The age of patients was reported in one SR[9] (median [range] = 48 years [41.9 to 71 years]), but not in the other.[10]

One RCT[11] included adult patients (N = 97; mean age = 46.5 years) presented to the emergency department (ED) with acute exacerbation from chronic pain. The other RCT[12] included adult patients (N = 147; mean age = 56 years) with chronic pain underwent lumbar fusion surgery.

The target population was patients with chronic pain considered for ketamine infusions in the ASRM/AAPM/ASA guideline,[13] and working-age adults who have chronic pain in the ACOEM guideline.[14] The intended users of the guidelines were all healthcare providers .

Interventions and Comparators

One SR[9] included RCTs that compared intravenous (IV) ketamine with placebo. The median dose of ketamine was 0.35 mg/kg (range, 0.23 to 0.6 mg/kg), which was infused continuously or intermittently. The median duration of infusion was five hours (range, 0.5 to 100 hours). The median number of days of infusion was one day (range, 1 to 10 days).

The other SR[10] included trials investigating the efficacy of N-methyl-D-aspartate (NMDA) receptor antagonists for neuropathic pain, of which 21 trials involving ketamine that compared ketamine of different formulations (three oral, five topical and 13 IV trials) with placebo. The oral dose was 30 mg three times a day, 0.5 mg/kg every 6 hours for one week, or 20 mg increasing to maximum 100 mg. Topical dose varied from 1% to 10% ketamine in ointment or cream. The IV ketamine dose ranged between 0.2 to 0.6 mg/kg/hour, infusing continuously or intermittently. Treatment duration was not reported in the SR for every trial.

One included RCT[11] had three treatment groups that compared IV ketamine 0.5 mg/kg, IV ketamine 0.25 mg/kg and placebo. Infusion time was 20 minutes.

The other included RCT[12] compared IV ketamine with placebo. Bolus dose was 0.5 mg/kg, and infusion dose was 0.25 mg/kg/hour. Infusion was discontinued when surgery was completed.

The interventions and practices considered in the ASRM/AAPM/ASA guideline[13] was ketamine infusions for chronic pain, while in the ACOEM guideline[14] was various types of management of patients with chronic pain of specific disorders (i.e., chronic persistent pain, CRPS, fibromyalgia, and neuropathic pain).

Outcomes

The primary outcome considered in both SRs[9,10] was pain. Visual analog scale (VAS) either on 0 to 10 scale (0 = no pain and 10 = worst pain) [9] or 100-mm scale (0 = no pain and 100 = worst pain) was used to assess pain.[10] Other scales included the McGill Pain Questionnaire, and sensory testing using both light stroking (with a small brush rated as normal or abnormal sensation) and quantitative method.[10] The secondary outcomes considered in one SR[9] were adverse events, and positive response (defined as reduction in pain scores ≥ 30% or ≥ 50% from baseline to 48 hours or longer after intervention).

The outcomes considered in one included RCT[11] were pain reduction of at least 20 mm in 100-mm of the visual analogue scale (VAS), and adverse events. Pain and adverse events were assessed at 20, 40 and 60 minutes. Patients were followed up by telephone at 24 to 48 hours following discharge from the ED to assess persistent or recurrent pain using a numeric rating scale (0 to 10; 0 = no pain and 10 = worst pain).

In the other included RCT,[12] the outcomes were cumulated patient-controlled analgesia IV morphine consumption from 0 to 24 hours after surgery, pain at rest and during mobilization from recumbent position to sitting bedside, and adverse events (i.e., nausea and sedation). Pain was evaluated using 100-mm VAS at 2, 6, 12, 18, and 24 hours after surgery. Nausea and sedation were assessed from 0 to 24 hours using a verbal rating scale with none, light, moderate, and severe (0 to 3). Persistent pain was evaluated at 6 months using five written questionnaires: DaneSpine Questionnaire, Oswestry Low Back Pain Disability Questionnaire, Short Form 36 survey, EuroQoL 5D, and Douleur Neuropathique 4 Questionnaire.

The ASRM/AAPM/ASA guideline[13] had recommendations for ketamine infusions for chronic pain, in terms of indications, dosing range and dose response, relative contraindications, role of oral NMDA receptor antagonist as follow-on treatment, preinfusion tests, positive response, and personnel and monitoring. The ACOEM guideline[14] had recommendations on the evaluation and treatment of working-age adults who have chronic pain, focusing on specific disorders such as chronic persistent pain, CRPS, fibromyalgia, and neuropathic pain. Both guidelines formulated its recommendations for ketamine indications for treatment of non-cancer chronic pain based on on clinical evidence for benefits and harms.

Summary of Critical Appraisal

The detailed quality assessments of the included SRs,[9,10] (Table 5) RCTs,[11,12] (Table 6) and guidelines[13,14] (Table 7) are presented in Appendix 3.

The SR[9] with meta-analysis of IV ketamine for chronic pain fulfilled more items of the AMSTAR checklist for methodological quality assessment than the narrative SR[10] on NMDAR for neuropathic pain. The SR[9] on IV ketamine had a protocol published prior to the conduct of the review, and the review authors used a comprehensive literature search strategy, performed study selection and data extraction in duplicate, used appropriate technique to assess the risk of bias of the included studies, and reported conflict of interest as well as the source of funding received for conducting the review, while the other SR[10] did not. The authors of both SRs[9,10] provided appropriate research questions, explanations for selection of the study designs for inclusion in the review, and described the included studies in adequate details, but did not provide a list of excluded studies, and the sources of funding of the included studies. Overall, one SR[9] was of high quality, and the other[10] was of low quality.

Both included RCTs[11,12] were explicit in reporting (i.e., clearly described the objective of the study, the main outcomes, the characteristics of the participants, the interventions, and the main findings of the study). The authors in both RCTs provided estimates of the random variability (e.g., standard deviation or 95% confidence interval) in the data of the main outcome, and reported important adverse events associated with the treatments. Both RCTs had limitations in terms of external validity as it was unclear if the participants were representative of the entire population from which they were recruited, and whether the treatment settings were representative of the treatment received by the majority of the patients. As both were well conducted RCTs, they fulfilled all items for internal validity such as randomization, allocation concealment, blinding, appropriate statistical analysis, appropriate tools or methods to measure the main outcomes, balance in characteristics of patients in different intervention groups, and sample size calculation.

Both included guidelines[13,14] were explicit in terms of scope and purpose (i.e., objectives, health questions and populations), and had clear presentation (i.e., specific and unambiguous recommendations, different options for management of the condition or health issue, and easy to find key recommendations). In terms of stakeholder involvement, both of the guidelines clearly defined target users and the development groups included individuals from all relevant professional groups; however, it was unclear if they sought the views and preferences of the target populations. For rigour of development, both guidelines explicitly reported details of systematic searches for evidence, criteria for selecting evidence, strengths and limitations of the body of evidence, methods of formulating the recommendations, health benefits, side effects, and risks in formulating the recommendations, and were peer-reviewed prior to publication. The guidelines provided a procedure for updating. For applicability, the guidelines were explicit in terms of facilitators

and barriers to application, advice and/or tools on how the recommendations can be put into practice, resource (cost) implications, and monitoring and or auditing criteria. For editorial independence, it was unclear if the funding bodies had any influence on the content of the guidelines. The competing interests of the guideline development group members were reported. Overall, the included guideline were of high methodological quality.

Summary of Findings

The main findings and authors' conclusions of the SRs,[9,10] (Table 8), RCTs,[11,12] (Table 9), and guidelines[13,14] (Table 10) are presented in Appendix 4.

Clinical Effectiveness of Ketamine

Pain reduction

The meta-analysis of data from six RCTs included in the SR[9] showed that IV ketamine infusions significantly reduced pain scores between 48 hours and two weeks after treatment compared to placebo in patients with various chronic pain. Subgroup analyses revealed that there were no significant differences in terms of dose response (i.e., high versus low), types of pain (neuropathic versus non-neuropathic; CRPS versus without CRPS), and adjunct medication (with versus without). Subgroup analysis regarding different time points revealed that administration of IV ketamine resulted in a significant reduction in pain scores when compared to placebo at 2 weeks after treatment, but not at longer time points.

In the SR[10] of ketamine for the treatment of chronic neuropathic pain, only one of five included RCTs showed that ketamine cream was efficacious for neuropathic pain relief on the limbs of patients with CRPS, while the other studies showed no significant difference in pain scores for ketamine versus placebo. Of three RCTs with oral ketamine included in the SR, only one small RCT (N = 42; 14 participants per group) showed that ketamine alone significantly improved pain in patients with chronic neuropathic pain compared with both methadone, or combination of methadone and ketamine groups. All 13 RCTs with IV ketamine showed a significant improvement in pain in various conditions, including chronic neuropathic pain, CRPS, chronic phantom limb pain, peripheral nerve injury, and spinal cord injury. The duration of ketamine effect was not reported in this SR.

One included RCT[12] investigating the effect of intraoperative IV ketamine in patients with chronic pain underwent lumbar fusion surgery found that IV ketamine had no significant difference in pain scores compared with placebo during mobilization or at rest when assessed at 2 to 24 hours postoperatively. There was also no significant difference in persistent pain between IV ketamine and placebo assessed six months after surgery.

Positive response

In the findings of the SR[9] investigating the efficacy of IV ketamine for chronic pain, meta-analysis of data from three included RCTs showed that patients treated with IV ketamine compared with placebo achieved higher positive response rate, defined as reduction in pain scores by ≥ 30% or ≥ 50% from baseline to 48 hours or longer after intervention.

In one included RCT,[11] IV ketamine for treatment of acute exacerbation from chronic pain resulted in a significantly higher positive response rate compared to placebo within 60 minutes of treatment. Positive response was defined as VAS pain reduction by 20 mm over the course of the study. There was no significant difference in pain relief between high (0.5

mg/kg) and low (0.25 mg/kg) ketamine doses. During follow-up at 24 to 48 hours, there was no significant difference in pain scores between three groups.

IV morphine consumption

One included RCT[12] investigating the effect of intraoperative IV ketamine in patients with chronic pain underwent lumbar fusion surgery found that IV ketamine was associated with a significant reduction in cumulated patient-controlled analgesia IV morphine consumption from 0 to 24 hours after surgery.

Adverse events

From the findings of one SR,[9] IV ketamine was associated with significantly higher rates of nausea, vomiting and psychotomimetic effects (e.g., delusion, hallucination and dysphoria) compared to placebo. There were no significant differences between IV ketamine and placebo for headache, tiredness and sedation.

One included RCT[11] examining IV ketamine for treatment of acute exacerbation for chronic pain found that IV ketamine at both doses (0.5 mg/kg and 0.25 mg/kg) was associated with significantly higher rates of adverse events compared with placebo (40% and 40% versus 3%). Adverse events associated with IV ketamine was nausea, dizziness, hallucination, anxiety, palpitation and dysphoria. Dizziness (3%) was the only adverse event found in the placebo group.

One included RCT[12] investigating the effect of intraoperative IV ketamine in patients with chronic pain who underwent lumbar fusion surgery found no significant differences between ketamine and placebo groups from 2 to 24 hours postoperative in terms of nausea, vomiting, hallucinations and nightmares. Sedation was significantly reduced at 6 hours and 24 hours postoperatively in the ketamine groups compared to placebo.

Cost-effectiveness of Ketamine

No studies regarding the cost-effectiveness of ketamine for treating chronic non-cancer pain in adults were identified; therefore, no summary can be provided.

Guidelines Regarding the Use of Ketamine for Chronic Non-cancer Pain

The ASRA/AAPM/ASA guideline[13] on the use of IV ketamine infusion for chronic pain provided consensus statements that there is weak evidence to support short-term improvement for spinal cord injury (Grade C, low certainty), that there is moderate evidence to support improvement for up to 12 weeks in CRPS (Grade B, low to moderate certainty), and that there is weak or no evidence for immediate improvement in other pain conditions (e.g., mixed neuropathic pain, fibromyalgia, headache and spinal pain) (Grade D, low certainty).

The ACOAM guideline[14] does not recommend IV ketamine infusion for chronic persistent pain, CRPS, fibromyalgia and neuropathic pain due to insufficient evidence.

Limitations

There were several limitations within the SRs. Many of the included RCTs in the SR had small number of patients enrolled (median sample size of 24 participants in one SR[9] and 17 in the other SR[10]) Patient populations were heterogeneous in terms of types of chronic pain, and the clinically meaningful reduction in pain was not defined for each patient population. There was also wide variation in patient selection, dosing, and monitoring among studies. The significant reduction in pain scores may therefore not truly reflect the

clinical effect. Quality of life, an important component of chronic pain management, was not assessed in addition to pain reduction.

Both included RCTs[11,12] did not use a validated tool, such as the Common Terminology Criteria, to recognize the adverse events.

There were no cost-effectiveness studies that could be identified in this review. There was no evidence on the effectiveness of ketamine compared to other pharmacological treatments.

The ASRA/AAPM/ASA guideline[13] did not provided explicit recommendations regarding the use of IV ketamine infusion for chronic pain.

Based on the study findings and the guideline recommendations, there was low evidence and weak recommendation for the use of ketamine in patients with chronic pain. The effect of IV ketamine in improving pain is limited and may vary widely among chronic pain patients. These limitations would be also applicable to the Canadian context.

Conclusions and Implications for Decision or Policy Making

This review included two SRs[9,10] and two RCTs,[11,12] regarding the clinical effectiveness of ketamine for treating patients with chronic non-cancer pain, and two guidelines[13,14] regarding the use of ketamine for this population.

Based on findings of one SR[9] compared to placebo, IV ketamine infusions significantly reduced pain scores, and had significantly higher positive response rates for short-term period (i.e., between 48 hours and two weeks), but not at a longer period (i.e., four to 12 weeks) of follow-up. The short-term effect of ketamine was independent to dose, types of chronic pain or adjunct medication. IV ketamine was associated with a significantly higher incidence of nausea, vomiting and psychomimetic effects (e.g., delusion, hallucination and dysphoria).

Based on the findings of another SR,[10] topical ketamine and oral ketamine were not efficacious for treatment of neuropathic pain. IV ketamine, on the other hand, was effective in pain improvement for various conditions of chronic neuropathic pain.

One RCT[11] found that IV ketamine significantly reduced acute pain compared to placebo within 60 minutes of treatment in chronic pain patient experienced acute exacerbation. Incidence of adverse events was significantly higher in the ketamine group than that in the placebo group. However, there was no significant difference in pain scores between treatment groups at 24 to 48 hours of follow-up.

One RCT[12] found that intraoperative ketamine infusion significantly reduced immediate postoperative IV morphine consumption after spinal fusion surgery in chronic pain patients. However, there were no significant differences between treatment groups regarding acute pain (two to 24 hours postoperative), persistent pain (six months postoperative), and adverse events (nausea, vomiting, hallucinations, or nightmares).

One included guideline[14] does not recommend IV ketamine infusion for various chronic pain conditions such as chronic persistent pain, CRPS, fibromyalgia and neuropathic pain due to insufficient evidence. The other guideline[13] found no high-quality evidence to support ketamine infusion for immediate pain improvement in those pain conditions.

Taken together, evidence in this review suggests that IV ketamine compared to placebo could only provide significant short-term pain relief in patients with chronic non-cancer pain, with increased risks of some adverse events such as nausea, vomiting and psychotomimetic effects. Future well-controlled studies with larger population and longer follow-ups are needed to determine the optimal treatment protocol of ketamine for specific type of chronic pain. Economic studies are also warranted to determine the cost-effectiveness of ketamine for treating chronic non-cancer pain.

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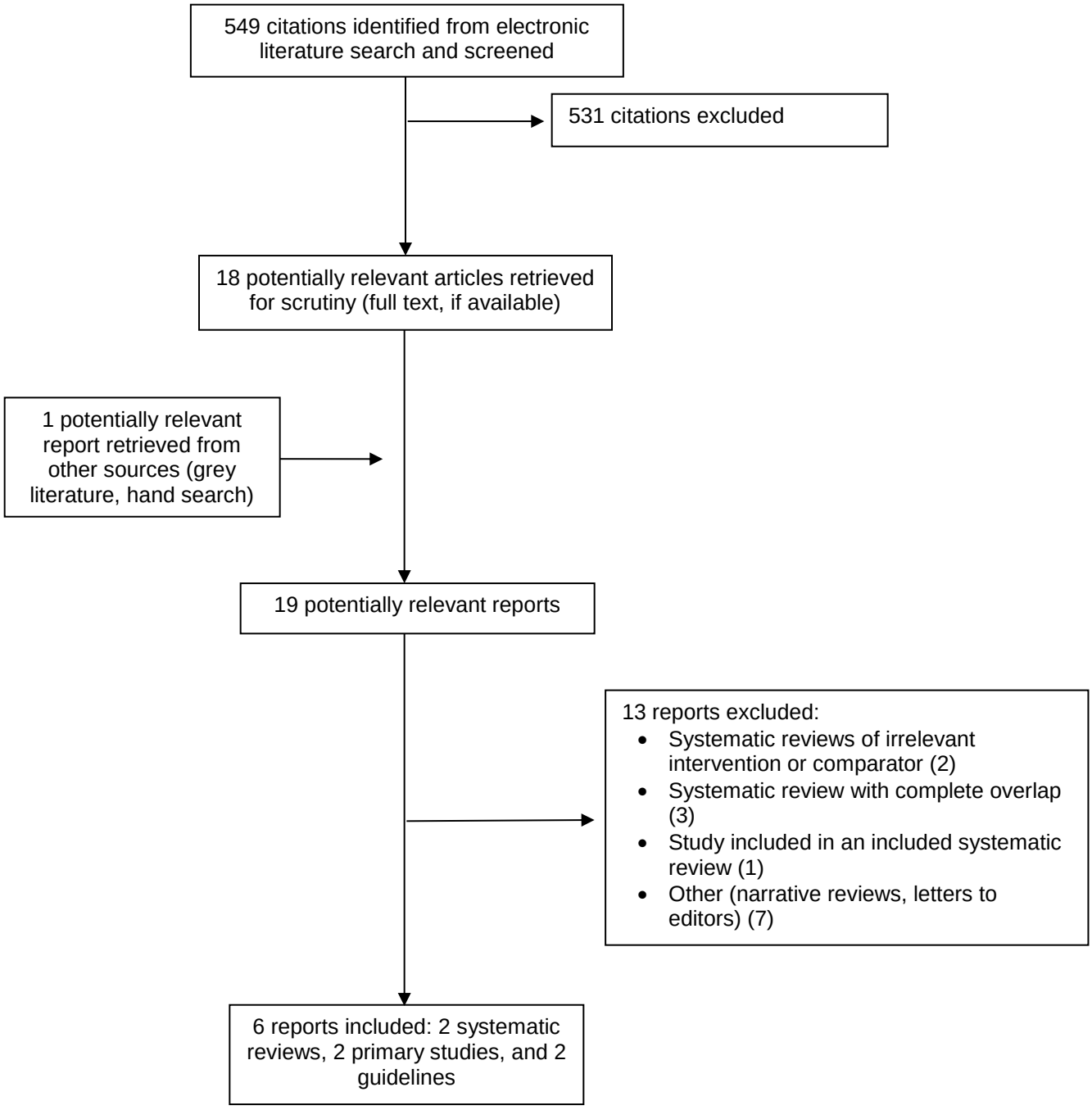
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions and comparators	Outcomes
Orhurhu et al., 2019[9] USA Funding: US Department of Defense	Objective: To investigate the effectiveness of IV ketamine for pain relief in chronic pain conditions. Total 7 RCTs (n = 211) Quality assessment tool: Cochrane risk-of-bias instrument Quality of evidence tool: GRADE Databases: MEDLINE, Embase, Google Scholar, and clinical trials website from inception to December 16, 2017. Data analysis: Random-effects meta-analysis; analysis of pre-specified subgroups for primary outcome (i.e., dose-response, types of pain, with or without adjunct medications, different time points).	Adult patients (≥ 18 years) with chronic pain for ≥ 3 months Median (range) age: 48 years (range, 41.9 to 71 years) Types of chronic pain: phantom limb pain, post-spinal cord injury pain, CRPS types I and II, cancer related pain[a], fibromyalgia and ischemic limb pain	Intervention: IV ketamine (n = 108) Comparator: Placebo (n = 103) Median (range) duration of infusion: 5 hours (range, 0.5 to 100 hours) Median (range) number of days: 1 day (1 to 10 days) Median (range) dose: 0.35 mg/kg (0.23 to 0.6 mg/kg); continuous or intermittent	Primary outcome: – Pain scores (VAS on 0 to 10 scale) Secondary outcomes: – Positive response (reduction in pain scores by ≥ 30% or ≥ 50% from baseline to 48 hours or longer after intervention) – Adverse events
Aiyer et al., 2018[10] USA Funding: Not reported	Objective: To investigate the efficacy of N-methyl-D-aspartate receptor (NMDAR) antagonists for neuropathic pain. Total: 58 RCTs; 21 RCTs involving ketamine Quality assessment tool: None Databases: PubMed from 1966 to April 2017	Adult patients (≥ 18 years) with neuropathic pain Mean age: Not reported	Intervention: Ketamine (3 oral, 5 topical, and 13 IV trials) Comparator: Placebo Oral dose: 30 mg three times a day; 0.5 mg/kg every 6 hours for one week; 20 mg increasing to maximum 100mg Topical dose: 1% to 10% ketamine in ointment or cream	Pain Scales: – VAS (100-mm; 0 = no pain and 100 = worst imaginable pain) – McGill pain questionnaire – NRS (0 to 10; 0 = no pain to 10 = worst pain imaginable) – Light stroking with a small brush rated as a normal or

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions and comparators	Outcomes
	Data analysis: Narrative synthesis		IV dose: 0.2 to 0.6 mg/kg/hour; continuous or intermittent Treatment duration: Not reported in every study	abnormal sensation – Quantitative sensory testing

CRPS = complex regional pain syndrome; GRADE = Guidelines of Recommendations, Assessment, Development, and Evaluation; IV = intravenous; NMDAR = N-methyl-D-aspartate receptor; NRS = numerical rating scale; RCTs = randomized controlled trials; SR = systematic review; VAS = visual analog scale.

[a] A small trial of 20 patients with cancer pain refractory to opioids was included in the SR; however, its finding was not included in the meta-analysis of primary outcome.

Table 3: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
Lumanauw et al., 2019[11] USA Funding: Grant from the Air Force Research Laboratories	Single-centre, double blinded, parallel, 1:1:1 RCT Sample size calculation: Yes; number of patients was reached ITT: Yes; modified ITT Statistical analysis: Appropriate	Adult patients with chronic pain presented to ED with acute exacerbation Mean (SD) age: 46.5 (12.6) years % Male: 41 Mean (SD) baseline VAS: 91.9 (8.9) mm Types of pain: Mostly musculoskeletal pain (70%) and radicular pain (14.4%) Duration of pain: 3 months to > 5 years Pain medications used at home: varied from one drug to multiple types	IV ketamine – 0.25 mg/kg (n = 35) – 0.5 mg/kg (n = 30) Infusion time: 20 minutes	Placebo (n = 32)	– Pain reduction at least 20 mm in VAS (VAS; 100 mm) – Adverse events Pain assessment: at 20, 40, or 60 min Rescue therapy with additional analgesic medication was allowed at the discretion of the treating physician. Follow-up: By telephone at 24 to 48 hours following discharge from the ED to assess for persistence or recurrence pain using numeric rating scale for pain (0 to 10, where 0 = no pain and 10 = worst pain)

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
Nielsen et al., 2017[12] Denmark Funding: Grant from university hospital	Single-centre, triple blinded, parallel, 1:1 RCT Sample size calculation: Yes; number of patients was reached ITT: Yes; modified ITT Statistical analysis: Appropriate	Adult patients with chronic pain underwent lumbar fusion surgery Mean (SD) age: 56 (13.5) years Male: 50% Mean (SD) baseline VAS at rest: 55 (24) Mean (SD) baseline VAS at mobilization: 68 (21) Pain medications used at home: Opioids (morphine, tramadol, oxycodone, ketobemidone, fentanyl, buprenorphine)	IV ketamine (bolus 0.5 mg/kg and infusion 0.25 mg/kg/h) Before surgery, all patients received usual dose of opioids and oral paracetamol 1,000 mg. Immediate after induction of anesthesia, patients received study medication according to randomization. Infusion was discontinued at last suture of the skin. Postoperative pain treatment during the first 24 hours: 1,000 mg paracetamol very 6 hours, starting 2 hours postoperatively, and patients' usual opioids. All patients received IV patient-controlled analgesia (PCA) with morphine (bolus 2.5 mg, lock-out time 5 minutes, and no background infusion).	Placebo	– Cumulated PCA IV morphine consumption (from 0 to 24 hours after surgery) – Pain at rest and during mobilization from recumbent position to sitting bedside (100-mm VAS) evaluated at 2, 6, 12, 18 and 24 hours after surgery – Adverse effects from 0 to 24 hours: nausea and sedation (VRS: none, light, moderate, and severe [0 to 3]) – Persistent pain at 6 months assessed using five written questionnaires: DaneSpine Questionnaire[a], Oswestry Low Back Pain Disability Questionnaire[b], Short Form 36 survey[c], EuroQoL 5D[d], and Douleur Neuropathique 4 Questionnaire[e].

ED = emergency department; ITT = intension-to-treat; IV = intravenous; PCA = patient-controlled analgesia; RCT = randomized controlled trial; SD = standard deviation; VAS = visual analog scale; VRS = verbal rating scale.

[a] The DaneSpine Questionnaire included questions about demographic data, back and leg pain (VAS 0 to 100 mm), back and leg pain compared with preoperative pain levels (0 = no pain and 5 = worse), use of analgesics, duration of sick leave, working capacity, and contentment with the results of the operation.

[b] The Oswestry Low Back Pain Disability Questionnaire is summarized as an Oswestry Index Score with a range of 0 to 100: 0 to 20 for minimal disability; 21 to 40 for moderate disability; 41 to 60 for severe disability; 61 to 80 for crippling back pain; 81 to 100 for bedbound.

[c] The Short Form 36 survey (SF-36) has two summary scores, physical component summary score and mental component summary score. Anytime a cle score is below 50, health status is below average relative to the general Swedish population.

[d] The EuroQoL 5D Questionnaire has 5 questions with a score of 1 to 3; higher score corresponds to severe problems. An index score is calculated from the median of all questions.

[e] The Douleur Neuropathic 4 Questionnaire (DN4) is summarized as one total score. Answering positively to one question adds 1 point. Minimum score is 0 and maximum score is10. A total score ≥ 4 indicates that pain is likely to be neuropathic.

Table 4: Characteristics of Included Guidelines

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users and Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
ASRA/AAPM/ASA, Cohen et al., 2018[13] USA Funding: US government	Intended users: All healthcare professionals involved in the care of patients with chronic pain Target population: Patients with chronic pain considered for ketamine infusions	Ketamine infusions	Clinical efficacy and adverse effects of ketamine infusions for chronic pain.	Systematic methods used to search for evidence, selection and synthesis. A comprehensive review was performed.	Panel members were selected based on expertise in evaluating clinical trials, past research experience, and clinical experience in developing protocols and treating patients with ketamine. Questions were developed and refined by the committee. The answers to the questions were composed based on consensus. Conclusions for each question were graded from A to D or as insufficient,[a] according to the US Preventive Service task force grading of evidence guidelines, with the level of certainty[b] rated as high, moderate or low.	The guideline was peer-reviewed
ACOEM 2017[14] USA Funding: Unclear	Intended users: All healthcare providers Target population: Working-age adults who have chronic pain	General approach to the evaluation and management of patients with chronic pain, with specific disorders (i.e., complex regional pain syndrome,	Examinations of baseline status, diagnostic tests, imaging, physical activity, return to work, medications, physical therapy, injections,	Systematic methods used to search for evidence, selection and synthesis. A comprehensive review of the evidence was performed.	Panels reviewed and modified draft recommendations formulated by the research team. The recommendations were finalized for all clinical questions and were categorized[c] based on the confidence levels for study design.[d] Panel unanimity or	The guideline was peer-reviewed

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users and Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
		fibromyalgia, neuropathic pain), as well as psychological and behavioral aspects of chronic pain.	rehabilitation, psychological evaluations, and behavioral treatment.		consensus was sought when finalizing the recommendations.	

AAPM = American Academy of Pain Medicine; ACOEM = American College of Occupational and Environmental Medicine; ASA = American Society of Anesthesiologists; ASRA = American Society of Regional Anesthesia and Pain Medicine.

[a] Strength of recommendation:

- Grade A: Strongly recommended
- Grade B: Recommended
- Grade C: No recommendation
- Grade D: Not recommended
- Grade I: Insufficient evidence to make a recommendation

[b] Level of certainty of net benefit:

- High: The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations.
- Moderate: The available evidence is sufficient to determine the effects of the preventive service on health outcomes.
- Low: The available evidence is insufficient to assess effects on health outcomes.

[c] Categories of recommendations:

- Strongly recommended, “A” level
- Moderately recommended, “B” level
- Recommended, “C” level
- Insufficient – Recommended (consensus-based), “I” level
- Insufficient – No recommendation (consensus-based), “I” level
- Insufficient – Not recommended (consensus-based), “I” level
- Not recommended, “C” level
- Moderately not recommended, “B” level
- Strongly not recommended, “A” level

[d] Confidence levels of study designs:

- I: Randomized controlled trials
- II: Prospective cohort study; prospective comparative study; case-crossover study; large, population-based study
- III: Retrospective study; Case-control study, cross-sectional study

Appendix 3: Critical Appraisal of Included Publications

Table 5: Quality Assessment of Systematic Reviews

AMSTAR 2 Checklist[5]	Orhurhu et al., 2019[9]	Aiyer et al., 2018[10]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	No (only PubMed was used)
5. Did the review authors perform study selection in duplicate?	Yes	No
6. Did the review authors perform data extraction in duplicate?	Yes	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	No
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	NA (narrative synthesis)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	No	NA
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No	NA
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Yes	NA
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	No

AMSTAR = Assessing the Methodological Quality of Systematic Reviews; NA = not applicable; PICO = Population, Intervention, Comparator, and Outcome; RoB = risk of bias.

Table 6: Quality Assessment of Randomized Controlled Trials

Downs and Black Critical Appraisal Checklist[6]	Lumanauw et al., 2019[11]	Nielsen et al., 2017[12]
Reporting	--	--
1. Is the hypothesis/aim/objective of the study clearly described?	Yes	Yes
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes	Yes
3. Are the characteristics of the patients included in the study clearly described?	Yes	Yes
4. Are the interventions of interest clearly described?	Yes	Yes
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	NA	NA
6. Are the main findings of the study clearly described?	Yes	Yes
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes (SD provided)	Yes (SD and 95% CI provided)
8. Have all important adverse events that may be a consequence of the intervention being reported?	Yes	Yes
9. Have the characteristics of patients lost to follow-up been described?	NA	NA
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes	Yes
External validity	--	--
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Probably not (only from one ED)	Probably not (only from one centre)
12. Were the subjects who were prepared to participate representative of the entire population from which they were recruited?	Unclear	Unclear
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of the patients receive?	Probably not (patients were treated at one ED)	Probably not (patients were treated at one centre)
Internal validity – bias	--	--
14. Was an attempt made to blind study subjects to the intervention they have received?	Yes	Yes
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes	Yes
16. If any of the results of the study were based on “data dredging”, was this made clear?	Yes (no retrospective unplanned subgroup analyses were reported)	Yes (no retrospective unplanned subgroup analyses were reported)
17. In trials and cohort studies, so the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes (same length of follow-up for all patients)	Yes (same length of follow-up for all patients)

Downs and Black Critical Appraisal Checklist[6]	Lumanauw et al., 2019[11]	Nielsen et al., 2017[12]
18. Were the statistical tests used to assess the main outcomes appropriate?	Yes	Yes
19. Was compliance with the intervention/s reliable?	Yes	Yes
20. Were the main outcome measures used accurate (valid and reliable)?	Yes	Yes
Internal validity – confounding (selection bias)	--	--
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes	Yes
22. Were study subjects in different intervention groups (trial and cohort studies) or were the cases and controls (case-controls studies) recruited over the same period of time?	Yes	Yes
23. Were study subjects randomized to intervention groups?	Yes	Yes
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Yes	Yes
25. Was the adequate adjustment for confounding in the analyses from which the main findings were drawn?	NA (no significant differences in the baseline between groups)	NA (no significant differences in the baseline between groups)
26. Were losses of patients to follow-up taken into account?	NA	NA
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Yes	Yes
28. Other concerns	No validated tools used to recognize AEs	No validated tools used to recognize AEs

AEs = adverse events; CI = confidence interval; ED = emergency department; NA = not applicable; RCT = randomized controlled trial; SD = standard deviation.

Table 7: Quality Assessment of Guidelines

AGREE II checklist[7]	ASRA/AAPM/ASA, Cohen et al., 2018[13]	ACOAM 2017[14]
Scope and purpose	--	--
1. Objectives and target patient population were explicit	Yes	Yes
2. The health question covered by the guidelines is specifically described	Yes	Yes
3. The population to whom the guideline is meant to apply is specifically described	Yes	Yes
Stakeholder involvement	--	--
4. The guideline development group includes individuals from all relevant professional groups	Yes	Yes
5. The views and preferences of the target population have been sought	Unclear	Unclear
6. The target users of the guideline are clearly defined	Yes	Yes

AGREE II checklist[7]	ASRA/AAPM/ASA, Cohen et al., 2018[13]	ACOAM 2017[14]
Rigour of development	--	--
7. Systematic methods were used to search for evidence	Yes	Yes
8. The criteria for selecting the evidence are clearly described	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described	Yes	Yes
10. The methods of formulating the recommendations are clearly described	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication	Yes	Yes
14. A procedure for updating the guideline is provided	Yes	Yes
Clarity of presentation	--	--
15. The recommendations are specific and unambiguous	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented	Yes	Yes
17. Key recommendations are easily identified	Yes	Yes
Applicability	--	--
18. The guideline describes facilitators and barriers to its application	Yes	Yes
19. The guidelines provides advice and/or tools on how the recommendations can be put into practice	Yes	Yes
20. The potential resource (cost) implications of applying the recommendations have been considered	Yes	Yes
21. The guideline presents monitoring and/or auditing criteria	Yes	Yes
Editorial independence	--	--
22. The views of the funding body have not influenced the content of the guideline	Unclear	Unclear
23. Competing interests of guideline development group members have been recorded and addressed	Yes	Yes

AAPM = American Academy of Pain Medicine; ACOEM = American College of Occupational and Environmental Medicine; AGREE = Appraisal of Guidelines, Research and Evaluation; ASA = American Society of Anesthesiologists; ASRA = American Society of Regional Anesthesia and Pain Medicine.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions
Orhurhu et al., 2019[9]	
IV Ketamine versus placebo for chronic pain **Pain scores** (between 48 hours and 2 weeks after treatments; 6 RCTs; n = 191) MD (95% CI) = -1.83 (-2.35 to -1.31); I^2 = 48.5%; P < 0.0001 Subgroup analysis Dose response High dose (cumulative dose exceeding 400 mg; 3 RCTs; n = 119) MD (95% CI) = -2.11 (-2.87 to -1.35); I^2 = 69.2%; P < 0.0001 Low dose (cumulative dose lower than 400 mg; 3 RCTs; n = 72) MD (95% CI) = -1.30 (-2.01 to -0.59); I^2 = 0.0%; P = 0.0001 Meta-regression showed that the use of high-dose ketamine was not significantly different from the use of low-dose ketamine for primary outcome (P = 0.213) Types of pain Neuropathic and mixed neuropathic-nociceptive pain syndromes (spinal cord injury, phantom limb pain, and CRPS types I and II); 3 RCTS; n = 79 MD (95% CI) = -1.75 (-2.08 to -1.43); I^2 = 0.0%; P < 0.00001 Non-neuropathic (nociceptive or nociplastic); 3 RCTs; n = 112 MD (95% CI) = -1.97 (-3.04 to -0.90); I^2 = 69.5%; P < 0.00001 Meta-regression showed that there was no significant difference between both groups for primary outcome (P = 0.720) CRPS (2 RCTs; n = 79) MD (95% CI) = -2.38 (-3.53 to -1.23); I^2 = 34.9%; P < 0.0001 Without CRPS (4 RCTs; n = 112) MD (95% CI) = -1.71 (-2.01 to -1.41); I^2 = 0.0%; P = 0.001 Meta-regression showed that there was no significant difference between both groups for primary outcome (P = 0.079) Adjunct medication versus stand-alone therapy Ketamine alone (3 RCTs; n = 103) MD (95% CI) = -1.80 (-3.04 to -0.56); I^2 = 17.2%; P < 0.0001 Ketamine with adjuncts (opioids, gabapentin, and calcitonin) (3 RCTs; n = 88) MD (95% CI) = -1.90 (-3.26 to -0.53); I^2 = 48.5%; P < 0.0001 Meta-regression showed that there was no significant difference between both groups for primary outcome (P = 0.127) Different time points At week 2 (3 RCTs; n = 119) MD (95% CI) = -2.23 (-2.59 to -1.87); I^2 = 0.0%; P < 0.001 At week 4 (3 RCTs; n = 119) MD (95% CI) = -0.74 (-1.88 to 0.41); I^2 = 58.6%; P = 0.208 At week 8 (3 RCTs; n = 103) MD (95% CI) = -0.68 (-1.75 to 0.40); I^2 = 48.2%; P = 0.174 At week 12 (2 RCTs; n = 79) MD (95% CI) = -0.55 (-1.50 to 0.39); I^2 = 0.0%; P =0.251	*"Evidence suggests that IV ketamine provides significantly 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."*[9] (p. 241)

Main Study Findings	Author's Conclusions
Positive response (defined as reduction in pain scores by ≥ 30% or ≥ 50% from baseline to 48 hours or longer after intervention); 3 RCTs; n = 64 RR (95% CI) = 2.43 (1.10 to 5.40); I^2 = 0.0%; P = 0.029 **Adverse events** Nausea (3 RCTs; n = 99) RR (95% CI) = 3.52 (1.74 to 7.14); I^2 = 0.0%; P < 0.00001 Psychotomimetic effects (4 RCTs; n = 148) RR (95% CI) = 5.92 (2.95 to 11.89); I^2 = 0.0%; P < 0.00001 Headache (2 RCTs; n = 79) RR (95% CI) = 1.26 (0.67 to 2.34); I^2 = 0.0%; P = 0.475 Tiredness (2 RCTs; n = 59) RR (95% CI) = 2.16 (0.64 to 7.33); I^2 = 0.0%; P = 0.218 Vomiting (1 RCT; n = 60) Rate (95% CI) of ketamine versus placebo: 55.3% (40.4 to 69.9) versus 11.0% (1.2 to 26.4); P < 0.05 Sedation (1 RCT; n = 20) Rate (95% CI) of ketamine versus placebo: 50.0 (23.7 – 73.6) versus 20.0 (5.7 – 51.0); NS	
Aiyer et al., 2018[10]	
Ketamine for the treatment of neuropathic pain (21 RCTs): 3 oral, 5 topical and 13 IV. **Pain** – Of 5 RCTs with topical ketamine, only one found that ketamine cream inhibited allodynia to lightly brushing the symptomatic limb, inhibited pain evoked by pricking the skin 3 times with a firm von Frey bristle and inhibited pin-prink sensations slightly in that limb. Other studies showed no significant difference in pain scores for ketamine versus placebo. – Of 3 RCTs with oral ketamine, only one RCT found that ketamine alone significantly improved pain compared with both methadone or combination of methadone and ketamine groups. – All 13 RCTs with IV ketamine showed significant improvement in pain in various conditions, including chronic neuropathic pain, CRPS, chronic phantom limb pain, peripheral nerve injury, and spinal cord injury.	*"There are a variety of NMDAR antagonist agents that should be considered for treatment of NeuP. Nevertheless, continued and further investigation of the 8 pharmacologic agents id needed to continue to evaluate their efficacy for treatment of NeuP."*[10] (p. 450)

CI = confidence interval; CRPS = complex regional pain syndrome; IV = intravenous; MD = mean difference; NeuP = neuropathic pain; NMDAR = N-methyl-d-aspartate receptor; NS = not significant difference; RCT = randomized controlled trials; RR = relative risk.

Table 9: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusions
Lumanauw et al., 2019[11]	
IV ketamine versus placebo for treatment of acute exacerbation from chronic pain IV ketamine 0.5 mg/kg (n = 30) versus IV ketamine 0.25 mg/kg (n = 35) versus placebo (n = 32) **Positive response** (defined as VAS pain reduction by 20 mm over the course of the study) within 60 minutes of treatment. – 83.3% versus 80% versus 40.6%; P = 0.001 for comparison between both ketamine groups and placebo. – There was no significant difference in pain relief between ketamine doses.	*"Ketamine infusions at both 0.5 and 0.25 mg/kg over 20 minutes were effective in treating acute exacerbations of chronic pain but resulted in more adverse event compared to placebo. Ketamine did not demonstrate long-term pain control over the next 24 to 48 hours."*[11] (p.1044)

Main Study Findings	Author's Conclusions
Adverse events – 40% (12/30) versus 40% (14/35) versus 3% (1/32); P < 0.05 – Adverse events associated with both ketamine groups: nausea (9.2%), dizziness (16.9%), hallucination (3.1%), anxiety (3.3%), anxiety and dizziness (4.6%), anxiety and palpitation (2.9%), and dysphoria (3.3%) – Adverse event in placebo: Dizziness (3%) **Pain during follow-up at 24 to 48 hours** (89 patients; 89% of initial population): There was no significant difference in pain scores between three groups.	
Nielsen et al., 2017[12]	
IV ketamine (n = 74) versus placebo (n = 73) in adult patients with chronic pain underwent lumbar fusion surgery **Cumulated PCA IV morphine consumption** (from 0 to 24 hours after surgery) – 79 ± 47 mg versus 121 ± 53 mg – MD (95% CI) = - 42 mg (-59 to -25); P < 0.001 **Acute pain** (2 to 24 hours postoperative) Pain during mobilization – 63 ± 21 mm versus 64 ± 18 mm – MD (95% CI) = 1 mm (-8 to 5); P = 0.63 Pain at rest – 46 ± 19 mm versus 48 ± 20 mm – MD (95% CI) = 2 mm (-8 to 5); P = 0.62 **Adverse events** (2 to 24 hours postoperatively) – Nausea, vomiting, hallucinations, nightmares: No significant difference between ketamine and placebo groups – Sedation: Significantly reduced at 6 hours (P = 0.005) and 24 hours (P = 0.04) postoperatively in the ketamine groups compared to placebo. **Persistent pain** (6 months postoperatively) – Back pain level (VAS): No significant difference between ketamine and placebo groups – Leg pain level (VAS): No significant difference between ketamine and placebo groups – Daily use analgesics: No significant difference between ketamine and placebo groups – SF-36 survey, EuroQoL 5D, or the Douleur Neuropathique 4: No significant difference between ketamine and placebo groups – Oswestry Low Back Pain Disability index score: There was significantly less disability in the ketamine group compared with placebo (P = 0.006).	*"In conclusion, intraoperative ketamine significantly reduced morphine consumption 0 to 24 hours after lumbar fusion surgery in opioid-dependent patients."*[12] (p. 463)

IV = intravenous; MD = mean difference; PCA = patient-controlled analgesia; VAS = visual analog scale;

Table 10: Summary of Recommendations of Included Guidelines

Recommendations
ASRA/AAPM/ASA, Cohen et al., 2018[13]
"ASRA/AAPM/ASA recommendations for ketamine infusions for chronic pain *1) For spinal cord injury, there is weak evidence to support short-term improvement (Grade C, low certainty)* *2) In CRPS, there is moderate evidence to support improvement for up to 12 weeks (Grade B, low to moderate certainty)* *3) For other pain conditions such as mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache, and spinal pain, there is weak or no evidence for immediate improvement (Grade D, low certainty)"*[13] (p. 538)
ACOAM 2017[14]
"Ketamine infusion for chronic persistent pain – Not recommended, Insufficient evidence (I)"[14] (p. 46) *"Ketamine infusion for CRPS – Not recommended, Insufficient evidence (I)"*[14] (p. 105) *"Ketamine infusion for fibromyalgia – Not recommended, Insufficient evidence (I)"*[14] (p. 251) *"Ketamine infusion for neuropathic pain – Not recommended, Insufficient evidence (I)"*[14] (p. 560)

AAPM = American Academy of Pain Medicine; ACOEM = American College of Occupational and Environmental Medicine; AGREE = Appraisal of Guidelines, Research and Evaluation; ASA = American Society of Anesthesiologists; ASRA = American Society of Regional Anesthesia and Pain Medicine; CRPS = complex regional pain syndrome.