



Canadian Journal of Health Technologies

December 2023 Volume 3 Issue 12

CADTH Health Technology Review

Ketamine for Chronic Non-Cancer Pain: A 2023 Update

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Rapid Review

Key Messages

What Is the Issue?

- Doctors use ketamine to induce loss of consciousness as general anesthesia during surgery. At low doses that do not produce dissociation, practitioners use ketamine to relieve acute or chronic pain.
- The previous CADTH report published in 2020 found that IV ketamine, compared to placebo, could only provide short-term pain relief in patients with chronic non-cancer pain, with increased risks of nausea, vomiting, and psychomimetic effects. The included guidelines did not provide definitive recommendations due to insufficient evidence.
- Decision-makers want to know if there is any new evidence to support the use of ketamine for treating of chronic non-cancer pain in adults.

What Did We Do?

- To inform decisions about the use of ketamine for treating of chronic non-cancer pain, CADTH sought to update the previous report by identifying and summarizing literature comparing the clinical effectiveness and cost-effectiveness of ketamine with placebo or other pharmacological therapies for chronic non-cancer pain. We also attempted to identify evidence-based recommendations from most recent guidelines for the use of ketamine for chronic non-cancer pain.
- A research information specialist conducted a literature search of the peer-reviewed and grey literature with a search strategy focused on ketamine, chronic non-cancer pain, and adults. The search was limited to English-language documents published since 2020 up to November 06, 2023. One reviewer screened articles for inclusion based on predefined criteria, critically appraised the included studies, and narratively summarized the findings.

What Did We Find?

- We found 3 SRs and 1 randomized controlled trial on the use of ketamine for the treatment of patients with neuropathic pain, complex regional pain syndrome, fibromyalgia, and other chronic pain conditions. Collective evidence from the included studies suggests that ketamine treatment was associated with short-term pain reduction in patients with chronic non-cancer pain. However, the long-term efficacy of ketamine in pain relief remains unclear.
- Adverse events (AEs) associated with ketamine treatment were with psychedelic effects, discomfort, dizziness, fatigue, headache, and nausea; all of those events appeared to be short-lasting.



Key Messages

- There were mixed results regarding the effect of ketamine on quality of life and functional improvement.
- We did not find any studies on the cost-effectiveness of ketamine or new evidence-based guidelines on the use of ketamine for treating chronic non-cancer pain.

What Does It Mean?

- The findings in this review are consistent with the previous CADTH report published in 2020.
- Well-controlled studies with larger populations and longer follow-ups are needed to determine the optimal treatment protocol of ketamine for each specific type of chronic pain.
- Given that ketamine is a dissociative drug that could be associated with the development of a substance use disorder, decision-makers may wish to consider the use of ketamine for long-term treatment of chronic non-cancer pain. The long-term effects and dangers of ketamine remain to be determined.

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Abbreviations

AE	adverse event
CI	confidence interval
CP	chronic pain
CRPS	complex regional pain syndrome
IV	intravenous
MA	meta-analysis
MD	mean difference
NP	neuropathic pain
QoL	quality of life
RCT	randomized controlled trial
RR	risk ratio
SMD	standardized mean difference
SR	systematic review

Context and Policy Issues

Chronic Pain in Canada

Chronic pain is defined as pain that persists or recurs for a period longer than 3 months, including chronic cancer-related pain, chronic postsurgical or posttraumatic pain, chronic neuropathic pain, chronic headache or orofacial pain, chronic visceral pain, and chronic musculoskeletal pain.¹ Chronic pain is associated with significant emotional distress, like anxiety, anger, frustration and depression. The WHO recognizes it as a disease by itself listed in the International Classification of Disease version 11.^{1,2} This report addresses the role of ketamine in treating chronic non-cancer pain.

In 2019, it was estimated that 1 in 5 or 7.6 million Canadians live with chronic non-cancer pain, leading to substantial social and economic costs.² Health Canada's analyses estimated total direct and indirect costs related to chronic non-cancer pain in 2019 to be between \$38.2 billion and \$40.3 billion. By 2030, these numbers are projected to increase to 9 million people affected and \$52 billion to \$55 billion in total costs.²

What Is the Current Practice?

Treatment and management of chronic non-cancer pain is complex and difficult, involving multiple interventions, including pharmacological and psychological interventions.³ Pharmacological interventions considered for chronic non-cancer pain include nonopioid analgesics (e.g., nonsteroidal anti-inflammatory drugs, acetaminophen), antidepressants, antiepileptic drugs, other adjuvant medications (e.g., topical agents, cannabis and cannabinoids), opioids, and infusion therapies (e.g., ketamine, lidocaine).⁴

Ketamine, an *N*-methyl-D-aspartate receptor antagonist, has been approved and primarily used as an anesthetic induction drug in doses ranging between 1 and 4.5 mg/kg.⁵ 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.⁶ In hospitals and emergency departments, ketamine has been used for pain management of acute conditions such as burns, trauma, or postoperative pain.⁴ Recently, IV (IV) ketamine infusions at subanesthetic doses have 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 (NP), and other refractory chronic pain (CP) conditions.⁴ However, off-label use of ketamine in providing short- or long-term benefit in chronic pain has not been extensively studied.⁷ Major side effects of ketamine treatment are psychotomimetic effects (e.g., euphoria, dysphoria, psychomotor retardation, hallucinations, vivid dreams, and nightmares), gastrointestinal distress, somnolence, cardiovascular stimulation, and, to a lesser extent, hepatotoxicity.⁸

Why Is It Important to Do This Review?

Given the availability of ketamine of different formulations and its potential opportunities for use in pain management, there is a need to determine its benefits and risks in the treatment of chronic non-cancer pain. In 2020, CADTH published a report⁹ reviewing the clinical effectiveness, cost-effectiveness and recommendations from evidence-based guidelines regarding the use of ketamine for the treatment

of chronic non-cancer pain in adults. The report⁹ included 2 SRs, 2 randomized controlled trials, and 2 guidelines. We did not identify any economic studies at that time. The report⁹ concluded that IV ketamine appeared to provide significant short-term pain relief in patients with chronic non-cancer pain, with increased risks of some AEs such as nausea, vomiting and psychotomimetic effects. The long-term effect of ketamine on pain relief was unclear in that report.⁹ In addition, the guidelines included in the report⁹ did not provide definitive recommendations on the use of IV ketamine for the treatment of chronic non-cancer pain due to insufficient evidence.

There is interest in finding out if any new clinical and economic evidence exists since the publishing of the previous report. There is also interest in determining whether there are any new guidelines that could provide more concrete recommendations with possibly new evidence that may have emerged lately.

Objective

This report aims to summarize new evidence since 2020 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?

Methods

Literature Search Methods

The literature search strategy used in this report is an update of 1 developed for a previous CADTH report.⁹ For the current report, an information specialist conducted a literature search on key resources including MEDLINE, the Cochrane Database of Systematic Reviews, the International Health Technology Assessment Database, Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The initial search⁹ was limited to English-language documents published between January 01, 2015 and April 27, 2020. For the current report, database searches were rerun on November 06, 2023 to capture any articles published or made available since the initial search date. The search of major health technology agencies was also updated to include documents published since April 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first screening level, titles and abstracts were reviewed, and potentially relevant articles were retrieved and assessed for inclusion. As an update to a previous CADTH report, articles were included if they were made available since the previous search date and were not included in the 2020 CADTH report.⁹ The final selection of full-text articles was based on the inclusion criteria presented in [Table 1](#).

Table 1: Selection Criteria

Criteria	Description
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 (e.g., tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, nonsteroidal anti-inflammatory drugs, opiate agonists, antiepileptics, gabapentinoids, botulinum toxin, cortisone injections, topical or IV lidocaine, topical capsaicin) or no treatment (e.g., placebo)
Outcomes	Q1: Clinical effectiveness (e.g., therapeutic response in signs and symptoms, pain, functional status, use of opioid analgesics) and safety (e.g., morbidity, mortality, adverse drug reactions) Q2: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained, cost per 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, nonrandomized studies, economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in [Table 1](#), or were published before 2020. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive SRs were excluded. Primary studies retrieved by the search were excluded if they were captured in 1 or more included SRs.

Critical Appraisal of Individual Studies

One reviewer critically appraised the included publications using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)¹⁰ for systematic reviews (SRs) and the Downs and Black checklist¹¹ for randomized controlled trial (RCT). Summary scores were not calculated for the included studies; rather, each publication's strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

We identified a total of 435 citations from the literature search. Following the screening of titles and abstracts, we excluded 409 citations and retrieved 26 potentially relevant reports from the electronic search for full-text review. We found no potentially relevant publications from the grey literature search. Of the 26 potentially relevant articles, we excluded 22 publications for various reasons and included 4 publications that met the inclusion criteria. These comprised 3 SRs, and 1 RCT. [Appendix 1](#) presents the PRISMA¹² flow chart of the study selection.

Summary of Study Characteristics

[Appendix 2](#) provides details regarding the characteristics of 3 included SRs¹³⁻¹⁵ ([Table 2](#)), and primary study¹⁶ ([Table 3](#)).

Study Design

The SR with meta-analysis (MA) by Guimaraes Pereira et al. (2022)¹³ included 18 RCTs (published between 1994 and 2019) with a total of 706 patients, ranging from 8 to 214 patients with NP in each RCT. All included studies were relevant to our report. The authors of the SR¹³ searched multiple databases since inception to November 18th, 2021, without restrictions for language, publication status, date of publication, or country. The authors calculated pooled risk ratio (RR) for dichotomous outcomes, mean difference (MD) for continuous outcomes and standardized mean difference (SMD) for continuous outcomes measured by different scales, with a corresponding 95% confidence interval (CI). A random-effect model was chosen to deal with substantial heterogeneity among studies.

The SR by Chitneni et al. (2021)¹⁴ included 14 studies (3 RCTs and 11 observational studies published between 2004 and 2020) with a total of 455 patients, ranging from 4 to 114 patients with CRPS in each study. All included studies were relevant to our report. The authors of the SR¹⁴ have searched multiple databases since its inception. The final date of the search was not reported. Due to substantial heterogeneity in study designs, methodology and outcomes, the authors of the SR¹⁴ narratively summarized the results of the included studies without pooling.

The SR by Pastrak et al. (2021)¹⁵ included 7 studies (4 RCTs, 1 prospective trial, and 2 case studies published between 1995 and 2018) with a total of 118 patients, ranging from 1 to 34 patients with fibromyalgia in each study. All included studies were relevant to our report. The authors of the SR¹⁵ searched 1 database (PubMed) with restriction to the English language only. Date of search was not reported. The authors narratively summarized the findings in each of the included studies, without pooling.

The included primary study by Dadabayev et al. (2020)¹⁶ was a single centre, parallel, 4 arms (1:1:1:1 ratio) double-blind, RCT with a total of 41 patients with chronic pain (CP) with or without posttraumatic stress disorder (PTSD). The authors calculated the sample size to detect a hypothesized treatment difference between groups. The results were analyzed using per-protocol analysis. The study was published in 2020.

[Appendix 5](#) presents the overlap of included primary studies between 2 SRs.^{13,14} There were 2 primary studies that were included in both SRs.^{13,14} The third SR¹⁵ did not have any included studies that overlapped with those in the other 2 SRs.^{13,14}

Country of Origin

The SR with MA by Guimaraes Pereira et al. (2022)¹³ was conducted by authors from Brazil. The primary studies included in this SR were conducted by authors from Brazil (4) Canada (1), Denmark (1), Egypt (2), Fance (1), Italy (1), The Netherlands (3), Norway (1), South Korea (1), UK (1), and US (2).

The SR by Chitneni et al. (2021)¹⁴ was conducted by authors from US. The primary studies included in this SR were conducted by authors from US (8), The Netherlands (3), Poland (1), UK (1), and Australia (1).

The SR by Pastrak et al. (2021)¹⁵ was conducted by authors from Canada. The primary studies included in this SR were conducted by authors from US (3), The Netherlands (1), and Sweden (3).

The included primary study by Dadabayev et al. (2020)¹⁶ was conducted by authors from US.

Patient Population

Patients in the studies included in the SR by Guimaraes Pereira et al. (2022)¹³ were adults with NP, including postherpetic neuralgia, chronic posttraumatic pain, neuropathic CP, peripheral nerve or root lesions of traumatic origin, CRPS, or pain resistant to conventional treatments. The duration of the diseases was not reported. The mean age of patients in the included studies was between 40 and 72 years. In 15 included studies, the proportions of male and female were 53.8% and 46.2%, respectively. One study included only female patients, while 2 studies did not specify gender distribution. Patients' comorbidities were not reported.

Patients in the studies included in the SR by Chitneni et al. (2021)¹⁴ were those with treatment-resistant CRPS. Duration of the diseases was not reported. The mean age ranged between 15 and 68 years. The characteristics of the included studies, including setting, follow-up time, control and population, were not adequately described.

Patients in the studies included in the SR by Pastrak et al. (2021)¹⁵ were those with fibromyalgia. The characteristics of the included studies were not adequately reported.

Patients in the included RCT¹⁶ were veterans with CP with or without PTSD. Duration of the disease was not reported. The mean age was 45.5 years. The proportion of male and female participants were 75.6% and 24.4%, respectively. The majority of patients (70.7%) had low back pain. Patients' comorbidities were not reported.

Interventions and Comparators

In the SR by Guimaraes Pereira et al. (2022),¹³ ketamine was administered through IV, epidural, oral, iontophoretic, and topical. Doses of IV ketamine ranged from 0.1 to 0.75 mg/kg/hour. Epidural ketamine was administered at 0.1 mg/kg or 0.2 mg/kg. Oral doses of ketamine varied from 30 mg/day to 400 mg/day. For ionotropic administration, ketamine dose was 50 mg or 75 mg. Ketamine was also administered as

1% topical cream 3 times/day. Ketamine was added to standard treatment, which was not described. The comparators included saline, magnesium sulphate, methadone, clonidine in 1% lidocaine, and amitriptyline plus carbamazepine. The treatment protocols (e.g., starting dose, total dose per day, maximum dose, or duration of treatment) varied among studies.

In the SR by Chitneni et al. (2021),¹⁴ IV ketamine infusions were used for the treatment of CRPS, and the dose ranged from 0.15 to 7 mg/kg/hour (11 studies), and from 10 to 200 mg/hour (3 studies). The comparators were baseline (in prepost studies) or placebo (in RCTs). The treatment protocols varied among studies.

In the SR by Pastrak et al. (2021),¹⁵ the dose of IV ketamine in 6 studies ranged from 0.1 to 0.5 mg/kg administered over 7 minutes to 30 minutes. The comparators were baseline (in prepost studies) or placebo (in RCTs). One case study administered IV ketamine over 4 hours at a dose escalating from 200 mg to 800 mg for 5 days, with a booster of 800 mg 2 weeks later. Another case study administered 10 consecutive ketamine infusions with escalating doses from 428 mg to 1,063 mg. The treatment protocols varied among studies.

The included RCT¹⁶ compared ketamine (single IV infusion of 0.5 mg/kg over 40 minutes) with ketorolac (15 mg reconstituted in 500 mL of normal saline and administered over 40 minutes). Patients were randomized into 4 groups: CP only (ketamine), CP only (ketorolac), CP plus PTSD (ketamine), and CP plus PTSD (ketorolac).

Outcomes

The main outcome reported in all included SRs¹³⁻¹⁵ and primary study¹⁶ was pain reduction measured using different scales.

- The studies in the SR with MA by Guimaraes Pereira et al. (2022)¹³ measured pain using a numerical rating scale (NRS), visual analogue scale (VAS), or Short-Form McGill Pain Questionnaire (SF-MPQ). Follow-up across studies ranged from 1 day to 12 weeks. VAS or NRS ranges from 0 (no pain) to 10 (worst possible pain). The SF-MPQ has 2 subscales for pain rating – sensory subscales with 11 words, and affective subscales with 4 words. Each word is rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate, and 3 = severe.
- The studies in the SR by Chitneni et al. (2021)¹⁴ assessed pain using VAS or NRS. One study measured pain threshold, defined as the amount of stimulation before the pain is experienced. The follow-up period varied from the time right after infusion to 3 years.
- The studies in the SR by Pastrak et al. (2021)¹⁵ assessed pain using VAS. Follow-up varied from 20 minutes after infusion to 3 months.
- The included RCT¹⁶ assessed pain using VAS and the short-form Brief Pain Inventory (SF-BPI). SF-BPI is a 9-item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning. The patient is asked to rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10-point scale. Follow-up was up to 7 days.

All included 3 SRs¹³⁻¹⁵ and the included primary study¹⁶ reported adverse events (AEs) following ketamine treatment. The methods used to assess AEs in all 3 included SRs¹³⁻¹⁵ were not reported. The RCT¹⁶ used Clinician-Administered Dissociative States Scales (CADSS) and the Patient-Rated Inventory of Side Effects (PRISE) to assess AEs. CADSS is a 28-item instrument contained 23 interview items and 5 observer items. Patients were instructed to report dissociative states experienced during the preceding therapy session, and clinicians rated the reported and observed severity on a 5-point Likert scale ranging from 0 (not at all) to 4 (extreme), with item-specific anchors provided for each score. PRISE assesses the level of tolerance (0: absent, 1: tolerable, 2: painful) for each symptom experienced during the last 7 days in the different domains explored; that is., gastrointestinal, cardiovascular, skin, nervous, sensory (eyes and ears) and urogenital systems, but also: sleep, sexual function, and other side effects.

The SR by Chitneni et al. (2021),¹⁴ reported other outcome measures such as morphine-equivalent intake, quality of life (QoL), morphine-equivalent intake, and cognitive effects. The included RCT¹⁶ reported a reduction of PTSD symptoms severity.

Summary of Critical Appraisal

[Appendix 3](#) provides details regarding the strengths and limitations of the included SRs¹³⁻¹⁵ ([Table 4](#)) and primary study¹⁶ ([Table 5](#)).

Systematic Reviews

Of the 3 included SRs,¹³⁻¹⁵ 2 SRs^{14,15} narratively summarized the findings from the included studies, and 1 SR¹³ quantitatively synthesized the findings of the included studies through MA.

All 3 SRs¹³⁻¹⁵ were explicit in their objectives, inclusion criteria for the review, and selection of the study designs for inclusion. The literature search strategy in the SR with MA¹³ was comprehensive and clearly described. At the same time, that in the other 2 SRs^{14,15} was partially comprehensive in that the authors did not report whether grey literature or the reference lists of reviewed studies were searched for relevant studies. Providing details of the literature search strategy increases the reproducibility of the review. One SR¹⁵ did not report whether a protocol had been published before the review, which may introduce bias in modifying the methods after the review had been conducted. One SR¹³ performed study selection and data extraction in duplicate, while 2 SRs^{14,15} did not report whether study selection and data extraction were performed in duplicate. Therefore, it is unclear whether a fully systematic approach was taken in study selection and data extraction in those SRs; specifically, it is unclear whether the included and excluded studies were appropriate or whether the data extraction was accurate.^{14,15} None of the 3 SRs¹³⁻¹⁵ reported the funding sources for the included studies. This is potentially a concern because funding received from industry can introduce bias in favour of the intervention. All 3 SRs¹³⁻¹⁵ did not provide a list of excluded studies and the reasons for exclusion were not provided. No justification for the excluded studies could bias the results of the review. The characteristics of the included studies were described in adequate detail in terms of design, setting, follow-up time, intervention, control and outcomes in 2 SRs,^{13,14} but not in the other.¹⁵ Patient characteristics were not adequately described in all 3 SRs.¹³⁻¹⁵ Only the SR with MA¹³ used appropriate tools to assess the methodological quality of the included studies (i.e., the Cochrane risk of bias tool for RCTs). The review authors of this SR¹³ use appropriate methods for statistical combination of results.

As the overall quality of all included studies in the SR with MA¹³ was considered high, the review authors did not assess the potential risk of bias in individual studies in the results of the MA. The review authors of the SR with MA¹³ could not investigate publication bias since no single meta-analysis pooled more than 10 studies. The review authors in 2 SRs^{13,14} discussed the heterogeneity (e.g., comparators, doses and routes of administration) observed in the results, which was the main limitation of the review. The review authors of 2 SRs^{14,15} did not report the source of funding for the work. Overall, the 2 SRs^{14,15} that narratively summarized the findings from the included studies had several methodological limitations regarding literature search strategy, reporting, data collection process, and analysis that may increase the uncertainty of the findings.

Primary Study

For reporting, The included RCT¹⁶ clearly described the objective of the study, the intervention of interest, the main outcomes, and the main findings of the study. However, the characteristics of the participants included in the study were not clearly described. It was unclear if there was any group differences (i.e., potential confounders) in demographics of the randomized participants. The authors reported AE of the intervention and actual probability for the main outcomes. For external validity, the study was conducted in an outpatient hospital setting, which was representative of the treatment the majority of the patients receive. However, patients were recruited from a single centre and sample size was small (N = 41); therefore, it was unlikely that the patients who participated were representative of the entire population from which they were recruited. For internal validity related to bias, there were low risks of selection, performance, and detection biases, as all study personnel, including rater, patients and data analysts were blinded to randomization order. All patients were followed up for the same period, which was 7 days. Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. For internal validity related to confounding, patients in both intervention groups appeared to be recruited from the same population and over the same period. The study's authors performed a sample size calculation to provide 80% power to detect a hypothesized treatment difference between groups, and the required participation was met. However, the methods of randomization and allocation concealment were not described, and patients lost to follow-up were not considered in the analysis. Overall, this study had several limitations related to reporting and external validity due to the small sample size, which may reduce the certainty of the findings.

Summary of Findings

[Appendix 4](#) presents the main study findings, which were summarized by outcome (i.e., pain reduction is presented in [Table 6](#), AEs in [Table 7](#), and other outcomes in [Table 8](#)).

Clinical Effectiveness of Ketamine for Treating Chronic Non-Cancer Pain in Adults

Pain Reduction

The SR with MA¹³ found that addition of ketamine to standard treatment of NP resulted in statistically significant reduction of pain intensity compared with various controls after 1 week (5 RCTs; $P < 0.00001$), 15 days (5 RCTs; $P < 0.00001$), and 30 days (4 RCTs; $P < 0.00001$) of treatment.

The SR with MA¹³ also found that addition of ketamine to standard treatment for NP resulted in statistically significant reduction in pain intensity compared with baseline after 1 week (5 RCTs; $P < 0.00001$), 15 days

(5 RCTs; $P < 0.00001$), 30 days (3 RCTs; $P < 0.00001$), and up to 2 months (2 RCTs; $P = 0.03$) of treatment. However, a non-statistically significant difference in pain was observed between baseline and after 3 months of treatment with ketamine (2 RCTs; $P = 0.15$).

Pooling of the results from studies measuring pain intensity using different multidimensional pain scales yielded a non-statistically significant difference between ketamine and various controls (5 RCTs, $P = 0.93$).

The author's SR with MA¹³ noted that the certainty of the evidence was very low because of imprecision (low number of patients and wide CI) and inconsistency.

The SR¹⁴ that reviewed clinical studies on the use of IV ketamine infusion for patients with treatment-resistant CRPS found that 13 studies (out of 14) reported a decrease in pain scores or pain threshold after treatment. One study with only 4 patients did not find a significant change in pain relief in patients with longstanding and severe CRPS.

The SR¹⁵ that examined the effect of ketamine infusion on pain relief in patients with fibromyalgia summarized the findings from the included studies as follows:

- IV infusion of low-dose ketamine (0.3 to 0.5 mg/kg) revealed a short-term reduction (a few hours after infusion) in pain intensity scores or improvement in pain threshold and pain tolerance relative to placebo. (4 RCTs) One study found that pain alleviation lasted 2 to 7 days. The rest of the studies did not observe the prolonged effect of ketamine action.
- Low-dose IV ketamine followed by dextromethorphan treatment showed a VAS reduction of more than 50% in 18 of 34 patients after infusion. However, long-term benefit from a 1-time ketamine infusion was not observed. (1 prospective trial).
- Higher doses and longer repeated ketamine infusions may result in long-term reduction in pain. (2 case studies).

The included RCT¹⁶ found that both ketamine and ketorolac treatments provided comparable improvement in pain scores in patients with CP with or without PTSD that persisted for 7 days after infusion. The data were graphically reported.

Adverse Events

The SR with MA¹³ found that addition of ketamine to standard treatment of NP resulted in statistically significant increase in psychedelic effects ($P < 0.001$; 9 RCTs) and discomfort ($P = 0.03$; 2 RCTs) compared with various controls. There were no statistically significant differences between ketamine and controls regarding nausea and vomiting ($P = 0.56$; 6 RCTs), fatigue ($P = 0.81$; 4 RCTs), and dizziness ($P = 0.18$; 4 RCTs).

The SR¹⁴ that examined the use of ketamine infusions for treatment of CRPS reported that treatment with ketamine was associated with mild symptoms of fatigue, headache, and nausea (7 studies), and mild-to-moderate psychotomimetic effects, such as hallucinations (2 studies).

The SR¹⁵ that examined the effect of ketamine infusion on pain relief in patients with fibromyalgia summarized the following AEs:

- Ketamine was associated with short-lasting (up to 15 minutes) feeling of unreality, dizziness, and changes in hearing. (1 RCT).
- Both treatment groups (i.e., ketamine and midazolam) were associated with short-lasting (about 30 minutes) drowsiness and euphoria. (1 RCTs).
- Ketamine was associated with short-lasting (about 30 minutes) dizziness, confusion, euphoria, and nausea. (1 prospective study).
- Ketamine was associated with nausea and agitation (1 case study).
- No side effects were observed. (2 RCTs, 1 case study).

The included RCT¹⁶ reported that both ketamine and ketorolac treatments was associated with significant increase in dissociative symptoms in the CP group, but less effect on dissociative symptoms in the CP plus PTSD group. Patients generally tolerated both ketamine and ketorolac treatments well with respect to Patient-Rated Inventory of Side Effects.

Other Outcomes

The SR¹⁴ that examined the use of ketamine infusions for treatment of CRPS reported other outcomes including morphine-equivalent intake, QoL, functional improvements and cognitive effects.

- For morphine-equivalent intake:
 - While ketamine reduced pain intensity, it did not reduce overall opioid intake. (1 study)
- For QoL:
 - ketamine treatment was associated with significant improvement in QoL in the majority of patients at 3- and 6-months follow-up. (1 study)
 - there were no significant changes in QoL scores following treatment in either ketamine or placebo groups. (1 study).
- For functional improvement:
 - ability to work was significantly improved after 3 months of ketamine treatment, with an even greater improvement by 6 months. (1 study)
 - there were no significant changes in activity level between pre- and post-treatment, but the number of nighttime awakenings in the ketamine group decreased by 85% after treatment. (1 study)
 - ketamine treatment did not cause functional improvement in active range of motion and the ability to walk without support. (2 studies).
- For cognitive effects,
 - there were significant improvements in brief auditory attention and processing speed, no changes in learning, memory or motor speed, and a slight decline in motor strength. (1 study).

The included RCT¹⁶ reported that both ketamine and ketorolac treatments yielded a statistically significant decrease in PTSD symptom scores from baseline to 7 days after infusion ($P < 0.01$) in the CP + PTSD group. The difference between ketamine and ketorolac effect on PTSD symptoms was not statistically significant ($P > 0.05$).

Cost-Effectiveness of Ketamine for Treating Chronic Non-Cancer Pain in Adults

We did not identify any studies on cost-effectiveness of ketamine for treating chronic non-cancer pain in adults; therefore, no summary can be provided.

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

We did not identify any evidence-based guideline on the use of ketamine for treating chronic non-cancer pain in adults; therefore, no summary can be provided.

Limitations

The included SRs¹³⁻¹⁵ had several limitations. First, many of the included studies in the SRs¹³⁻¹⁵ had small sample size. The sample size in most RCTs included the SR with MA by Guimaraes Pereira et al. (2022),¹³ varied from 8 to 92. Sample size in most included studies in the SR by Chitneni et al. (2021)¹⁴ varied from 4 to 63. The numbers of patients in the studies included in the SR by Pastrak et al. (2021)¹⁵ varied from 1 to 34. Second, there was substantial heterogeneity among included studies in all 3 SRs, regarding ketamine treatment protocols such as doses varied from 0.1 to 7.0 mg/kg, treatment duration, different presentations and pathology of pain conditions, and tools used to measure variables and outcomes. Third, in the SR with MA,¹³ the mode of administration (i.e., IV, oral topical, iontophoretic, epidural), and the comparators (i.e., placebo, magnesium sulphate, methadone, clonidine in 1% lidocaine, or amitriptyline + carbamazepine) were heterogeneous; thus, reducing the certainty of the pooled results. Fourth, due to low number of studies included in the SR with MA,¹³ sensitivity analyses could not be performed to explore the causes of high heterogeneity. Fifth, not all data could be pooled from all eligible studies in the SR with MA¹³ due to outcomes reported differently. This may limit the strength of the evidence. Sixth, pain intensity is subjective and hard to measure accurately despite using validated scales. These limitations rendered low certainty in the evidence, mostly due to inconsistency and imprecision.

The included RCT¹⁶ also had a small sample size ($N = 41$), though this met the calculated sample size. The lack of placebo control limits the interpretation of the results. The study did not address depression and suicide ideation, which are common comorbidities in patients with PTSD.

No cost-effectiveness studies or evidence-based guidelines could be identified in this review.

Conclusions and Implications for Decision- or Policy-Making

This review included 3 SRs¹³⁻¹⁵ and 1 RCT¹⁶ regarding the clinical effectiveness of ketamine for treating patients with chronic non-cancer pain, including NP,¹³ CRPS,¹⁴ fibromyalgia,¹⁵ and various types of CP.¹⁶

Evidence from 3 included SRs¹³⁻¹⁵ and 1 RCT¹⁶ suggest that ketamine treatment was associated with short-term pain reduction in patients with chronic non-cancer pain. The long-term efficacy of ketamine in pain relief remains unclear. Concerning AEs, ketamine treatment appeared to be associated with an increase in psychedelic effects such as hallucinations, discomfort, dizziness, fatigue, headache, and nausea. These AEs appeared to be short-lasting and manageable. There were mixed findings of effects of ketamine on QoL and functional improvement.

The previous CADTH report published in 2020⁹ on the effect of ketamine for the treatment of chronic non-cancer pain found that IV ketamine, compared to placebo, provided significant short-term, but not long-term, pain relief, with increased risks of some AEs, such as nausea, vomiting and psychotomimetic effects. The guidelines included in the previous CADTH report⁹ did not provide explicit recommendations regarding the use of IV ketamine infusion for CP due to insufficient evidence. The current review did not identify any new evidence-based guidelines or add any new information to the findings in the previous CADTH report. 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 CP. Economic studies are also warranted to determine the cost-effectiveness of ketamine for treating chronic non-cancer pain.

Ketamine administration at low doses appears to be an attractive option for the management of chronic non-cancer pain during a short period of time. The optimal protocol of ketamine in long-term pain relief remains to be determined. Although ketamine administration does not seem to cause serious AEs, the increase in psychedelic effects during ketamine treatment is a concern.

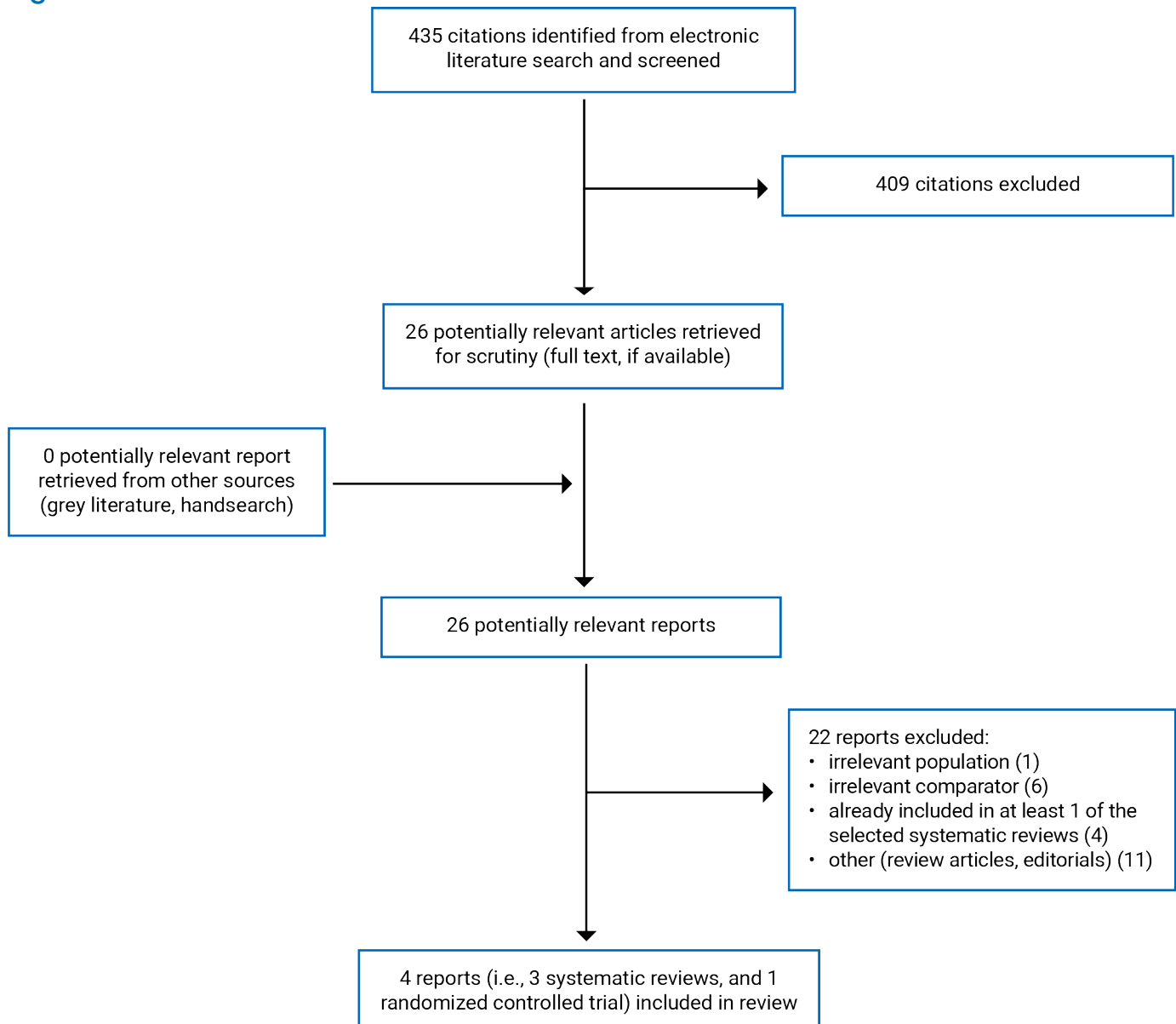
Given that ketamine is a dissociative drug that could be associated with the development of a substance use disorder and that it has become popular as a recreational drug, decision-makers may wish to consider with cautions on the use of ketamine for long-term treatment of chronic non-cancer pain. Several concerning AEs have been found during acute (e.g., neuropsychiatric effects) and chronic (e.g., cystitis, cholangiopathy) use of ketamine as a recreational drug.¹⁷ Thus, the long-term effects and dangers of ketamine remain unclear.

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Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Guimaraes Pereira et al. (2022) ¹³ Country: Brazil Funding source: Hospital	SR with MA Total 18 RCTs (total 706 patients) Sample size: Range from 8 to 214 patients. Countries of the primary studies: Brazil (4) Canada (1), Denmark (1), Egypt (2), Fance (1), Italy (1), Netherlands (3), Norway (1), South Korea (1), UK (1), US (2) Publication year: 1994 to 2018	Adult patients with neuropathic pain. Range of mean age, years: 40 to 71.9 Sex, % (in 15 studies): <ul style="list-style-type: none"> • Male: 53.8 • Female: 46.2 1 study included only female patients; 2 studies did not specify gender distribution.	Intervention: Ketamine addition to standard treatment. Route of administration: <ul style="list-style-type: none"> • IV (11 RCTs) • Epidural (2 RCTs) • Oral (2 RCTs) • Topical (3 RCTs) Dose of IV ketamine: ranging from 0.1 to 0.75 mg/kg/day Comparator: Saline (placebo), magnesium sulphate, methadone, clonidine in 1% lidocaine, or amitriptyline + carbamazepine	Outcomes: <ul style="list-style-type: none"> • Pain reduction (measured by VAS or NRS^a, SF-MPQ^b) • AEs Follow-up: 1 day to 12 weeks
Chitneni et al. (2021) ¹⁴ Country: US Funding source: NR	SR Total 14 studies (3 RCTs and 11 observational studies; total 455 patients) Sample size: Range from 4 to 114 patients. Countries of the primary studies: US (8), The Netherlands (3), Poland (1), UK (1), Australia (1) Publication year: 2004 to 2020	Patients with treatment-resistant complex regional pain syndrome. Age, range years: 15 to 68	Intervention: IV ketamine Dose: <ul style="list-style-type: none"> • 0.15 to 7 mg/kg/hour (11 studies) • 10 to 200 mg/hour (3 studies) Comparator: Baseline, placebo	Outcomes: <ul style="list-style-type: none"> • Pain reduction (measured by VAS or NRS, or pain threshold) • Morphine-equivalent intake • QoL • Functional improvement • Cognitive effects • AEs Follow-up: <ul style="list-style-type: none"> • Pre- and post-infusion (1 study) • 3 hours to 5 days (4 studies) • 1 month to 6 months (8 studies) • 3 years (1 study)

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Pastrak et al. (2021) ¹⁵ Country: Canada Funding source: NR	SR Total 7 studies (4 RCTs, 1 prospective trial, and 2 case studies; total 118 patients) Sample size: Range from 1 to 34 patients. Countries of the primary studies: US (3), The Netherlands (1), Sweden (3) Publication year: 1995 to 2018	Patients with fibromyalgia Characteristics: NR	Intervention: IV ketamine ranging from 0.1 to 0.5 mg/kg Comparator: Baseline, placebo	Outcomes: • Pain reduction (measured by VAS) • AEs Follow-up: • 20 to 80 minutes, and 2 to 7 days (1 study) • 2.5 hours, 1 week, or 8 weeks (1 study) • > 1 year (1 study) • Up to 3 months (1 study) • NR (3 studies)

AEs = adverse events; IV = IV; MA = meta-analysis; NR = not reported; NRS = numeric rating scale; QoL = quality of life; SF-MPQ = Short-Form McGill Pain Questionnaire; SR = systematic review; VAS = visual analogue scale.

^aVAS or NRS range from 0 (no pain) to 10 (worst possible pain).

^bSF-MPQ has 2 subscales for pain rating – Sensory subscales with 11 words, and affective subscales with 4 words. Each word is rated on an intensity scale ranging as 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

^cPain threshold was defined as the amount of stimulation before the pain is experienced.

Table 3: Characteristics of Included Primary Clinical Study

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Dadabayev et al. (2020) ¹⁶ US Funding source: The authors reported that no funding was received.	Single centre, double-blind, RCT Total 41 patients Sample size calculation: Yes ITT analysis: No	Veterans with CP and with or without PTSD Mean age: 45.5 years Gender, %: • Male: 75.6 • Female: 24.4 Primary location of pain, %: • Low back pain: 70.7 • Neck: 4.9 • Joint(s): 4.9 • Headache: 7.3 • Other: 12.2	Intervention: Ketamine (single IV infusion of 0.5 mg/kg over 40 minutes) • CP + PTSD (N = 11) • CP only (N = 10) Comparator: Ketorolac (15 mg reconstituted in 500 mL of normal saline and administered over 40 minutes) • CP + PTSD (N = 10) • CP only (N = 10) 4 mg IV ondansetron was administered to all patients to prevent nausea and vomiting, a known side effect of ketamine.	Outcomes: • PTSD severity (using IES-R ^a) • CP severity (using VAS ^b) • Pain (using SF-BPI ^c) • Side effects (using PRISE ^d and CADSS ^e) Follow-up: up to 7 days

CADSS = Clinician-Administered Dissociative States Scales; CP = chronic pain; IES-R = Impact of Event Scale-Revised; PRISE = Patient-Rated Inventory of Side Effects; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SF-BPI = Short-Form Brief Pain Inventory; VAS = visual analogue scale.

^aIES-R: A screening instrument for PTSD, which consists of 22 items, the assessment of which ranges from 0 (“not at all”) to 4 (“extremely”).

^bVAS: A 10 cm line with 2 ends, representing 0 for “no pain” and 10 for “unbearable pain.”

^cSF-BPI: A 9-item self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning. The patient is asked to rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10-point scale.

^dPRISE: A tool used to identify side effects and assess the level of tolerance (0: absent, 1: tolerable, 2: painful) for each symptom experienced during the last 7 days in the different domains explored, i.e., gastrointestinal, cardiovascular, skin, nervous, sensory (eyes and ears) and urogenital systems, but also: sleep, sexual function, and other side effects.

^eCADSS: A 28-item instrument contained 23 interview items and 5 observer items. Patients were instructed to report dissociative states experienced during the preceding therapy session, and clinicians rated the reported and observed severity on a 5-point of The Likert scale, which ranges from 0 (not at all) to 4 (extreme) with item-specific anchors provided for each score.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 4: Strengths and Limitations of Systematic Reviews Using AMSTAR 2¹⁰

Strengths	Limitations
Guimaraes Pereira et al. (2022)¹³	
<ul style="list-style-type: none"> • The research question or objective and the inclusion criteria for the review clearly include the components of PICO. • A study protocol was published before conducting the review. • The review authors explained their selection of study designs, which were RCTs. • The literature search strategy was comprehensive and clearly described, using multiple combinations of keywords. The authors also hand searched the reference lists of the included studies. • The review authors performed study selection, data extraction and quality assessment of the included studies in duplicate. This reduced the risk of missing relevant studies and making errors in data extraction. • The characteristics of the included studies were described in adequate detail, including design, setting, follow-up time, intervention, control and outcomes. • The methodological quality of the included studies was assessed using the Cochrane risk of bias tool. • For meta-analysis, the review authors use appropriate methods for statistical combination of results. Treatment outcomes were expressed as RR for dichotomous outcomes, MD for continuous outcomes, and SMD for continuous outcomes measured by different scales, with the corresponding 95% CI. An overall RR, MD or SMD was pooled using a random-effects model. • As the overall quality of all included studies was considered high, the review authors did not assess the potential risk of bias in individual studies in the results of the meta-analysis. • The review authors provided a discussion of the heterogeneity observed in the results, which was the main limitation of the review. • The review authors reported the source of funding and declared no conflict of interest in this work. 	<ul style="list-style-type: none"> • Patient characteristics were not adequately described. • A list of excluded studies and the reasons for exclusion were not provided. Therefore, it was not possible to assess whether any relevant articles were excluded and if so, for what reasons. • The review authors did not report the sources of funding for the included studies. This is potentially a concern because funding received from industry can introduce bias in favour of the intervention. • The review authors could not carry out an investigation of publication bias since no single meta-analysis pooled more than 10 studies.
Chitneni et al. (2021)¹⁴	
<ul style="list-style-type: none"> • The research question or objective and the inclusion criteria for the review clearly include the components of PICO. • A study protocol was published before conducting the review. • The review authors explained their selection of study designs, which were RCTs, nonrandomized studies. 	<ul style="list-style-type: none"> • The review authors partially used a comprehensive literature search strategy. The authors did not report whether grey literature or the reference lists of reviewed studies were searched for relevant studies. • The review authors did not report whether study selection and data extraction of the included studies were performed in

Strengths	Limitations
<ul style="list-style-type: none"> The characteristics of the included studies were described in adequate detail, including design, setting, follow-up time, intervention, control and outcomes. The review authors provided a discussion of the heterogeneity observed in the results, which was the main limitation of the review. The review authors declared no conflict of interest in this work. 	<p>duplicate. Therefore, it is unclear whether a fully systematic approach was taken in study selection and data extraction.</p> <ul style="list-style-type: none"> Patient characteristics were not adequately described. A list of excluded studies and the reasons for exclusion were not provided. Therefore, it was not possible to assess whether any relevant articles were excluded and if so, for what reasons. The review authors did not use any technique to assess the risk of bias of the included studies. The review authors did not report the sources of funding for the included studies. The source of funding for the work was not reported.
Pastrak et al. (2021)¹⁵	
<ul style="list-style-type: none"> The research question or objective and the inclusion criteria for the review clearly include the components of PICO. The review authors explained their selection of study designs, which were both prospective and retrospective studies, as well as case series and case reports. 	<ul style="list-style-type: none"> The report of the review did not contain any statement indicating the review methods were established before the conduct of the review. The review authors partially did not use a comprehensive literature search strategy (only PubMed). The authors did not report whether grey literature or the reference lists of reviewed studies were searched for relevant studies. The review authors did not report whether study selection and data extraction were performed in duplicate. Therefore, it is unclear whether a fully systematic approach was taken in study selection and data extraction. A list of excluded studies and the reasons for exclusion were not provided. Therefore, it was not possible to assess whether any relevant articles were excluded and if so, for what reasons. The characteristics of the included studies were not described in adequate detail. The review authors did not use any technique to assess the risk of bias of the included studies. The review authors did not report the sources of funding for the included studies. The review authors did not provide a discussion of the heterogeneity observed in the results. The review authors did not report the source of funding for the work. They declared however that they had no financial or proprietary interest in the subject matter of the article.

AMSTAR 2 = A Measurement Tool to Assess systematic Reviews 2; CI = confidence interval; MD = mean difference; OR = odds ratio; PICO = population, intervention, comparator, and outcome; RCT = randomized controlled trial; RMD = standardized mean difference; RR = risks ratio.

Table 5: Strengths and Limitations of Clinical Study Using the Downs and Black Checklist¹¹

Strengths	Limitations
Dadabayev et al. (2020)¹⁶	
<p>Reporting:</p> <ul style="list-style-type: none"> • The objective of the study, the main outcomes to be measured, the interventions of interest, and the main findings were clearly described. • The number of patients lost to follow-up was low. • Adverse events of the intervention were reported. • Actual P values were reported for the main outcomes. <p>External validity:</p> <ul style="list-style-type: none"> • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of the patients receive. The study was conducted in an outpatient hospital setting. <p>Internal validity – bias:</p> <ul style="list-style-type: none"> • All study personnel, including rater, patients and data analysts were blinded to randomization order. • All patients were followed up for the same period of time, which was 7 days. • Statistical tests were used appropriately, and the main outcome measures were accurate and reliable. • The primary outcomes (i.e., PTSD and CP symptom severity) were accurately measured. <p>Internal validity – confounding:</p> <ul style="list-style-type: none"> • Patients in both intervention groups appeared to be recruited from the same population and over the same period of time. • A sample size calculation was performed. 	<p>Reporting:</p> <ul style="list-style-type: none"> • The characteristics of the participants included in the study were not clearly described. • It was unclear if there was any group differences (i.e., potential confounders) in demographics of the randomized participants. <p>External validity:</p> <ul style="list-style-type: none"> • Patients were recruited from a single centre. Sample size was small (N = 41); therefore, it was unlikely that the patients who participated were representative of the entire population from which they were recruited. <p>Internal validity – confounding:</p> <ul style="list-style-type: none"> • Methods of randomization and allocation concealment were not described. • Patients lost to follow-up was not considered in the analysis.

CP = chronic pain; PTSD = posttraumatic stress disorder.

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 6: Summary of Findings by Outcome – Pain

Study citation, study design, condition	Method of measurement	Result	Notes
Guimaraes Pereira et al. (2022) ¹³ SR with MA Neuropathic pain	VAS or NRS	Overall pain reduction in ketamine compared to various controls: <ul style="list-style-type: none"> MD (95% CI) = -1.68 (-2.36 to -0.96); I² = 90%; P < 0.00001 (6 RCTs) 	Controls: saline solution, amitriptyline + carbamazepine, magnesium sulphate Ketamine: IV (4 RCTs), oral (1 RCT), epidural (1 RCT).
		Pain reduction in ketamine compared to various controls after the end of ketamine at different time points: 1 week <ul style="list-style-type: none"> MD (95% CI) = -2.14 (-2.65 to -1.63); I² = 79%; P < 0.00001 (5 RCTs) 15 days <ul style="list-style-type: none"> MD (95% CI) = -1.30 (-2.04 to -0.57); I² = 84%; P = 0.0005 (5 RCTs) 30 days <ul style="list-style-type: none"> MD (95% CI) = -1.68 (-2.25 to -1.12); I² = 77%; P < 0.00001 (4 RCTs) 	Controls: saline solution, amitriptyline + carbamazepine, magnesium sulphate Ketamine: IV (4 RCTs), oral (1 RCT), epidural (1 RCT).
		Pain reduction in ketamine treatment compared to baseline pain levels after the end of ketamine at different time points: 1 week <ul style="list-style-type: none"> MD (95% CI) = -4.12 (-5.72 to -2.51); I² = 98%; P < 0.00001 (5 RCTs) 15 days <ul style="list-style-type: none"> MD (95% CI) = -3.60 (-4.75 to -2.44); I² = 94%; P < 0.00001 (5 RCTs) 30 days <ul style="list-style-type: none"> MD (95% CI) = -3.86 (-4.51 to -3.21); I² = 78%; P < 0.00001 (3 RCTs) 2 months <ul style="list-style-type: none"> MD (95% CI) = -2.22 (-4.22 to -0.21); I² = 95%; P = 0.03 (2 RCTs) 3 months <ul style="list-style-type: none"> MD (95% CI) = -3.22 (-7.66 to 1.22); I² = 98%; P = 0.15 (2 RCTs) 	Ketamine: IV (4 RCTs), oral (2 RCTs), epidural (1 RCT).
	McGill Pain Questionnaire, Neuropathic Pain	Pain reduction in ketamine compared to various controls measured by multidimensional pain scales: <ul style="list-style-type: none"> SMD (95% CI) = -0.02 (-0.43 to 0.39); I² = 0%; P = 0.93 (5 RCTs) 	Controls: Topical placebo, saline solution, magnesium sulphate Ketamine: Topical (1

Study citation, study design, condition	Method of measurement	Result	Notes
	Questionnaire, VAS		RCT), oral (1 RCT), iontophoretic (1 RCT), IV (2 RCTs).
Chitneni et al. (2021) ¹⁴ SR Complex regional pain syndrome	VAS or NRS (13 studies) Pain threshold (1 study)	<ul style="list-style-type: none"> • Ketamine infusion improved VAS or NRS pain scores or pain threshold. (13 studies) • Ketamine infusion did not show significant change in pain relief in patients with longstanding severe CRPS. (1 study) 	No numerical data reported. Comparator: baseline or placebo Pain threshold is defined as the amount of stimulation before the pain is experienced.
Pastrak et al. (2021) ¹⁵ SR Fibromyalgia	VAS	<ul style="list-style-type: none"> • IV infusion of low dose ketamine (0.3 to 0.5 mg/kg) revealed a short-term reduction (few hours after infusion) in pain intensity scores or improvement in pain threshold and pain tolerance relative to placebo. (4 RCTs) • Low-dose IV ketamine followed by dextromethorphan treatment showed a VAS reduction of > 50% in 18 of 34 patients after infusion, but long-term benefit from 1-time ketamine infusion was not observed. (1 prospective trial). • Higher doses and longer, repeated ketamine infusions may result in long-term reduction in pain. (2 case studies) 	No numerical data reported.
Dadabayev et al. (2020) ¹⁶ RCT Chronic pain	VAS, BPI	<ul style="list-style-type: none"> • Both treatments of ketamine and ketorolac showed comparable improvement in pain scores in patients with or without PTSD that persisted for 7 days after infusion. • There was no statistically significant difference between groups, medications, and time points. 	No numerical data reported.

BPI = Brief Pain Inventory; CI = confidence interval; CRPS = complex regional pain syndrome; MA = meta-analysis; MD = mean difference; NRS = numerical rating scale; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SMD = standardized mean difference; SR = systematic review; VAS = visual analogue scale.

Table 7: Summary of Findings by Outcome – Adverse Events

Study citation, study design, condition	Method of measurement	Result	Notes
Guimaraes Pereira et al. (2022) ¹³ SR with MA Neuropathic pain	NR	Psychedelic effects observed in ketamine compared to various controls: <ul style="list-style-type: none"> • RR (95% CI) = 4.94 (2.76 to 8.84); I² = 0%; P < 0.00001 (9 RCTs). 	Control: Saline solution, magnesium, methadone Ketamine: IV (7 RCTs), iontophoretic (1 RCT), oral (1 RCT).
		Discomfort observed in ketamine compared to various controls: <ul style="list-style-type: none"> • RR (95% CI) = 4.06 (1.18 to 13.95); I² = 0%; P = 0.03 (2 RCTs). 	Controls: Saline solution Ketamine: IV (2 RCTs).

Study citation, study design, condition	Method of measurement	Result	Notes
		Nausea and vomiting observed in ketamine compared to various controls: <ul style="list-style-type: none"> RR (95% CI) = 1.40 (0.45 to 4.33); $I^2 = 65%$; $P = 0.56$ (6 RCTs). 	Controls: Saline solution, methadone Ketamine: IV (4 RCTs), iontophoretic (1 RCT), oral (1 RCT).
		Fatigue observed in ketamine compared to various controls: <ul style="list-style-type: none"> RR (95% CI) = 1.17 (0.33 to 4.16); $I^2 = 49%$; $P = 0.81$ (4 RCTs). 	Controls: Saline solution, magnesium Ketamine: IV (4 RCTs).
		Dizziness observed in ketamine compared to various controls: <ul style="list-style-type: none"> R various controls R (95% CI) = 2.13 (0.71 to 6.33); $I^2 = 42%$; $P = 0.18$ (4 RCTs). 	Controls: Saline solution, methadone Ketamine: IV (2 RCTs), ionotropic (1 RCT), oral (1 RCT).
Chitneni et al. (2021) ¹⁴ SR Complex regional pain syndrome	NR	<ul style="list-style-type: none"> Mild symptoms of fatigue, headache, and nausea. (7 studies) Mild-to-moderate psychotomimetic effects, such as hallucinations. (2 studies). 	No numerical data reported.
Pastrak et al. (2021) ¹⁵ SR Fibromyalgia	NR	<ul style="list-style-type: none"> Ketamine was associated with short-lasting (up to 15 minutes) feeling of unreality, dizziness, and changes in hearing. (1 RCT) Both treatment groups (i.e., ketamine and midazolam) was associated with short-lasting (about 30 minutes) drowsiness and euphoria. (1 RCTs) No side effects were observed. (2 RCTs) Ketamine was associated with short-lasting (about 30 minutes) dizziness, confusion, euphoria, and nausea. (1 prospective study) Ketamine was associated with nausea and agitation (1 case study) No side effects were observed. (1 case study) 	No numerical data reported.
Dadabayev et al. (2020) ¹⁶ RCT Chronic pain	PRISE and CADSS	<ul style="list-style-type: none"> Both ketamine and ketorolac treatment was associated with significant increase in dissociative symptoms in the CP group, but less effect on dissociative symptoms in the CP + PTSD group. Patients generally tolerated well with both ketamine and ketorolac treatments with respect to Patient-Rated Inventory of Side Effects. 	No numerical data reported.

CADSS = Clinician-Administered Dissociative States Scales; CP = chronic pain; NR = not reported; PRISE = Patient-Rated Inventory of Side Effects; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial.

Table 8: Summary of Findings by Outcome – Other Outcomes

Study citation, study design, condition	Method of measurement	Result	Notes
Chitneni et al. (2021) ¹⁴ SR Complex regional pain syndrome	NR	Morphine-equivalent intake: <ul style="list-style-type: none"> • While ketamine reduced pain intensity, it did not reduce overall opioid intake. (1 study) Quality of life (QoL): <ul style="list-style-type: none"> • Ketamine treatment was associated with significant improvement in QoL in the majority of patients at 3- and 6-months follow-up. (1 study) • There were no significant changes in QoL scores following treatment in either ketamine or placebo groups. (1 study) Functional improvement (e.g., ability to work, activity level, active range of motion, and effect on movement disorder): <ul style="list-style-type: none"> • Ability to work was significantly improved after 3 months of ketamine treatment, with an even greater improvement by 6 months. (1 study) • There were no significant changes in activity level between pre- and post-treatment, but the number of nighttime awakenings in the ketamine group decreased by 85% after treatment. (1 study) • Ketamine treatment did not cause functional improvement in active range of motion and the ability to walk without support. (2 studies) Cognitive effects: <ul style="list-style-type: none"> • There were significant improvements in brief auditory attention and processing speed, no changes in learning, memory or motor speed, and a slight decline in motor strength. (1 study) 	No numerical data reported.
Dadabayev et al. (2020) ¹⁶ RCT Chronic pain	IES-R	PTSD severity in the CP + PTSD group: <ul style="list-style-type: none"> • Both ketamine and ketorolac treatments yielded a statistically significant decrease in PTST symptom scores from baseline to 7 days after infusion ($P < 0.01$). • There was no statistically significant difference between ketamine and ketorolac effect on PTSD symptoms ($P > 0.05$). 	No numerical data reported.

IES-R = Impact of Event Scale-Revised; NR = not reported; QoL = quality of life; RCT = randomized controlled trial; SR = systematic review.

Appendix 5: Overlap Between Included Systematic Reviews

Note that this appendix has not been copy-edited.

Table 9: Overlap in Relevant Primary Studies Between Included Systematic Reviews

Primary study citation	Guimaraes Pereira et al. (2022) ¹³	Chitneni et al. (2021) ¹⁴
Sigtermans MJ, van Hilten JJ, Bauer MCR, et al. <i>Pain</i> . 2009;145(3):304 to 311.	Yes	Yes
Schwartzman RJ, Alexander GM, Grothusen JR, Paylor T, Reichenberger E, Perreault M. <i>Pain</i> . 2009;147(1 to 3):107 to 115.	Yes	Yes
Amr Y. <i>Anesth Essays Res</i> . 2011;5(1):83 to 86.	Yes	–
Amr Y. <i>Pain Physician</i> . 2010;13(3):245 to 249.	Yes	–
Antonio Moreira de Barros G, Amante Miot H, Massarico Braz A, Ramos F, Aristoteles Borges M. <i>An Bras Dermatol</i> . 2012;87(3):504 to 505.	Yes	–
Niesters M, Aarts L, Sarton E, Dahan A. <i>BJA</i> . 2013;110(6):1010 to 1016.	Yes	–
Kim YH, Lee PB, Oh TK. <i>J Clin Anesth</i> . 2015;27(4):296 to 300.	Yes	–
Ferreira J, Karine Rigo F, Trevisan G, et al. <i>Pain Physician</i> . 2017;20(3):207 to 215.	Yes	–
Fallon MT, Wilcock A, Kelly CA, et al. <i>JAMA Oncol</i> . 2018;4(6):870 to 872.	Yes	–
Pickering G, Pickering G, Pereira B, et al. <i>Anesthesiology</i> . 2020;133(1):154 to 164.	Yes	–
Kvarnstrom A, Karlsten R, Quiding H, Emanuelsson B-M, Gordh T. <i>Acta Anaesthesiol Scand</i> . 2003;47(7):868 to 877.	Yes	–
Lynch ME, Clark AJ, Sawynok J, Sullivan MJL. <i>Anesthesiology</i> . 2005;103(1):140 to 146.	Yes	–
Vranken JH, Dijkgraaf MGW, Kruis MR, van Dasselaar NT, van der Vegt MH. <i>Pain</i> . 2005;118(1 to 2):224 to 231.	Yes	–
Eide P, Jorum E, Stubhaug A, Bremnes J, Brcivik H. <i>Pain</i> . 1994;58(3):347 to 354.	Yes	–
Max M, Byas-Smith G, Gracely R, Bennett G. <i>Clin Neuropharmacol</i> . 1995;18(4):360 to 368.	Yes	–
Mercadante S, Arcuri E, Tirelli W, Casuccio A. <i>J Pain Symptom Manage</i> . 2000;20(4):246 to 252.	Yes	–
Rocha Lauretti G, de Menezes Rodrigues A, Maria Alves Gomes J, Paulino Dos Reis M. <i>Rev Bras Anesthesiol</i> . 2002;52(1):34 to 40.	Yes	–
Tonet C, Sakata R, Issy A, Garcia J, Marcelino A. <i>Rev Bras Med</i> . 2008;65(7):214 to 218.	Yes	–
Kirkpatrick AF, Saghafi A, Yang K, Qiu P, Alexander J, Bavry E, Schwartzman R. <i>Clin J Pain</i> . 2020, 36:516 to 23.	–	Yes
Kiefer RT, Rohr P, Ploppa A, et al. <i>Pain Med</i> . 2008, 9:44 to 54.	–	Yes
Goldberg ME, Torjman MC, Schwartzman RJ, Mager DE, Wainer IW. <i>Pain Physician</i> . 2010, 13:379 to 87.	–	Yes

Primary study citation	Guimaraes Pereira et al. (2022) ¹³	Chitneni et al. (2021) ¹⁴
Sheehy KA, Muller EA, Lippold C, Nouraie M, Finkel JC, Quezado ZM. BMC Pediatr. 2015, 15:198.	—	Yes
Kiefer RT, Rohr P, Ploppa A, et al. Pain Med. 2008, 9:1173 to 201.	—	Yes
Puchalski P, Zyluk A. Handchir Mikrochir Plast Chir. 2016, 48:143 to 47.	—	Yes
Koffler SP, Hampstead BM, Irani F, Tinker J, Kiefer RT, Rohr P, Schwartzman RJ. Arch Clin Neuropsychol. 2007, 22:719 to 29.	—	Yes
Correll GE, Maleki J, Gracely EJ, Muir JJ, Harbut RE. Pain Med. 2004, 5:263 to 75.	—	Yes
Sigtermans M, Noppers I, Sarton E, Bauer M, Mooren R, Olofsen E, Dahan A. Eur J Pain. 2010, 14:302 to 307.	—	Yes
Goebel A, Jayaseelan S, Sachane K, Gupta M, Frank B. Br J Anaesth. 2015, 115:146 to 47.	—	Yes
Dahan A, Olofsen E, Sigtermans M, et al. Eur J Pain. 2011, 15:258 to 67.	—	Yes
Patil S, Anitescu M. Pain Med. 2012, 13:263 to 69.	—	Yes

The third SR¹⁵ did not have any included studies that overlapped with those in the other 2 SRs.^{13,14}

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ISSN: 2563-6596

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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