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Codeine for Acute Pain in Patients Undergoing Orthopedic Surgery: A Review of Clinical Effectiveness

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Authors: Dave K. Marchand, Suzanne McCormack

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Questions or requests for information about this report can be directed to Requests@CADTH.ca

Abbreviations

AMSTAR 2	A Measurement Tool to Assess Systematic Reviews 2
CRD	University of York Centre for Reviews and Dissemination
MA	meta-analysis
MeSH	Medical subject headings
NRS	Non-randomized study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International prospective register of systematic reviews
RCT	randomized controlled trial
SR	systematic review

Context and Policy Issues

Orthopedic (i.e., musculoskeletal) surgery, as with most surgical procedures, can bring about inflammation, tissue injury (e.g., mechanical, thermal, chemical), or nerve injury (e.g., transection, stretching, compression).[1] These three noxious stimuli cause specialised sensory nerves located almost everywhere in the body, called nociceptors, to send an impulse along their nerve fiber to the dorsal horn of the spinal cord which then relays the signal to neurones projecting to the brain.[2,3] As the signal ascends and reaches the brain, it is distributed to various central structures where it can be processed further.[3] Although the physiology of pain is elaborate and poorly understood, it is thought that at this point in transmission, pain becomes a conscious experience,[3] and subject to modulation by many additional factors such as chemical mediators of pain, the endogenous opiate system, and other domains such as a person's personality, circumstances, and emotional state.[2] Pain can be classified as acute (lasting for minutes to several weeks), or chronic (lasting months to years).[3,4] This report will focus on acute pain as a result of orthopedic surgery.

The goals of therapy for postoperative acute pain include the recognition that the patient is experiencing pain, to anticipate and pre-emptively relieve the pain, to rapidly reduce the intensity of the pain, and to generally minimise discomfort.[1,3-5] Treatment should be continued as long as the patient is experiencing pain.[5]

Typically, therapeutic options for orthopedic postoperative pain control are multimodal and tailored to the patient's characteristics, their needs, and the level of pain associated with the surgery.[1] These factors will determine the type of analgesic technique (systemic, regional, local), as well as the category of pharmacotherapy (e.g., opioid, non-opioid) that should be privileged. Opioids (e.g., morphine, fentanyl, hydromorphone, oxycodone, codeine) are the most widely used treatment of postoperative pain;[1,3] however, non-opioids (e.g., non steroidal anti-inflammatory drugs, acetaminophen, salicylates) can also be used.[3,4]

This being said, opioid prescribing practices have come under scrutiny in recent years as Canada battles with an opioid epidemic.[6] Overprescribing by physicians,[7-9] and the diversion of non-consumed supplies, have been recognised as a contributor to the national opioid epidemic.[10] As a result there has been a desire to optimize opioid prescribing after surgery, when patient and surgical factors make this possible.[9] Specifically, the role of codeine in orthopedic post-operative pain management is being questioned and will be the focus of the present report.

In Canada, several formulations of codeine are available for treatment of pain. Codeine primarily agonises the mu receptor.[11,12] It is metabolised in the liver by the cytochrome P450 system, specifically via the CYP2D6 isoenzyme, to various metabolites including

morphine,[4,11] which accounts for some of its analgesic effect.[4,11,12] The rate of metabolism by the CYP2D6 isoenzyme is known to vary in the general population,[4,11] which highlights the variety of pain relief that can been observed when codeine is used as a single agent.[4] It is a relatively weak opioid,[12] and may also be used in combination with acetaminophen, where an additive analgesic effect is seen.[4]

A previous CADTH report, published in 2010, sought clinical effectiveness and guideline evidence on pre-hospital orthopedic injury or fracture pain management.[13] The objective of the present report is to investigate the clinical effectiveness of codeine or codeine with acetaminophen for the management of acute pain in adults post orthopedic surgery.

Research Questions

1. What is the clinical effectiveness of codeine for patients who have undergone orthopedic surgery?
2. What is the clinical effectiveness of codeine with acetaminophen for patients who have undergone orthopedic surgery?

Key Findings

Two systematic reviews on pharmacotherapies for the management of pain after orthopedic surgery were identified but did not contain any relevant literature regarding the clinical effectiveness of codeine, or codeine with acetaminophen, for pain management in patients who have undergone orthopedic surgery.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, Embase, 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 codeine and orthopedic surgery. No search filters were applied to limit 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, 2014 and October 1, 2019.

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	Adult patients with acute pain who have undergone orthopedic surgery
Intervention	Q1: Codeine Q2: Codeine with acetaminophen (codeine as a single product, plus acetaminophen as a single product)
Comparator	Q1: Other opioids, placebo, narcotics, non-opiate adjuncts, non-steroidal anti-inflammatory drugs Q2: Acetaminophen only
Outcomes	Q1-Q2: Clinical effectiveness (e.g., pain control, pain measurement), safety (e.g., overdose, liver function, AEs, hospitalizations)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

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 2014.

Critical Appraisal of Individual Studies

One reviewer critically appraised the included systematic reviews (SR) using A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) checklist.[14] Summary scores were not calculated, rather, a review of the strengths and limitations of the included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 345 citations were identified in the literature search. Following screening of titles and abstracts, 310 citations were excluded and 35 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 33 publications were excluded for various reasons, and two SRs met the inclusion criteria and were included in this report. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[15] flowchart of the study selection.

Appendix 4 includes two additional references that did not meet the inclusion criteria of this report but may be of interest.

Summary of Study Characteristics

Two SRs[16,17] met the inclusion criteria for this report; however, none of their primary studies met the eligibility criteria for this report, as the scope of the SRs was broader than the scope of this report. Detailed characteristics of the SR are available in Appendix 2.

Study Design

One SR[16] published in 2018 searched two databases for English language randomized controlled trials (RCTs) published between January 2012 and September 2017. Authors

aimed to assess the evidence on the efficacy and safety of pharmacological and non-pharmacological therapies for postoperative pain after lumbar spine procedures.[16] The second SR[17] published in 2015 searched four databases for English literature (SRs, meta-analyses [MA], literature reviews, RCTs, and trials) published between 1946 and February 2013. Authors aimed to review the literature on pain management after elective foot and ankle surgery.[17] Although in line with the research questions of this CADTH report, these SRs contained no primary studies specific to codeine with or without acetaminophen.

Country of Origin

The first authors of the SRs were from Italy[16] and the United States of America.[17]

Patient Population

The first SR included adult patients who had various types of lumbar spine surgery,[16] while the second SR included adult patients with foot and ankle surgery.

Interventions and Comparators

Both SRs looked at a variety of pharmacological interventions for pain (e.g., opioids, gabapentin, nonsteroidal anti-inflammatory drugs, ketamine) compared to each other,[16,17] to a control group,[16,17] or to no comparator;[17] however, there were no included primary studies specific to codeine with or without acetaminophen.

Outcomes

The outcomes considered in the first SR were analgesic efficacy, as well as safety and clinical complications,[16] while the second SR considered outcomes relating to postoperative pain scores, supplemental analgesic requirements, and adverse events.[17]

Summary of Critical Appraisal

Systematic Reviews

The strengths and limitations of the SRs[16,17] were assessed using the relevant components of AMSTAR 2;[14] however, as none of the primary studies included in the SRs were relevant to this report, a number of the checklist items were not applicable.

In both SRs,[16,17] the research questions and the inclusion criteria were well described, the study selection was completed in duplicate, and although the included studies were partially described, greater detail regarding the population characteristics (such as age, gender, type of surgery, presence of complications during surgery) could have been provided. Neither SR[16,17] reported how many people were involved in data extraction, provided a justification of their choice of included study designs, nor provided a list of excluded studies. It is possible this may have resulted in missed studies. Furthermore, although the authors searched at least two databases, their restrictions (i.e., language, study design) were not justified, they did not search the reference lists of included studies, they did not consult experts in the field, nor did they search the grey literature.[16,17] Here too, it is possible this may have resulted in missed studies. One SR[16] established methods prior to the conduct of the review and registered their work with the International prospective register of systematic reviews (PROSPERO), reducing the risk of reporting bias. In addition, this SR only included RCTs and it is possible that additional evidence may have been available in non-randomized studies (NRS). The second SR[17] made no mention of a written protocol, and thus it is unknown if any changes to the protocol were made throughout the review process or if there was selective reporting of SR results. Also, the authors declared conflicts of

interests related to this SR;[17] however, they did not discuss how these were managed during the review design, data interpretation and analysis, as well as authorship.

Summary of Findings

Clinical Effectiveness of Codeine for Patients who Have Undergone Orthopedic Surgery

The identified SRs[16,17] did not include any relevant primary studies comparing the clinical effectiveness of codeine versus other opioids, placebo, narcotics, non-opiate adjuncts, non-steroidal anti-inflammatory drugs for adults with acute pain who have undergone orthopedic surgery; therefore, no summary can be provided.

Clinical Effectiveness of Codeine with Acetaminophen for Patients who Have Undergone Orthopedic Surgery

The identified SRs[16,17] did not include any relevant primary studies comparing the clinical effectiveness of codeine with acetaminophen versus acetaminophen only for adults with acute pain who have undergone orthopedic surgery; therefore, no summary can be provided.

Limitations

A primary limitation of this report is the lack of relevant comparative evidence. Two SRs[16,17] were identified but did not contain any literature regarding the clinical effectiveness of codeine or codeine with acetaminophen for patients who have undergone orthopedic surgery.

Conclusions and Implications for Decision or Policy Making

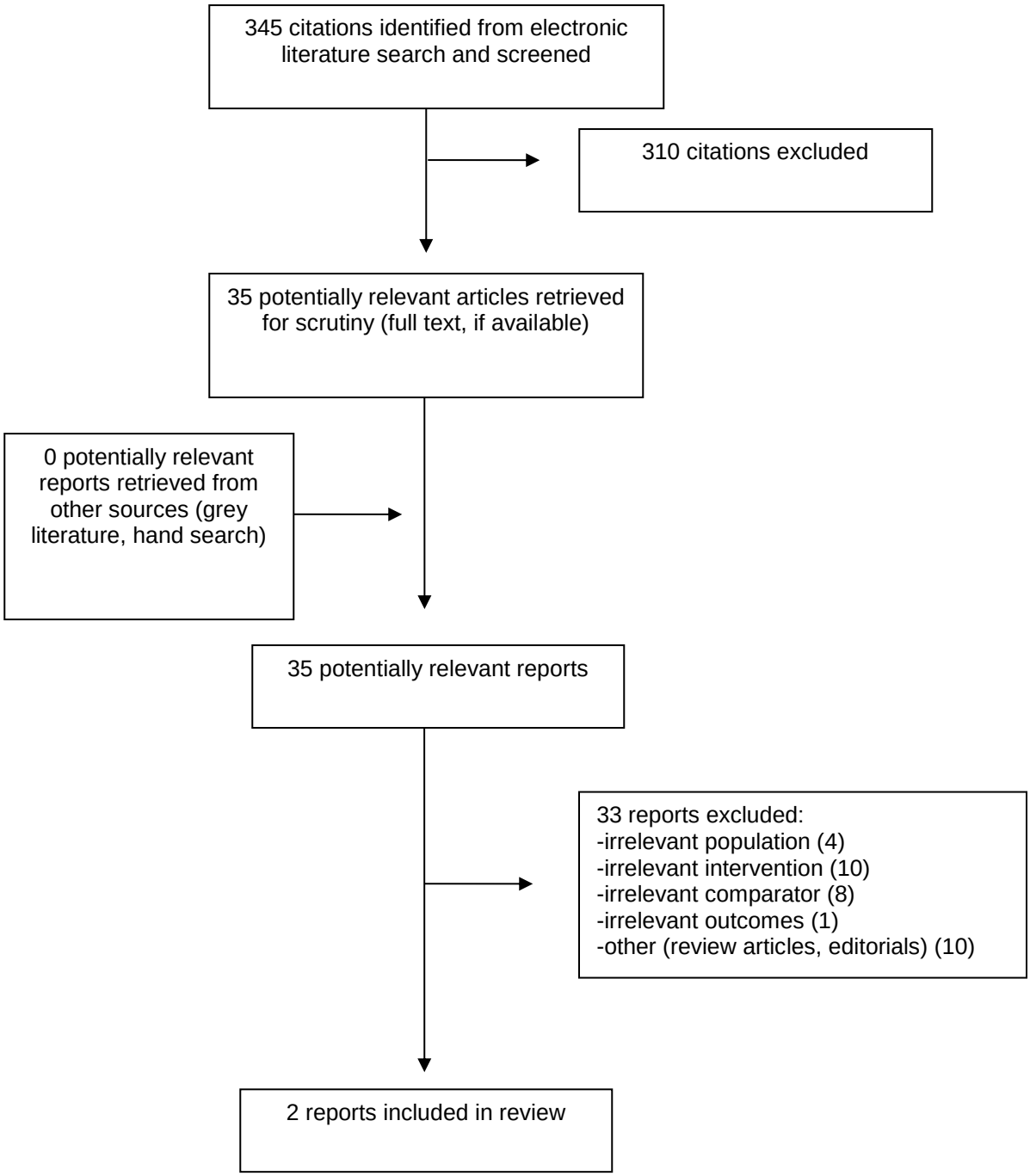
No relevant literature was identified regarding the clinical effectiveness of codeine as compared with other opioids, placebo, narcotics, non-opiate adjuncts, non-steroidal anti-inflammatory drugs, or the clinical effectiveness of codeine with acetaminophen compared with acetaminophen only for acute pain post orthopedic surgery; therefore, no conclusions can be provided.

There is a distinct lack of comparative studies regarding these interventions in the orthopedic post-surgery setting. Further research investigating the clinical effectiveness of codeine or codeine with acetaminophen for acute pain after orthopedic surgery compared with alternatives, especially by way of large, methodologically-sound RCTs would help reduce the uncertainty on this topic.

References

1. Mariano ER. Management of acute perioperative pain. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2019: https://www.uptodate.com Accessed 2019 Oct 17.
2. Henry JL. Pathophysiology of Chronic Pain In: Rashiq S, Schopflocher D, Taenzer P, Jonsson E, eds. *Chronic pain: A health policy perspective*. Weinheim (DE): John Wiley & Sons; 2008.
3. Baumann TJ, Herndon CM, Strickland J. Pain Management. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 9th ed. New York (NY): McGraw-Hill Education; 2014.
4. Bailey B. Acute Pain. In: Jovaisas B, ed. *Compendium of therapeutic choices*. 7th ed. Ottawa (ON): Canadian Pharmacists Association; 2014.
5. Woolf CJ, Chong M-S. Preemptive Analgesia—Treating Postoperative Pain by Preventing the Establishment of Central Sensitization. *Anesth Analg.* 1993;77(2):362-379.
6. Morin KA, Eibl JK, Franklyn AM, Marsh DC. The opioid crisis: past, present and future policy climate in Ontario, Canada. *Subst Abuse Treat Prev Policy.* 2017;12(1):45.
7. Tepolt FA, Bido J, Burgess S, Micheli LJ, Kocher MS. Opioid Overprescription After Knee Arthroscopy and Related Surgery in Adolescents and Young Adults. *Arthroscopy.* 2018;34(12):3236-3243.
8. Roberts K, Moser S, Schaffer N, et al. Prescribing and Consumption of Opioids After Primary, Unilateral Total Hip and Knee Arthroplasty in Opioid Naive Patients. *The Journal of Arthroplasty.* 2019.
9. Thiels CA, Anderson SS, Ubl DS, et al. Wide Variation and Overprescription of Opioids After Elective Surgery. *Ann Surg.* 2017;266(4):564-573.
10. Morris BJ, Mir HR. The opioid epidemic: impact on orthopaedic surgery. *J Am Acad Orthop Surg.* 2015;23(5):267-271.
11. Sweetman SC, ed *Martindale: The complete drug reference.* London (GB): Pharmaceutical Press; 2011.
12. United States Pharmacopeia Dispensing Information. *Drug information for the health care professional.* Vol 1. Montvale (NJ): Micromedex Medical Economics; 2005.
13. Pre-Hospital Orthopedic Pain Management: Clinical Effectiveness and Guidelines. Ottawa (ON): CADTH; 2010: https://cadth.ca/sites/default/files/pdf/k0219_pre-hospital_orthopedic_pain_management_htis-1-5.pdf. Accessed 2019 Oct 22.
14. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2019 Oct 16.
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
16. Terracina S, Robba C, Prete A, Sergi PG, Bilotta F. Prevention and Treatment of Postoperative Pain after Lumbar Spine Procedures: A Systematic Review. *Pain Practice.* 2018;18(7):925-945.
17. Wang J, Liu GT, Mayo HG, Joshi GP. Pain Management for Elective Foot and Ankle Surgery: A Systematic Review of Randomized Controlled Trials. *J Foot Ankle Surg.* 2015;54(4):625-635.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Terracina, 2018[16] **Italy**	**Objective**: to assess the evidence on the efficacy and safety of pharmacological and non-pharmacological therapies for postoperative pain after lumbar spine procedures **Study design**: A SR of relevant RCTs **Literature search strategy**: Limited to English literature published between January 2012 and September 2017, the search was conducted in PubMED and EMBASE **Number of studies included**: A total of 59 RCTs were identified; however, none were relevant to this report. **Quality assessment tool**: Risk of bias was assessed using the Cochrane criteria for RCTs. Level of evidence were categorized according to OCEBM	Adults patients post lumbar spine procedures (i.e., open and percutaneous procedures, microdiscectomy, percutaneous endoscopic lumbar discectomy, spine fusion, and laminectomy)	**Intervention**: a variety of pharmacological interventions (e.g., opioids, gabapentin, nonsteroidal anti-inflammatory drugs, ketamine) as well as non pharmacological interventions (e.g. electrical stimulation) **Comparator**: the above compared to each other, or a control group	**Outcomes**: - Analgesic efficacy - Safety and clinical complications **Follow-up**: NR
Wang, 2015[17] **United States of America**	**Objective**: To review the literature on pain management after elective foot and ankle surgery **Study design**: SR of relevant SRs, MAs, literature reviews, RCTs, and trials.	Adult patients with foot and ankle surgery pain managed by analgesics.	**Intervention**: a variety of pharmacological interventions (e.g., opioids, gabapentin, nonsteroidal anti-inflammatory drugs, ketamine, acetaminophen, corticosteroids)	**Outcomes**: - Postoperative pain scores - Supplemental analgesic requirements - Adverse events **Follow-up**: NR

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Literature search strategy: Limited to English literature published between January 1946 and February 2013, the search was conducted in MEDLINE, Cochrane Database of SRs, DARE, and CENTRAL. This was supplemented by a manual search of the reference lists. **Number of studies included**: A total of 45 RCTs were identified; however, none were relevant to this report. **Quality assessment tool**: The Jadad instrument		**Comparator**: the above compared to each other, a control group, or none	

CENTRAL = Cochrane Central Register of Controlled Trials; DARE = Database of Abstracts of Reviews of Effects; EMBASE = Excerpta Medica database; MA = meta-analysis; MEDLINE = Medical Literature Analysis and Retrieval System Online; NA = not applicable; NR = not reported; OCEBM = Oxford Centre for Evidence-Based Medicine; PubMED = Public MEDLINE; RCT = randomized controlled trial; SR = systematic review.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[14]

Strengths	Limitations
Terracina, 2018[16]	
• The objectives and inclusion/exclusion criteria were clearly stated • Methods were established prior to the conduct of the review and registered with PROSPERO (CRD42015017759) • Study selection was completed in duplicate and described in detail • The included studies were partially described; however, greater detail on the population characteristics could have been provided (i.e., only the number of patients was provided) • Risk of Bias was assessed according to the Cochrane Collaboration's criteria for RCTs • The authors stated that they had no conflicts of interests related to this review	• The choice of included study designs was not justified • Although the authors searched at least two databases, their restrictions were not justified, and it was unclear if they searched the reference lists of included studies, consulted experts in the field, or if they searched the grey literature • Data extraction was not reported as completed in duplicate • A list of excluded studies was not provided • Review authors did not report on source of funding for the included studies • Funding of the SR was not declared
Wang, 2015[17]	
• The objectives and inclusion/exclusion criteria were clearly stated • Study selection was completed in duplicate and described in detail • The included studies were partially described; however, greater detail on the population characteristics could have been provided (i.e., only the number of patients was provided) • Although quality was assessed using the Jadad three-item instrument (addressing randomization, blinding, and withdrawals/dropouts), other types of bias (e.g., selection bias in reporting results or allocation concealment) were not assessed	• An *a priori* protocol was not reported for the review • The choice of included study designs was not justified • Although the authors searched at least two databases, their restrictions were not justified, and it was unclear if they searched the reference lists of included studies, consulted experts in the field, or if they searched the grey literature • Data extraction was not reported as completed in duplicate • A list of excluded studies was not provided • Review authors did not report on source of funding for the included studies • Although authors declared conflicts of interests related to this review, they did not discuss how these were managed

AMSTAR 2 = A Measurement Tool to Assess Systematic Reviews 2; PROSPERO = International prospective register of systematic reviews; RCT = randomized controlled trial; SR = systematic review.

Appendix 4: Additional References of Potential Interest

Alternative Comparator for Question 2 – Placebo

Abdel Shaheed C, Maher CG, McLachlan AJ. Efficacy and Safety of Low-dose Codeine-containing Combination Analgesics for Pain: Systematic Review and Meta-Analysis. *Clin J Pain*. 2019 Oct;35(10):836-843.
PubMed: PM31318725

Alternative Intervention – Codeine and Ibuprofen

Luo P, Lou J, Yang S. Pain Management during Rehabilitation after Distal Radius Fracture Stabilized with Volar Locking Plate: A Prospective Cohort Study. *Biomed Res Int*. 2018;2018:5786089.
PubMed: PM30519581