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Codeine for Pediatric Patients with Acute Pain: A Review of Clinical Effectiveness

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Abbreviations

AE	adverse events
CAS	Color Analog Scale
CENTRAL	Cochrane Central Register of Controlled Trials
GMS	Global Mood Scale
RCT	randomized controlled trial
NSAID	nonsteroidal anti-inflammatory drugs
VAS	Visual Analog Scale

Context and Policy Issues

Acute pain is pain related to injury or illness that is defined as lasting less than three or six months in duration.[1,2] Codeine is a narcotic pain medication used to treat mild to moderate pain, or to suppress dry coughs.[3] As a pain reliever, it is metabolized to morphine in the body and binds to pain receptors, to decrease the feeling of pain and physiological response to pain.[3,4] Codeine comes in tablet, long-acting tablet, oral solution, and injectable formulations.[3] It is often combined with other active ingredients such as acetaminophen in a single tablet or liquid.[3,5] Other commonly used pain medications for pediatric patients include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, naproxen, and ketorolac, as well as opioid analgesics such as morphine, hydromorphone, oxycodone and hydrocodone.[6]

In the past decade, various organization around the world have issued warnings regarding the use of codeine for pain in pediatric patients.[7] In 2011, the World Health Organization deleted codeine from its list of essential medications for children because of concerns regarding questionable efficacy and safety in an unpredictable portion of the population.[8] In 2013, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee recommended restricting the use of codeine when used for pain relief in children due to risk of adverse events (AEs).[4] In 2013, Health Canada recommended against the use of codeine in children younger than 12 years old after reviewing the safety of prescription pain and cough medications containing codeine.[7] The purpose of this report is to examine the clinical effectiveness of codeine and codeine with acetaminophen for pediatric patients with acute pain.

Research Questions

1. What is the clinical effectiveness of codeine for pediatric patients with acute pain?
2. What is the clinical effectiveness of codeine with acetaminophen for pediatric patients with acute pain?

Key Findings

One systematic review was identified regarding the clinical effectiveness of codeine or codeine with acetaminophen, three randomized controlled trials (RCT) were identified regarding the clinical effectiveness of codeine with acetaminophen, and one non-randomized study was identified regarding the clinical effectiveness of codeine. For the clinical effectiveness of codeine, the included systematic review[2] compared codeine to acetaminophen or ibuprofen; no difference was found between groups for minor AEs, including nausea, sleepiness and constipation (however it was unclear if between-group

differences were compared statistically). For comparisons with codeine plus acetaminophen, the included systematic review showed significantly higher rates of adverse events in the codeine plus acetaminophen group versus the ibuprofen group in a single RCT. The first included RCT, the patients in the codeine plus acetaminophen group had lower pain and distress compared to the acetaminophen group during restraint and needle aspiration of tympanocentesis. In the second included RCT, codeine plus acetaminophen was significantly less effective for play and eating functional outcomes. In the third included RCT, between-group differences were not tested statistically but pain scores were numerically similar between the acetaminophen and ibuprofen group. In the non-randomized study, there were no significant differences between patients treated with codeine and patients treated with hydrocodone for adverse events.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline and Embase via Ovid, 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, acute pain, and pediatric populations. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2009 and October 17, 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.

Although by convention the drug formulation is referred to as "acetaminophen with codeine", for the purposes of this report, this is referred to as "codeine with acetaminophen" or "codeine plus acetaminophen".

Table 1: Selection Criteria

Population	Pediatric patients with acute pain
Intervention	Q1: Codeine Q2: Codeine with acetaminophen
Comparator	Q1: Other opioids; nonsteroidal anti-inflammatory drugs Q2: Acetaminophen only; nonsteroidal anti-inflammatory drugs
Outcomes	Clinical effectiveness (e.g., pain control, pain measurement), safety (e.g., harms, adverse events, hospitalization, readmissions)
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, or they were duplicate publications.

Critical Appraisal of Individual Studies

The included systematic review was critically appraised by one reviewer using A Measurement Tool to Assess Systematic Reviews II (AMSTAR II);[9] and the randomized studies and non-randomized study were critically appraised using the Downs and Black checklist.[10] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively."

Summary of Evidence

Quantity of Research Available

A total of 84 citations were identified in the literature search. Following screening of titles and abstracts, 74 citations were excluded and 10 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full-text review. Of these potentially relevant articles, six publications were excluded for various reasons, and five publications met the inclusion criteria and were included in this report. These comprised one systematic review,[2] three randomized controlled trials (RCTs),[11-13] and one non-randomized study.[14] Appendix 1 presents the PRISMA[15] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

One systematic review[2] was identified regarding the clinical effectiveness of codeine and codeine with acetaminophen, three randomized controlled trials[11-13] were identified regarding the clinical effectiveness of codeine with acetaminophen, and one non-randomized study[14] was identified regarding the clinical effectiveness of codeine. Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

The included systematic review,[2] published in 2016, included a literature search from database inception to July 2015. There were no restrictions for inclusion on study design, language or publication status.[2] Of the 44 primary studies included in the systematic review,[2] three RCTs published from 2007 to 2009 regarding the clinical effectiveness of codeine with acetaminophen[11,12,16] were relevant under the inclusion criteria of this report and are reported here.

Three additional RCTs[11-13] were included regarding the clinical effectiveness of codeine with acetaminophen for acute pain in pediatric patients.

One non-randomized retrospective cohort study[14] was included regarding the clinical effectiveness of codeine.

Country of Origin

The included systematic review was by authors in Canada.[2] The three included RCTs[11-13] and one included non-randomized study[14] were conducted in the United States.[11-14]

Patient Population

The systematic review included studies that enrolled patients under 18 years old with acute pain who were treated in an ambulatory setting such as outpatient clinic or emergency department.[2] Studies on surgically induced pain were excluded.[2] A total of 2,300 participants were included in the systematic review, 740 of which were in the relevant RCTs.[2] The three relevant studies recruited between 68 and 336 participants.[2]

One[13] of the three additional included RCTs[11-13] recruited patients aged 6 to 36 months who needed pain management for the tympanocentesis procedure from an outpatient general pediatric clinic setting, while the other two included RCTs recruited patients aged 4 to 18 years with acute pain from arm fracture,[11] and aged 4 to 17 years with acute pain with extremity injuries,[12] respectively, from emergency departments of children's hospitals.[11,12]

The included non-randomized retrospective cohort study recruited patients without severe conditions aged 12 to 17 years enrolled in Tennessee Medicaid program for both medical and dental care, who filled outpatient opioid prescriptions.[14]

Interventions and Comparators

The systematic review[2] included relevant studies that compared codeine plus acetaminophen versus ibuprofen, and codeine versus acetaminophen plus ibuprofen. Other interventions considered were NSAIDs (naproxen, ibuprofen, nimesulide, ketorolac) and other opioids (morphine, oxycodone, codeine etc.).[2] A summary of the interventions and comparators considered in the systematic review,[2] is provided in Appendix 4.

One[13] of the three included RCTs[11-13] compared codeine plus acetaminophen (1 mg/kg codeine and 15 mg/kg acetaminophen), to acetaminophen monotherapy (15 mg/kg), and to ibuprofen plus midazolam (10 mg/kg ibuprofen plus 0.7 mg/kg midazolam).[13] Two of the RCTs[11,12] compared codeine plus acetaminophen (5 mg codeine/120mg acetaminophen per 5 mL, dosing by 1 mg/kg/dose of the codeine component) to ibuprofen (10 mg/kg).

The included non-randomized study[14] compared codeine (<27 or ≥27 mg morphine equivalents/day) to hydrocodone, oxycodone, or tramadol (comparators administered at a range of doses).

Outcomes

Two of the included RCTs[11,12] were captured by the included systematic review.[2] To avoid duplication in reporting, only the outcomes in the two RCTs[11,14] not already reported in the systematic review[2] were reported separately in the current report.

The relevant outcomes considered in the included systematic review[2] were adverse events such as nausea, vomiting, drowsiness, dizziness and dermatological symptoms.

In the first included RCT,[13] the relevant outcomes were pain and distress measured by change in heart rate, cry duration and the validated Global Mood Scale (GMS) ranging from one (best mood) to seven (worst mood). Pain was also assessed using a Visual Analog Scale (VAS) ranging from zero (no pain) to 100 (worst pain possible). The second RCT[11] reported outcomes that were treatment failure, pain scores, functional outcomes (play,

school, sleep, eating) and satisfaction. In the third RCT,[12] the outcomes were pain (measured on a Color Analog Scale ranging from zero [no pain] and 10 cm [worst pain]) and rescue medication use. The safety outcomes measured the second[11] and third[12] RCTs were reported in the included systematic review[2] and not reported in duplicate in this report.

The included non-randomized study[14] reported outcomes including opioid-related adverse events and opioid-related adverse events by dose.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Review

The included systematic review[2] had a number of strengths identified through the critical appraisal process. The research questions, objectives, and inclusion criteria were clearly reported. A protocol was established prior to the conduct of the review. The review authors used a comprehensive literature search strategy, providing the key search terms and searching multiple databases. To improve consistency in the process, study selection and data extraction were performed in duplicate (by two reviewers). The included studies were described in adequate detail. There were no concerns with the reported the sources of funding and the potential conflicts of interest.

There were also limitations in the included systematic review.[2] The review authors did not report the list of excluded studies. To assess the risk of bias in individual included studies, the McMaster University Harms scale, was used not in conjunction with another risk of bias assessment tool; therefore, basic study design features such as randomization and allocation concealment were not evaluated or reported. Additionally, the rationale for not performing meta-analysis was not reported. Lastly, an investigation of publication bias and its impact on the results of the review was not reported.

Randomized Controlled Studies

The common strengths of the three included RCTs[11-13] included clearly described objectives, main outcomes, characteristics, interventions, randomization, potential confounders and main findings. Patients from different treatment groups were recruited from the same population over the same time period. In these studies,[11-13] the statistical tests used to assess the main outcomes were appropriate. Patient adherence to the interventions was likely reliable with in-hospital observed administration of the medications. Two of the RCTs[11,13] reported power calculations to determine adequate sample sizes, which were achieved.

There were also several limitations identified in the included RCTs.[11-13] In the second[11] and third[12] RCTs, the participants were recruited via convenience sample (i.e., patients who presented to the emergency department while the researcher was present), and it was unclear whether they were representative of all pediatric patients with acute pain in the emergency department, which may lead to issues with the external validity of the studies.[11,12] Additionally, the authors of these two RCTs[11,12] did not report potential conflicts of interest. Lastly, in the first RCT,[13] patients' parents[13] were not blinded to the intervention group, which may lead to issues with internal validity of the study due to biased outcome reporting for pain.

Non-Randomized Studies

In the included non-randomized study,[14] there were strengths identified in the critical appraisal. The objective, main outcomes, characteristics, interventions, confounders and main findings of the study were clearly described. The important adverse events that may be associated with the opioid interventions were reported. Lastly, the authors declared that they had no potential conflicts of interest.

With respect to limitations, the study[14] was a retrospective cohort study with no blinding of study participants or outcome assessors and no randomization. Patients' adherence to the interventions was unknown as it was unclear whether the medication administration was observed and recorded by researchers.[14] The number of patients lost to follow-up was not reported. A power calculation was not conducted a priori to determine the required sample size.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical Effectiveness of Codeine

One systematic review[2] was identified regarding the safety of codeine for the treatment of acute pain in pediatric patients. The systematic review[2] included one relevant study[16] that compared codeine (1 mg/kg) to acetaminophen (15 mg/kg) and ibuprofen (10 mg/kg). No difference was found between groups for minor AEs, including nausea, sleepiness and constipation;[2] however, although the difference was reported as being "not significantly different", there were no primary data or *P*-values reported.[2]

One non-randomized study[14] was identified regarding the clinical effectiveness of codeine. The study[14] compared the opioid-related AEs of codeine to hydrocodone, oxycodone, and tramadol. There were no significant differences between patients treated with codeine (low dose [<27 mg morphine equivalents/day] or high dose [(≥ 27 mg morphine equivalents/day]) and patients treated with hydrocodone for all AEs, AEs with neurologic-respiratory symptoms, or serious AEs.[14] The comparisons between codeine and tramadol or oxycodone were indirect, with hydrocodone being the reference group; statistical tests were not conducted for these indirect comparisons.[14]

Clinical Effectiveness of Codeine with Acetaminophen

One systematic review[2] was identified regarding the safety of codeine with acetaminophen for the treatment of acute pain in pediatric patients. Two relevant RCTs[11,12] in the systematic review compared codeine plus acetaminophen (120 mg acetaminophen/5 mg codeine per 5 mL formulation, dosing by 1 mg/kg for codeine component) with ibuprofen (10 mg/kg). In the first RCT[11] there were numerically more AEs and higher rates of nausea and vomiting in children treated with codeine plus acetaminophen versus those treated with ibuprofen, however between-group differences were not tested statistically. In the second relevant RCT[12] in the systematic review, vomiting, pruritus or nausea occurred in less than 4% of the codeine plus acetaminophen group and the ibuprofen group, and no between-group statistical comparisons were reported.[12]

Three RCTs were identified regarding the clinical effectiveness of codeine with acetaminophen. The first RCT[13] compared codeine plus acetaminophen with acetaminophen alone or with ibuprofen plus midazolam. The pain and distress of the

patients were measured by change in heart rate, cry duration, VAS pain scale, and GMS scale.[13] Patients had a significantly lower mean heart rate in the codeine plus acetaminophen group compared to the acetaminophen monotherapy group, during the restraint and needle aspiration phase of the tympanocentesis procedure.[13] When comparing the GMS measures of pain and distress, the codeine plus acetaminophen group showed significantly higher GMS score (more pain) than the acetaminophen monotherapy group.[13] There were no statistically significant difference in VAS pain scale or cry duration between the three groups.[13]

The second included RCT[11] compared the effectiveness of codeine plus acetaminophen versus ibuprofen. There were no significant differences between groups in treatment failure rate, overall pain scores, overall daily maximum and minimum pain scores, and the median reduction in pain score. However, regarding functional outcomes, play and eating behaviours on Day 1 after injury were reported to be numerically greater in the codeine plus acetaminophen group (not compared statistically) compared to the ibuprofen group, and there was no differences between groups for the school and sleep functional outcomes (not compared statistically).[11]

In the third included RCT,[12] pain severity (measured by CAS pain score) and incidence of rescue medicine ordered for patients were reported to be numerically similar (not compared statistically) between the codeine plus acetaminophen group and the ibuprofen group.[12]

Limitations

As most[11-14] included studies were conducted in the United States (with one exception[2]), the applicability of the evidence to Canadian settings was unclear. With the different demographic components and health care systems, determining whether evidence is relevant and able to be generalized to the Canadian context requires an assessment of the differences in the health care systems. Additionally, the clinical effectiveness of codeine or codeine plus acetaminophen was only compared to ibuprofen; the effectiveness compared to other nonsteroidal anti-inflammatory drugs (NSAID) was not examined.

There was a paucity of studies on the topic of codeine in pediatric patients in the past 5 years, which is perhaps unsurprising given the warnings against codeine use were issued by various international health organizations.[7] Risk of respiratory depression was a concern in these warnings,[7] however most of the included studies did not report this as a specific safety outcome.[2,11-14] There was a gap in the evidence regarding the respiratory effects of codeine and codeine plus acetaminophen in pediatric patients with acute pain.

Conclusions and Implications for Decision or Policy Making

This report provides a summary of recent evidence regarding the use of codeine and codeine plus acetaminophen for acute pain in pediatric patients. One systematic review[2] was identified regarding the clinical effectiveness of codeine and codeine with acetaminophen, three randomized controlled trials[11-13] were identified regarding the clinical effectiveness of codeine with acetaminophen, and one non-randomized study[14] was identified regarding the clinical effectiveness of codeine.

Regarding the clinical effectiveness of codeine for acute pain, codeine was not found to be significantly different from ibuprofen[2] or hydrocodone[14] with respect to adverse events, based on the results of the included systematic review[2] and non-randomized study.[14] It may

be premature to draw conclusions about the comparative effectiveness of codeine versus NSAIDs given the paucity of clinical evidence for this comparison.

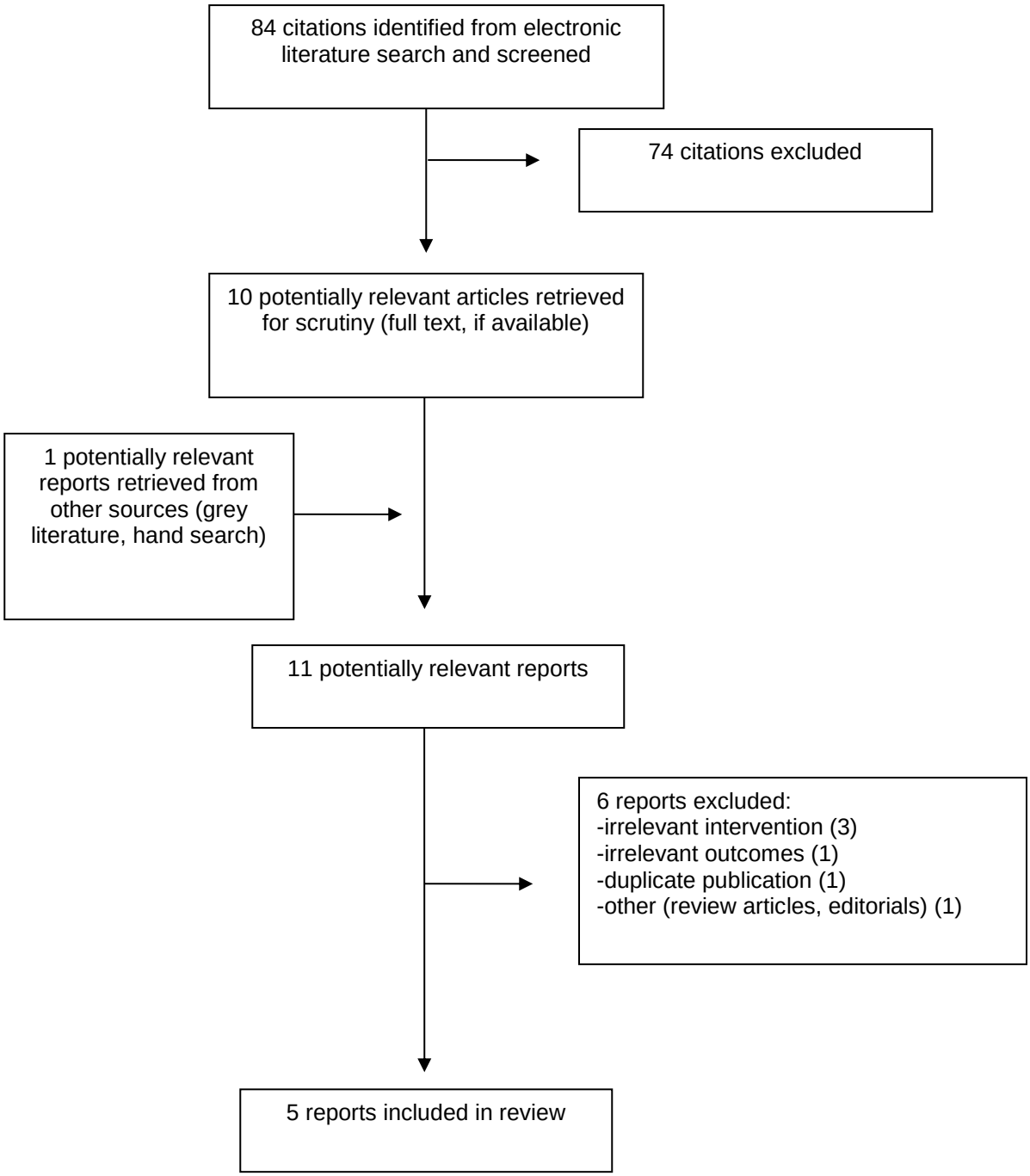
There were mixed results across outcome measures for the comparison of the clinical effectiveness of codeine with acetaminophen versus ibuprofen or acetaminophen monotherapies.[2,11-13] The included studies explored outcomes including adverse events, pain, treatment failure, and functional outcomes. There were significantly higher rates of adverse events in patients treated with codeine plus acetaminophen versus ibuprofen.[2] Patients receiving codeine with acetaminophen had numerically similar results in pain severity and treatment failure when compared to ibuprofen (statistical significance was not tested for this outcome).[12] Patients receiving codeine plus acetaminophen had lower pain and distress compared to those treated with acetaminophen.[13] Codeine plus acetaminophen was significantly less effective for some functional outcomes (playing and eating), compared to ibuprofen, but between-group differences for other functional outcomes (i.e., school and sleep) were unclear (i.e., no data or statistical comparisons reported).[11]

The limitations of the included studies and of this report should be considered when interpreting the results Additional studies of high methodological quality may further aid in making definitive conclusions about codeine with acetaminophen for the management of acute pain in pediatric patients.

References

1. Acute vs. chronic pain. Cleveland (OH): Cleveland Clinic; 2017: https://my.clevelandclinic.org/health/articles/12051-acute-vs-chronic-pain. Accessed 2019 Nov 9.
2. Hartling L, Ali S, Dryden DM, Chordiya P, Johnson DW, Plint AC, et al. How safe are common analgesics for the treatment of acute pain for children? A systematic review. *Pain Res Man.* 2016;2016:Article ID 5346819.
3. Codeine. *AboutKidsHealth*. Toronto (ON): The Hospital for Sick Children; 2010: https://www.aboutkidshealth.ca/Article?contentid=110&language=English. Accessed 2019 Nov 9.
4. Pharmacovigilance Risk Assessment Committee. PRAC recommends restricting the use of codeine when used for pain relief in children. Amsterdam (NLD): European Medicines Agency; 2013: https://www.ema.europa.eu/en/news/prac-recommends-restricting-use-codeine-when-used-pain-relief-children. Accessed 2019 Nov 9.
5. Acetaminophen and codeine (oral route). Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2019: https://www.mayoclinic.org/drugs-supplements/acetaminophen-and-codeine-oral-route/side-effects/drg-20074117?p=1. Accessed 2019 Nov 9.
6. Hauer J, Jones B. Evaluation and management of pain in children. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2019: https://www.uptodate.com/. Accessed 2019 Nov 11.
7. Tobias JD, Green TP, Cote CJ, Section On A, Pain M, Committee On D. Codeine: Time to say "no". *Pediatrics.* 2016;138(4):10.
8. Unedited report of the 18th Expert Committee on The Selection and Use of Essential Medicines. *(WHO Technical report series)*. Geneva (CHE)2011: https://www.who.int/selection_medicines/Complete_UNEDITED_TRS_18th.pdf. Accessed 2019 Nov 9.
9. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, 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 Nov 9.
10. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf. Accessed 2019 Nov 9.
11. Drendel AL, Gorelick MH, Weisman SJ, Lyon R, Brousseau DC, Kim MK. A randomized clinical trial of ibuprofen versus acetaminophen with codeine for acute pediatric arm fracture pain. *Ann Emergency Med.* 2009;54(4):553-560.
12. Friday JH, Kanegaye JT, McCaslin I, Zheng A, Harley JR. Ibuprofen provides analgesia equivalent to acetaminophen-codeine in the treatment of acute pain in children with extremity injuries: a randomized clinical trial. *Acad Emerg Med.* 2009;16(8):711-716.
13. Shaikh N, Hoberman A, Kurs-Lasky M, Rockette HE, Chandra A, Colborn DK, et al. Pain management in young children undergoing diagnostic tympanocentesis. *Clin Pediatr (Phila).* 2011;50(3):231-236.
14. Chung CP, Callahan ST, Cooper WO, Dupont WD, Murray KT, Franklin AD, et al. Individual short-acting opioids and the risk of opioid-related adverse events in adolescents. *Pharmacoepidemiol Drug Saf.* 2019;16:16.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, 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. Clark E, Plint AC, Correll R, Gaboury I, Passi B. A randomized, controlled trial of acetaminophen, ibuprofen, and codeine for acute pain relief in children with musculoskeletal trauma. *Pediatrics.* 2007;119(3):460-467.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review

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
Hartling, 2016[2] **Canada**	**Study design:** SR without MA **Literature search strategy:** The authors searched from database inception to July 2015 in CENTRAL, MEDLINE, EMBASE, International Pharmaceutical Abstracts, TOXNET, BIOSIS Previews, PubMed, and Web of Science; conference proceedings and abstracts from the American Pain Society (2011–2015), Canadian Pain Society (2011–2015), International Symposium of Pediatric Pain (2015), North American Congress of Clinical Toxicology (2011–2015), and the European Association of Poison Centers and Clinical Toxicologists (2011–2015), clinicaltrials.gov and the Australian New Zealand Clinical Trials Registry. The authors contacted the U.S. FDA and Health Canada for safety data. There were no restrictions on language or publication status. **Number of included studies:** 23 included studies: 17 RCTs, 2 non-randomized studies, 1 case report, 1 cross-sectional survey, 1 chart review, and 1 prospective cohort **Number of studies relevant to this report:** 3 RCTs Included studies published 1991-2014 (median year 2007) Studies conducted in the US (7 studies), Canada (5 studies), France (3 studies), Italy (3 studies), and Germany (2 studies) and 1 study each in Finland, New Zealand, and the UK **Quality assessment tool:** McMaster Quality Assessment Scale of Harms **Objective:** To compare the safety profiles of acetaminophen, NSAIDs, and opioids (including codeine), to manage acute, nonsurgical pain in children in ambulatory settings	N = 2,300 patients **Included:** Primary studies (any study design) with patients <18 years with acute pain who were treated in an ambulatory setting (e.g., outpatient clinics, emergency department) **Excluded:** Studies with patients with surgically induced pain	**Included interventions:** Acetaminophen NSAIDs (naproxen, ibuprofen, nimesulide, ketorolac) Opioids (morphine, oxycodone, codeine, codeine with acetaminophen) **Relevant Interventions:** Codeine, Codeine with acetaminophen	**Outcomes:** Adverse events **Length of follow-up**: not reported

CENTRAL = Cochrane Central Register of Controlled Trials; FDA = Food and Drug Administration; MA = meta-analysis; NSAIDS = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trial; SR = systematic review; UK = United Kingdom; US = United States.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design, Setting, Objectives	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Study				
Shaikh, 2011[13] **United States**	**Study design:** RCT **Setting:** outpatient general pediatric clinic **Objective:** to describe the pain and distress associated with diagnostic tympanocentesis in children with AOM aged 6 to 36 months, and to gather preliminary data comparing the efficacy of: acetaminophen, codeine plus acetaminophen, and ibuprofen plus midazolam.	**Inclusion criteria:** Patients aged 6 to 36 months with AOM, presenting to an outpatient general pediatric clinic, who required tympanocentesis, symptomatic and had bulging opaque tympanic memberanes **Excluded:** Pediatric patients with known sensitivity to acetaminophen, codeine, ibuprofen, or midazolam, children with known renal insufficiency, and children with craniofacial anomalies or tympanostomy tubes **Number of patients:** 58 **Mean age:** 15.3 months (range 6-34 months)	**Intervention of interest**: Codeine plus acetaminophen (1 mg/kg codeine and 15 mg/kg acetaminophen) (n = 20) **Comparator**: Acetaminophen (15 mg/kg) (n = 21); Ibuprofen plus midazolam (10 mg/kg ibuprofen plus 0.7 mg/kg midazolam) (n.= 17)	**Relevant Outcome:** pain and distress measured by physiological outcome: change in heart rate during and 5 minutes after the tympanocentesis; behavioral outcome: Global Mood Scale; cry duration, Visual Analog Pain Scale; proportion of patients who stated would not use the medication again (patient self-report) **Length of follow-up**: 5 minutes
Drendel, 2009[11, a] **United States**	**Study design:** double-blinded RCT **Setting:** data collected from a children's hospital Level I trauma center emergency department, between August 2003 and September 2007. **Objective:** to determine the efficacy of the ibuprofen and codeine plus acetaminophen for the outpatient treatment of children with arm fracture for the first 72 hours after the injury	**Inclusion criteria:** Patients aged 4 to 18 years, diagnosed by a pediatric radiologist with a fracture of the radius, ulna, or humerus, visualized on a standard 2-view radiograph, whose fracture did not require reduction or manipulation in the emergency department and was not an open fracture. **Excluded:** Pediatric patients with radiographs showing an isolated posterior fat pad of the elbow; weighed >60 kg; preferred tablets, were evaluated more than 12 hours after the initial injury, had developmental delay; with history of gastrointestinal bleeding or ulceration, a bleeding disorder, a low platelet count, kidney disease, uncontrolled chronic disease, regular use of or allergy to acetaminophen, ibuprofen, or codeine; patients or their parents were unable to understand English or inaccessible by telephone	**Intervention of interest**: Acetaminophen with codeine 120mg/5mg per 5 mL dosing by 1 mg/kg/dose of the codeine component) (n = 167) **Comparator**: Ibuprofen 10 mg/kg (n = 169)	**Relevant Outcome:** treatment failure (defined as the use of rescue medication); pain (score); effect of pain on parents and children reported functional outcomes (play, school, sleep, eating), adverse events[a] **Length of follow-up**: at least 1 and up to 4 years

First Author, Publication Year, Country	Study Design, Setting, Objectives	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Number of patients: 336 **Mean age:** 8 years		
Friday, 2009[12, a] **United States**	**Study design:** double-blinded RCT **Setting:** data collected from an urban, tertiary care children's hospital emergency department from November 2002 to February 2004 **Objective:** to compare the analgesic effectiveness of codeine plus acetaminophen with that of ibuprofen for children with acute traumatic extremity pain	**Inclusion criteria:** Patients aged 5 to 17 years of age who spoke English, complained of an isolated extremity injury with tenderness to palpation from the clavicle or femoral neck to the distal phalanges, and reported pain intensity of at least 5/10 points at triage **Excluded:** allergy or prior adverse reaction to acetaminophen, codeine, or ibuprofen; had any analgesic ≤6 hours of presentation; significant deformity or vascular insufficiency of the extremity requiring immediate treatment; inability to use the study pain instrument; any laceration near the suspected injury; chronic hepatic or renal disease; pregnancy; concurrent use of MAOI; use of CNS depressants such as barbiturates, benzodiazepines, ethanol, antidepressants, or recreational drugs. **Number of patients:** 66 patients **Mean age:** 10.1 ± 3.4 years in codeine plus acetaminophen group; 10.6 ± 3.4 years in ibuprofen group	**Intervention of interest**: 120mg/5mg per 5 mL dosing by 1 mg/kg/dose of the codeine component, maximum 60 mg (n = 32) **Comparator**: ibuprofen 10 mg/kg, maximum 400 mg (n = 34)	**Relevant Outcome:** change in pain at 40 minutes (measured by change in CAS score from Baseline); need for rescue medication, adverse events[a] **Length of follow-up**: 60 minutes for efficacy outcomes
Non-Randomized Study				
Chung, 2019[14] **United States**	**Study design:** Retrospective Cohort Study **Setting:** Data from the Tennessee Medicaid program (including both medical and dental care), collected between 1 January 1999 and 31 December 2011	**Inclusion criteria:** Patients aged 12 to 17 years old enrolled in Tennessee Medicaid for at least 1 year, who had filled an outpatient opioid prescription **Excluded:** Patients who had prior ICD9-CM diagnoses, CPT4 procedures, or prescriptions indicating severe conditions (cancer, sickle cell anemia, major congenital anomalies, hospitalization for a total of >30	**Intervention of interest**: Codeine (n = 89,228 patients, 142,915 prescriptions) **Comparator**: Hydrocodone (n = 140,560 patients, 312,316 prescriptions);	**Relevant Outcome:** Opioid-related adverse events: all AE, AE associated with self-harm or substance abuse, AE with neurologic-respiratory symptoms, serious AE

First Author, Publication Year, Country	Study Design, Setting, Objectives	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Objective: to compare the safety outcome of opioid-related AE in adolescents taking hydrocodone, codeine, oxycodone, or tramadol.	days in the preceding year, or history of organ transplant, institutional residence, or substance use disorder) **Number of patients:** 529,731 opioid prescriptions for 201,940 patients **Mean age:** 15 years	Oxycodone (n = 36,087 patients, 45,324 prescriptions); Tramadol (n = 18,933 patients, 29,176 prescriptions)	

AE = adverse events; AOM = acute otitis media; CAS = Color Analog Scale; CNS = central nervous system; CPT4 = Current Procedural Terminology, 4th Edition; MAOI = monoamine oxidase inhibitors; ICD9-CM = the International Classification of Diseases, 9th Revision, Clinical Modification; RCT = randomized controlled trials.

[a] The safety outcome of this primary study was covered by the included systematic review by Hartling et al. and therefore not extracted and reported here.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Review using AMSTAR II[9]

Strengths	Limitations
Hartling, 2016[2]	
• The research questions and inclusion criteria for the review included the components of population, intervention, comparison, and outcomes. • A protocol was established prior to the conduct of the review. • The review authors used a comprehensive literature search strategy. • The study selection and data extraction were performed in duplicate by two reviewers. • The included studies were described in adequate detail. • The sources of funding for the included studies were reported. • The discussion and explanation of any heterogeneity observed in the results of the review was reported. • The potential sources of conflict of interest and funding were disclosed.	• The review authors did not explain their selection of all study designs for inclusion in the review. • A list of excluded studies was not published. • The technique for assessing the risk of bias in individual included studies, the McMaster University Harms scale, was not used with another risk of bias assessment tool; therefore, basic study design features such as randomization and allocation concealment were not evaluated or reported. • The rationale for not performing meta-analysis was not reported. • An investigation of publication bias and its impact on the results of the review were not reported.

Table 5: Strengths and Limitations of Clinical Studies using Downs and Black Checklist[10]

Strengths	Limitations
Randomized Controlled Trials	
Shaikh, 2011[13]	
• The objective, main outcomes, characteristics, interventions, confounders and main findings of the study were clearly described. • Probability values were reported as exact *P*-values for the main outcomes. • The patients who were asked to participate and prepared to participate in the study were representative of the entire population from which they were recruited. • The statistical tests used to assess the main outcomes were appropriate. • The patient adherence to the interventions was likely reliable due to observed dosing of medication in hospital. • The patients were randomized to the treatment groups. • The main outcome measures used were valid and reliable. • The patients in different intervention groups were recruited from the same population and over the same time period. • The authors declared that they had no potential conflicts of interest. • A power calculation was conducted a priori to determine the required sample size.	• The parents of the patients were not blinded which may lead to bias in parent-reported pain levels. • It was unclear whether the patients who participated, staff, places, and facilities in the study in the United States were representative of the Canadian population.

Strengths	Limitations
Drendel, 2009[11], [a]	
• The objective, main outcomes, characteristics, interventions, confounders and main findings of the study were clearly described. • The statistical tests used to assess the main outcomes were appropriate. • The patient adherence to the interventions was likely reliable due to observed dosing of medication in hospital. • The patients were randomized to the treatment groups using a random number table and block randomization. • The study was double-blinded, including treating physicians, patients, patients' parents, and all researchers. • The patients in different intervention groups were recruited from the same population and over the same time period.	• Probability values were not reported as *P*-values for the main outcomes. • It was unclear whether the patients who participated, staff, places, and facilities in the study in the United States were representative of the Canadian population. • The patients who were asked to participate and prepared to participate in the study were recruited via convenience sample (patients presenting to the emergency department while the researcher was present). It was unclear whether they were representative of the entire population of pediatric patients with acute pain in the emergency department. • It was unclear whether the main outcome measures used were reliable, as the parents of patients administered the medication to their children at their own discretion and one of the outcomes was patients' and parents' reported effect of pain on functional outcomes. • Potential conflicts of interest were not reported in the article. • A power calculation was not conducted a priori to determine the required sample size.
Friday, 2009[12], [a]	
• The objective, main outcomes, characteristics, interventions, confounders and main findings of the study were clearly described. • The study was double-blinded. • The statistical tests used to assess the main outcomes were appropriate. • The patient adherence to with the interventions was likely reliable due to observed dosing of medication in hospital. • The patients were randomized to the treatment groups (methods not described). • The main outcome measures used were valid and reliable. • The patients in different intervention groups were recruited from the same population and over the same time period. • A power calculation was conducted a priori to determine the required sample size.	• Probability values were not reported as *P*-values for the main outcomes. • • It was unclear whether the patients who participated, staff, places, and facilities in the study in the United States were representative of the Canadian population. • The patients who were asked to participate and prepared to participate in the study were a convenience sample of patients presenting to the emergency department who were recruited by an investigator available primarily during evening hours. It was unclear whether they were representative of the entire population of pediatric patients with acute pain in the emergency department. • Potential conflicts of interest were not reported in the article.
Non-Randomized Study	
Chung, 2019[14]	
• The objective, main outcomes, characteristics, interventions, confounders and main findings of the study were clearly described. • The estimates of the random variability for the main outcomes data were reported as confidence intervals. • The important adverse events that may be associated with the opioid interventions were reported. • Probability values were reported as hazard ratios for the main outcomes.	• This was a retrospective cohort study with no blinding of study participants or outcome assessors and no randomization. • The number of patients lost to follow-up were not reported. • A power calculation was not conducted a priori to determine the required sample size. • It was unclear whether the patient adherence to with the interventions was reliable, with no record of medication administration and whether it was observed dosing.

Strengths	Limitations
• The subjects who were asked to participate and prepared to participate in the study were representative of the entire population from which they were recruited. • The staff, places, and facilities were representative of the treatment of the majority of the patients would receive. • The statistical tests used to assess the main outcomes were appropriate. • The main outcome measures used were valid and reliable. • The patients in different intervention groups were recruited from the same population and over the same time period. • The authors declared that they had no potential conflicts of interest.	• It was unclear whether the patients who participated in the study in the United States were representative of the Canadian population.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Review

<table>
<tr><th colspan="3">Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="4">Hartling, 2016[2]</td></tr>
<tr><td colspan="3">Relevant primary studies:
<table>
<tr><th>Author, year</th><th>Intervention and comparator</th><th>Summary of relevant findings, n/N, absolute risk (95% CI)</th></tr>
<tr><td>Drendel, 2009[11]</td><td>• Codeine + acet 120 mg/5 mg per 5 mL, n = 167
• Ibuprofen 100 mg/5 mL, n = 169</td><td>Nausea:
Ibuprofen group: 9/169, 0.05 (0.03, 0.10)
Codeine + acet group: 30/167, 0.18 (0.13, 0.24)

Vomiting:
Acet: 18/167, 0.11(0.07, 0.16)
Ibuprofen 4/169, 0.02 (0.01, 0.06)

GI symptoms (other than nausea and vomiting):
Ibuprofen: 4/169, 0.02, CI (0.01, 0.06)
Codeine + acet: 3/167, 0.02 (0.01, 0.05)

Drowsiness, sleepiness and tiredness :
Codeine + acet: 35/169, 0.21 (0.15, 0.27)
Ibuprofen + codeine: 51/167, 0.31 (0.24, 0.38)

Dizziness
Ibuprofen: 4/169, 0.02 (0.01, 0.06)
Codeine + acet: 9/167, 0.05 (0.03, 0.10)</td></tr>
<tr><td>Friday, 2009[12]</td><td>• Acet +codeine 1 mg/kg, max 60 mg, n = 34 (Note the primary study reported n = 32 for this study group)
• Ibuprofen 10mg/kg, max 400 mg, n = 34</td><td>Nausea:
Ibuprofen: 1/34, 0.03 (0.01, 0.15)
Codeine + acet: 0/34, 0.00 (0.00, 0.07)

Vomiting:
Ibuprofen: 0/34, 0.00 (0.00, 0.07)
Codeine + acet: 1/34, 0.03 (0.01, 0.15)

Dermatological symptoms (itchiness, rash pruritus):
Ibuprofen: 0/34, 0.00 (0.00, 0.07)
Codeine + acet: 1/34, 0.03 (0.01, 0.15)</td></tr>
<tr><td>Clark, 2007[16]</td><td>• Codeine 1 mg/kg, max 60 mg, n = 112
• Acet 15 mg/kg, max 650mg, n = 112
• Ibuprofen: 10 mg/kg, max 600 mg, n = 112</td><td>No significant difference (narratively reported) between groups for minor AEs (nausea, sleepiness, constipation)</td></tr>
</table></td><td>"Opioids trended towards greater "other GI AEs," including constipation. Codeine monotherapy showed cumulatively more GI AEs than all other analgesics. NSAIDS and acetaminophen reported less than 10% rate of GI AEs. Opioid/nonopioid combinations had varying degrees of GI AEs associated with them; of note, oral morphine demonstrated the highest reported risk of nausea, followed by acetaminophen with codeine combination medication. Placebo-related AEs of nausea and vomiting were equal to or greater than that of some pain medications."[2] (p. 4)

"Central Nervous System (CNS) (Figure 3). Opioid monotherapy showed the highest risk of CNS AEs, with drowsiness/ tiredness being noted in close to one-third of children receiving oxycodone or oral morphine and half of children receiving codeine. CNS symptoms of drowsiness and dizziness were notably higher for all opioid medications, when compared to nonopioid choices… Opioid/nonopioid combination medications had a lower risk of CNS AEs."[2] (p. 4, 10)

"Dermatological and Pulmonary System (Figure 4). Opioid medications demonstrated a greater risk of dermatologic symptoms. Children receiving only codeine had almost double the risk of experiencing dermatologic manifestations compared to all other medications."[2] (p. 10)</td></tr>
</table>

AE = adverse events; Acet = acetaminophen; CNS = central nervous system; NSAID = Nonsteroidal anti-inflammatory drugs; GI = gastrointestinal.

Table 7: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized Controlled Study	
Shaikh, 2011[13]	

Pain and distress measured by change in heart rate

	Baseline heart rate (beats/minute)	Heart rate during restraint (beats/minute)	Heart rate during cleaning (beats/minute)	Heart rate during needle aspiration (beats/minute)	Heart rate during after 5 minute recovery (beats/minute)
Acet + codeine	132	137	161	162	143
Acet	140	158	166	185	150
Ibuprofen + midazolam	138	139	162	186	152
P-value for 3-way comparison	0.45	0.02	0.90	<0.001	0.34

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Pain and distress measured by cry duration

	Cry duration	Total procedure time	Cry duration/total procedure time (%)
Acet + codeine	215	407	66%
Acet	290	442	69%
Ibuprofen + midazolam	244	423	66%
P-value for 3-way comparison	0.38	0.88	0.94

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Pain and distress measured by VAS and GMS

	VAS Pain Scale by physician (range 0-100)	VAS Pain Scale by nurse (range 0-100)	VAS Pain Scale by parent (range 0-100)	GMS (range 0-7) at baseline	GMS (range 0-7) at restraint	GMS (range 0-7) at cleaning	GMS (range 0-7) after 5 minute recovery
Acet + codeine	40	39	63	2.5	4.6	6.2	3.4
Acet	40	42	62	3.0	5.7	6.3	3.9
Ibuprofen + midazolam	31	43	62	3.3	3.7	6.2	3.7
P-values for 3-way comparison	0.40	0.81	0.98	0.12	<0.001	0.88	0.88

Shaikh, et al., Clinical Pediatrics
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"Our data suggest that acetaminophen alone is not as effective as acetaminophen plus codeine or ibuprofen plus midazolam in controlling the pain and distress associated with tympanocentesis. Children treated with acetaminophen alone had a higher mean heart rate than children treated with acetaminophen plus codeine during the restraint and needle aspiration phases of the procedure. Furthermore, children treated with acetaminophen alone exhibited more pain behaviors as measured by the Global Mood Scale during the restraint phase." [13] (p. 234-235)

Main Study Findings	Authors' Conclusion
Drendel, 2009[11a]	
Number of doses of medication Median doses of ibuprofen: 4.5 (IQR 2, 7) Median doses of codeine with acet: 4 (IQR 2, 6) No significant difference in the number of doses of medication the children in each of the study groups used during the first 3 days after discharge from the emergency department (*P* value not reported)[b] **Treatment failures (%)** Ibuprofen group: (20.3%) Codeine with acet group: (31.0%) Not statistically significant between group differences (95% CI -0.2% to 21.6%) Per-protocol analysis (exclude 13 children who did not use any pain medication): No significant difference (95% CI -0.6% to 22.1%) **Total mean pain scores for day 0 to day 3** (include awakening, bedtime, before and 1 hour after each dose) Ibuprofen group: 1.6 Codeine with acet scored 1.6 No statistical difference in the overall pain scores between the 2 groups (*P*-values not reported) **Overall daily maximum and minimum pain scores:** no differences were found between the 2 groups (*P*-value not reported) **Median reduction in pain score**: Ibuprofen group: 2.0 Codeine with acet: 1.5 Not clinically or statistically significantly different between the 2 groups (*P*-value not reported) **Patients' and parents' reported effect of pain on functional outcomes: play, school, sleep, eating**: Day 0, patients with fractures had at least 1 of the functions affected: 60% Day 3, patients who continued to have function affected by pain: 29.4% Day 1: the proportion of children who had any of these functions affected by pain analyzed was significantly different in the 2 study groups (*P*-values not reported) • A statistically significantly lower proportion of children using ibuprofen had play and eating affected by pain[b] • Difference between groups for the effect of pain on school and sleep not compared statistically[b] **Satisfaction measured by Likert scale:** Day 1, parents of children were very satisfied or satisfied: Ibuprofen group: 85.8% Codeine with acet group: 67.3% Difference 18.5%; 95% CI 7.3% to 29.6%, statistical significance not reported At the end of the study, patients who said they would not use the medication again if they experienced a broken arm: Ibuprofen group: 10.0% Codeine with acet group 27.5% Difference 17.8%; 95% CI 7.3% to 28.3%, statistical significance not reported Dissatisfaction due to taste: Ibuprofen group: 30.4% Codeine with acet group: 63.8%	"In conclusion, ibuprofen was at least as effective as acetaminophen with codeine in providing outpatient analgesia for children with arm fractures not requiring reduction. There was no significant difference in analgesic failure and pain scores, but children receiving ibuprofen had better functional outcomes; specifically, play. Children receiving ibuprofen had significantly fewer adverse effects, and both children and parents were more satisfied with ibuprofen. Ibuprofen is preferable to acetaminophen with codeine for outpatient treatment of children with uncomplicated arm fractures."[11] (p. 559)
Friday, 2009[12], [a]	

Main Study Findings	Authors' Conclusion

CAS pain scores change from baseline mean, cm (95% CI)

	20 minutes after administration	40 minutes after administration	60 minutes after administration
Codeine with acet	-0.8 (-1.5 to -0.1)	-1.7 (-2.4 to -1.0)	-2.3 (-3.0 to -1.6)
Ibuprofen	-1.4 (-1.9 to -0.8)	-2.1 (-2.9 to -1.3)	-2.1 (-2.9 to -1.3)
Difference in mean CAS (Negative values favor the ibuprofen group)	-0.6 (-1.5 to 0.3)	-0.4 (-1.4 to 0.6)	0.2 (-0.8 to 1.2)

Rescue medications ordered for patients
Codeine with acet group: 3 patients
Ibuprofen group: 3 patients

"We found similar performance of acetaminophen–codeine and ibuprofen in analgesic effectiveness among ED patients aged 5–17 years with acute traumatic extremity pain. Both drugs provided measurable analgesia."[12] (p. 715-716)

Non-Randomized Study

Chung, 2019[14]

Opioid-related AE:

	All AE		AE with self-harm or substance abuse		AE with neurologic-respiratory symptoms		Serious AE	
	Rate/10,000 patients	HR (95% CI) vs. hydrocodone	Rate per 10,000 patients	HR (95% CI) vs. hydrocodone	Rate per 10,000 patients	HR (95% CI) vs. hydrocodone	Rate per 10,000 patients	HR (95% CI) vs. hydrocodone
Hydrocodone	97.5	N/A	25.3	N/A	52.2	N/A	25.3	N/A
Codeine	91.2	1.27 (0.88 to 1.84)	20.4	1.58 (0.78 to 3.21)	29.9	0.77 (0.44 to 1.37)	15.7	1.09 (0.50 to 2.36)
Oxycodone	229.7	1.92 (1.26 to 2.94)	21.4	0.57 (0.19 to 1.67)	112.2	1.68 (0.91 to 3.09)	26.7	1.00 (0.32 to 3.17)
Tramadol	317.7	2.98 (2.03 to 4.39)	67.6	1.82 (0.87 to 3.81)	182.5	2.85 (1.72 to 4.74)	101.4	3.08 (1.64 to 5.79)

Opioid related AE by dose:

	Dose < 27 mg morphine equivalents/day		Dose ≥ 27 mg morphine equivalents/day	
	PY	HR (95% CI) vs. hydrocodone	PY	HR (95% CI) vs. hydrocodone
Hydrocodone	6,090	N/A	6,935	N/A
Codeine	5,109	1.28 (0.80 to 2.05)	1,251	1.16 (0.64 to 2.12)
Oxycodone	140	3.00 (1.06 to 8.54)	1,732	1.80 (1.16 to 2.81)
Tramadol	1,066	2.51 (1.50 to 4.20)	4,13	3.64 (2.07 to 6.39)

"There was no significantly increased risk for codeine for all (HR = 1.27, 0.88- 1.84), neurologic-respiratory (HR = 0.77, 0.44- 1.37), or serious (HR = 1.09, 0.50-2.36) adverse events…Codeine users had no significantly increased risk for either dose."[14] (p. 6)

"In this cohort study of short-acting opioid use in adolescents without cancer or other severe conditions,

Main Study Findings	Authors' Conclusion
	tramadol had a poorer safety profile than either hydrocodone or codeine."[14] (p. 6)

Acet = acetaminophen; AE = adverse events; CAS = Color Analog Scale; CI = confidence interval; ED = emergency department; GMS = Global Mood Scale; HR = hazard ratio; IQR = interquartile range; N/A = not applicable; PY = person; VAS = Visual Analog Scale.

[a] The safety outcome of this primary study was covered by the included systematic review by Hartling et al. and therefore not extracted and reported here.

[b] Shown graphically or described narratively, detailed data and statistical analysis values not reported.

Appendix 5: Additional References of Potential Interest

Related CADTH Reports

1. Codeine compared with other opioids for pain relief in pediatric patients: comparative clinical effectiveness, safety, and guidelines. *(CADTH Rapid response report: summary of abstracts)*. Ottawa (ON): CADTH; 2013 http://www.cadth.ca/media/pdf/htis/feb-2013/RB0567%20Codeine%20for%20Children%20Final.pdf Accessed 2019 Nov 9

2. Codeine and acetylsalicylic acid for the management of post-tonsillectomy or adenoidectomy pain: a review of the clinical evidence. *(CADTH Rapid response report: summary with critical appraisal)*. Ottawa (ON): CADTH; 2013. http://www.cadth.ca/media/pdf/htis/jul-2013/RC0459_ASAtonsillectomy_Final.pdf Accessed 2019 Nov 9

3. Medications for the management of post-surgical pain in pediatrics: Guidelines. *(CADTH Rapid response report: summary of abstracts)*. Ottawa (ON): CADTH; 2016. https://cadth.ca/medications-management-post-surgical-pain-pediatrics-guidelines Accessed 2019 Nov 9

4. Optimal pain management following tonsillectomy or adenoidectomy for pediatric patients: Clinical evidence and guidelines. *(CADTH Rapid response report: summary of abstracts)*. Ottawa (ON): CADTH; 2012. https://cadth.ca/optimal-pain-management-following-tonsillectomy-or-adenoidectomy-pediatric-patients-clinical 2019 Nov 9

Non-randomized Study – Alternative Intervention

5. Swanson CE, Chang K, Schleyer E, Pizzutillo PD, Herman MJ. Postoperative pain control after supracondylar humerus fracture fixation. *J Pediatr Orthop*. 2012 Jul-Aug;32(5):452-455.