

Codeine for the Treatment of Pain: A Synopsis of the Evidence

Key Messages

- CADTH reviewed the evidence on the clinical effectiveness of codeine for the treatment of pain related to seven-specific conditions. Overall, the evidence was either limited, mixed, or did not identify an important difference in the effectiveness of codeine used on its own or in combination with other drugs for the treatment of pain as compared to other comparator groups.
- In general, the evidence suggests that when compared to other drugs and drug combinations, codeine and codeine combination drugs may lead to increased adverse events.
- Additional, high-quality studies would help increase certainty about the clinical effectiveness of codeine and provide guidance for clinicians and decision-makers on its role in the treatment of pain.

Acute pain is pain that lasts for less than 6 months. Chronic pain is defined as ongoing pain that lasts longer than 6 months. There are many treatments available for the management of pain, with opioids being one of them. Canada is currently battling an opioid epidemic, being the second-highest consumer of opioids worldwide and experiencing a substantial increase in overdose-related deaths. The overprescribing of opioids and the diversion of non-consumed supplies has created a need to optimize opioid prescribing.

Codeine is a weak opioid that produces pain relief as it is metabolized by the liver into various metabolites, including morphine. How fast the liver metabolizes codeine varies in the general population, with individual differences being unpredictable. Patients who are poor metabolizers of codeine typically experience suboptimal pain control, while ultra-rapid metabolizers achieve higher pain control but are also at a higher risk of adverse events. Adverse events include nausea, vomiting, dizziness, drowsiness, and other reactions, with the risk of such effects increasing alongside higher doses of the medication. In addition to differences in people's ability to metabolize codeine, the potential for increased adverse events, concerns about its effectiveness compared to other less harmful medications, and risk of addiction and misuse in light of the opioid crisis, the use of codeine for the management of pain has come under question.

As a weak opioid, codeine can be used in conjunction with non-opioid analgesics such as acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen. CADTH conducted a limited literature search to review the evidence on the clinical effectiveness of codeine with and without acetaminophen and/or ibuprofen versus different comparators for the management of pain in various patient populations. Reports were completed between October 2019 and February 2021 with the following eligible study designs: health technology assessments, systematic reviews, randomized controlled trials, and non-randomized studies (e.g. non-randomized interventions, cohort studies). Depending on the date of the report, additional evidence may now be available and because of the methods used for Rapid Response reports, it is possible that some evidence may not have been included.

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Summary of Considerations for Practice Legend



- Reasonable amount of evidence to indicate effectiveness (although comparison with opioids may be lacking, making their place in therapy uncertain).
- Evidence indicates that risk of harms is low and/or side effects are mild to moderate.



- Some evidence to indicate effectiveness, but it may be conflicting, mixed, or of lower-quality.
- Evidence on harms is lacking or unclear.















- Evidence shows a lack of effectiveness.
- Limited evidence on harms.



- No evidence on effectiveness.
- No evidence on harms.

Table 1: Summary of the Evidence Regarding the Use of Codeine for the Treatment of Pain and Associated Adverse Effects Related to Specific Conditions

Condition	Intervention	Comparator	Outcome ^a
Pain related to osteoarthritis of the knee and hip 	Codeine	Placebo or no codeine	Codeine provided a moderate benefit for pain
		Acetaminophen or placebo	Codeine increased adverse events
Acute extremity pain 	Codeine	Placebo	No relevant evidence identified
	Codeine used in combination with other drugs (e.g., acetaminophen, acetaminophen and ibuprofen)	Other combination drugs (e.g., acetaminophen and hydrocodone, ibuprofen and acetaminophen)	No difference in pain scores and number of adverse events
Acute pain related to caesarean section 	Codeine	Placebo	No relevant evidence identified
	Codeine with acetaminophen	Acetaminophen or placebo	Codeine with acetaminophen provided better relief for patients experiencing high levels of pain No difference for patients experiencing moderate levels of pain

Acute dental pain and acute pain related to dental procedures 	Codeine alone or in combination with acetaminophen	Placebo	Codeine alone or in combination with acetaminophen provided better pain relief 
	Codeine with acetaminophen	Placebo, other drugs (e.g., naproxen sodium, etoricoxib)	Codeine with acetaminophen increased adverse events 
	Codeine in combination with other drugs (e.g., acetaminophen, ibuprofen)	Other drugs and drug combinations (e.g., acetaminophen, ibuprofen)	Codeine in combination with other drugs generally was not as effective and did not have added benefit for the treatment of pain 
Acute pain for urological or general surgery 	Codeine alone or in combination with acetaminophen	Various pain medications or placebo	No relevant evidence identified 
Pediatric patients with acute pain 	Codeine with acetaminophen	Ibuprofen	Similar results in pain severity and treatment failure  Codeine with acetaminophen increased adverse events 
		Acetaminophen	Codeine with acetaminophen was more effective at lowering pain. 
Acute pain in patient undergoing orthopedic surgery 	Codeine alone or in combination with acetaminophen	Various pain medications or placebo	No relevant evidence identified 

* Other outcomes were identified that were not included in this table. Please see the key messages from each report for more information.

[Codeine for Pain Related to Osteoarthritis of the Knee and Hip: A Review of Clinical Effectiveness \(2021\)](#)

Issue: Osteoarthritis is a progressive illness, with an estimated 1 in 4 Canadians to be diagnosed with the condition by 2035. With no cure, the goal of managing osteoarthritis is to control pain and improve function using a combination of self-management techniques, medications, and surgery. Typical pharmacological options used for pain include oral and topical NSAIDs, topical capsaicin, intra-articular glucocorticoid injections, acetaminophen, and opioids. Because of the risk of addiction and adverse events associated with opioids, they are reserved for severe pain or when other analgesics are contraindicated. A review of the clinical effectiveness of codeine, with and without acetaminophen and/or NSAIDs, may help inform decisions on the use of codeine for acute and chronic pain related to osteoarthritis of the knee or hip.

CADTH appraised and summarized the relevant evidence published up to November 2020 found in: 2 systematic reviews with meta-analysis^b and 3 randomized controlled trials.

^bOne review did not contain any relevant primary studies.

Key Messages

In patients with acute and/or chronic pain related to osteoarthritis of the knee or hip:

- Codeine was found to have a moderate benefit for pain and function compared to placebo or no codeine.
- Codeine was found to improve stiffness and sleep outcomes when compared to placebo.
- The evidence was mixed regarding the effectiveness of codeine in reducing the need for rescue analgesia compared to placebo.
- Increased adverse events and withdrawal due to adverse events were observed with codeine-containing drugs when compared to acetaminophen and placebo.

Note: The type of pain was not always specified in studies.

[Codeine for Acute Extremity Pain: A Review of Clinical Effectiveness \(2021\)](#)

Issue: When treating acute extremity pain, the attending health care provider aims to quickly reduce pain intensity. Non-opioid analgesics such as NSAIDs, acetaminophen, and salicylates may be sufficient for mild to moderate pain. Opioids such as codeine used alone or in combination with a non-opioid are often the next step for severe pain. Given the major increase in overdoses related to the use of opioids, the appropriate role of codeine for pain management is being questioned. A review of the clinical effectiveness of codeine, with and without acetaminophen and/or NSAIDs, may help inform decisions on the use of codeine for the treatment of acute extremity pain.

CADTH appraised and summarized the relevant evidence published between January 2010 and November 2020 found in: 2 systematic reviews,^c 5 randomized controlled trials, and 1 non-randomized study.

^cOne review did not contain any relevant primary studies.

Key Messages

In patients with acute extremity pain:

- No evidence was found on the effectiveness of codeine as a stand-alone therapy.
- Limited evidence suggests that codeine used in combination with other drugs (e.g., acetaminophen, ibuprofen) may not differ from comparator groups (e.g., acetaminophen and hydrocodone) with regards to patient satisfaction, pain scores, the need for additional analgesia, or in the number of adverse events.

Note: These findings should be interpreted with caution given significant limitations of the evidence.

[Codeine for Acute Pain Related to Caesarean Section: A Review of Clinical Effectiveness \(2021\)](#)

Issue: Caesarean section rates have increased over the past 3 decades. Medications containing codeine have been used to treat the acute post-operative abdominal pain commonly associated with caesarean sections. Concerns related to the use of codeine following caesarean sections include the potential for neonatal toxicity and opioid-related adverse events for the postpartum patient. A review of the clinical effectiveness of codeine, with and without acetaminophen and/or NSAIDs, will help determine whether the clinical benefits of codeine in patients who have undergone a caesarean section outweigh the potential risks.

CADTH assessed the relevant evidence found in: 1 randomized controlled trial.

Key Messages

In patients who have undergone a caesarean section:

- No evidence was found on the effectiveness of codeine as a stand-alone therapy for acute pain management.
- For those with high levels of pain, limited evidence suggests that codeine in combination with acetaminophen provides better pain relief compared to placebo or acetaminophen alone.
- For those with moderate levels of pain, limited evidence suggests there is no difference between codeine in combination with acetaminophen, placebo, or acetaminophen alone in providing pain relief.

[Codeine for Acute Pain for Acute Dental Pain and Acute Pain Related to Dental Procedures \(2021\)](#)

Issue: Acute dental pain and pain related to dental procedures can be debilitating and cause anxiety about seeking dental treatment; consequently, the effective management of acute dental pain is a priority for dental professionals. Although codeine is a commonly used opioid analgesic in dentistry and has been found to be more cost-effective when used with or without ibuprofen than ibuprofen and acetaminophen alone, the use of opioids is a source of debate. Those in dentistry acknowledge that other more clinically effective alternatives may exist. Given the potential benefits and harms of codeine, a review of its clinical effectiveness – with and without acetaminophen and/or NSAIDs – may help inform decision-makers on the best use of codeine for the management of acute dental pain.

CADTH appraised and summarized the relevant evidence published between January 2011 and January 2021 found in: 2 overviews of systematic reviews, 4 systematic reviews, and 9 randomized controlled trials.

Key Messages

In patients experiencing acute dental pain:

- Codeine alone or used in combination with acetaminophen was generally shown to offer a benefit to patients when compared to placebo.
- Codeine used in combination with other drugs (e.g., acetaminophen, ibuprofen) was generally not found to be as effective or to have added benefit compared to other combination drugs, particularly those that were acetaminophen- or ibuprofen-based.
- Codeine used in combination with acetaminophen was found to reduce sensitivity in patients undergoing tooth bleaching compared to an NSAID or placebo.^d
- When codeine was used in combination with acetaminophen, increased adverse events were observed compared to placebo and/or other drugs.

^d These findings should be interpreted with caution given significant limitations of the evidence.

[Codeine for Acute Pain for Urological or General Surgery Patients: A Review of Clinical Effectiveness \(2019\)](#)

Issue: Surgical procedures can cause inflammation, tissue injury, or nerve injury that result in pain. The therapeutic options for post-operative pain are multimodal and tailored to the patient's characteristics, needs, and the level of pain. Opioids, including codeine, are the most widely used treatment for post-operative pain management. Opioid prescribing has come under scrutiny in recent years and, as a result, there is a desire to optimize opioid prescribing after surgery. A review of the clinical effectiveness of codeine, with or without acetaminophen, may help inform decisions on the use of codeine-containing products for acute pain after urological or general surgeries.

CADTH appraised and summarized the relevant evidence published from January 2014 to October 2019 found in: zero publications.

Key Messages

For patients with acute pain due to urological or general surgery:

- No relevant evidence was identified regarding the use of codeine, with or without acetaminophen.

[Codeine for Pediatric Patients with Acute Pain: A Review of Clinical Effectiveness \(2019\)](#)

Issue: Various organizations around the world have issued warnings regarding the use of codeine for the management of pain in pediatric patients. In 2013, Health Canada recommended against the use of codeine in children younger than 12 after reviewing the safety of prescription pain and cough medications containing codeine. A review of the clinical effectiveness of codeine, with or without acetaminophen, may help inform decisions on the use of codeine-containing products for pediatric patients with acute pain.

CADTH appraised and summarized the relevant evidence published between January 2009 and October 2019 found in: 1 systematic review, 3 randomized controlled trials, and 1 non-randomized study.

Key Messages

For pediatric patients with acute pain:

- No difference was found in adverse events between codeine, ibuprofen, or hydrocodone groups.
- Mixed results were found when comparing codeine with acetaminophen to ibuprofen or acetaminophen alone:
 - Compared to ibuprofen alone, codeine with acetaminophen had similar results in pediatric pain severity and treatment failure, and had significantly more adverse events. Codeine with acetaminophen was significantly less effective compared with ibuprofen for some functional outcomes (playing and eating); however, between-group differences for other functional outcomes (i.e., school and sleep) were unclear.
 - Compared with acetaminophen alone, pediatric patients who received codeine with acetaminophen had lower pain and distress.

Codeine for Acute Pain in Patients Undergoing Orthopedic Surgery: A Review of Clinical Effectiveness (2019)

Issue: Surgical procedures can cause inflammation, tissue injury, or nerve injury that result in pain. The therapeutic options for post-operative pain are multimodal and tailored to the patient's characteristics, needs, and the level of pain. Opioids, including codeine, are the most widely used treatment for post-operative pain management. Overprescribing by physicians and the diversion of non-consumed supplies has been recognized as a contributor to the national opioid epidemic. As a result, there is a desire to optimize opioid prescribing after surgery. A review of the clinical effectiveness of codeine, with or without acetaminophen, may help inform decisions on the use of codeine-containing products for acute pain after orthopedic surgeries.

CADTH appraised and summarized the relevant evidence published between January 2014 and October 2019 found in: 2 systematic reviews.

Note: The reviews did not contain any relevant primary studies.

Key Messages

For patients with acute pain due to orthopedic surgery:

- No relevant evidence was identified regarding the use of codeine, with or without acetaminophen.

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July 2021