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SUMMARY WITH CRITICAL APPRAISAL

Codeine for Pain Related to Osteoarthritis of the Knee and Hip: A Review of Clinical Effectiveness

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

Abbreviations

CI	Confidence interval
MA	Meta-analysis
MD	Mean difference
OA	Osteoarthritis
NSAID	Non-steroidal anti-inflammatory drug
RCT	Randomized controlled trial
SMD	Standardized mean difference
SR	Systematic review
VAS	Visual analogue scale
WOMAC	Western Ontario and McMaster University Osteoarthritis

Context and Policy Issues

As the most common type of joint disease in older adults, osteoarthritis (OA) is a progressive illness characterized by cartilage breakdown, tendon and ligament deterioration, and synovial inflammation causing chronic pain and functional impairment.[1] Commonly involving knees, hips, big toes, hands, and the spine, OA affected approximately five million Canadians in 2017 and it is estimated that one in four Canadians will be diagnosed with OA by 2035.[2] Without a cure, the goal of OA management is to control pain and improve function using a combination of self-management techniques (e.g., physical exercise and weight management), medications, and orthopedic surgery.[2]

Throughout the course of disease, varying severity of joint pain and/or functional impairment will require different pharmacological options[3] that may be used as alternatives or adjuncts to nonpharmacological options. Typical pharmacological options used for symptom management may include oral and topical non-steroidal anti-inflammatory drugs (NSAIDs), topical capsaicin, intraarticular glucocorticoid injections, acetaminophen, and opioids.[4] Nonetheless, when used for extended durations, safety concerns such as abnormal liver function tests associated with acetaminophen and increased risk of gastrointestinal adverse events associated with NSAIDs require periodic monitoring.[1,4] Furthermore, due to risk of addiction and potential adverse events (e.g., drowsiness, respiratory depression), opioids including codeine are reserved for severe pain or when other analgesics are contraindicated.[1,4,5]

As a prodrug, codeine's analgesic activity on mu-opioid receptors relies primarily on the patient's ability to metabolize codeine to morphine by the cytochrome P450 enzyme CYP2D6.[6] Due to CYP2D6 polymorphisms across populations, different rates of codeine metabolism result in varying degrees of analgesic effect and adverse events.[6] Specifically, patients who are poor metabolizers of codeine may experience suboptimal pain control, while ultra-rapid metabolizers have a higher risk of adverse events.[6] Furthermore, with the second highest rate of opioid use in the world, Canada is experiencing a substantial increase in overdose-related deaths.[7] Thus, there is a desire to reduce inappropriate prescribing, opioid misuse, and associated harms.[7]

Three previously published CADTH reports reviewed the clinical effectiveness of codeine with or without acetaminophen for acute pain in patients undergoing urological or general surgery,[8] orthopedic surgery,[9] and in pediatric patients.[10] As a weak opioid, codeine can be used in conjunction with non-opioid analgesics such as acetaminophen or NSAIDs.[6] Thus, the objective of the present report is to evaluate the clinical effectiveness of codeine with or

without acetaminophen and/or an NSAID for patients with acute or chronic pain related to OA of the knee or hip.

Research Questions

1. What is the clinical effectiveness of codeine for patients with acute or chronic pain related to osteoarthritis of the knee or hip?

2. What is the clinical effectiveness of codeine with acetaminophen and/or a non-steroidal anti-inflammatory drug for patients with acute or chronic pain related to osteoarthritis of the knee or hip?

Key Findings

Two systematic reviews with meta-analyses and three randomized controlled trials were identified regarding the clinical effectiveness of codeine with or without acetaminophen or ibuprofen for patients with pain related to osteoarthritis of the knee or hip. While one systematic review did not contain primary studies relevant to this report, one systematic review contained three randomized controlled trials relevant to this report.

Although pooled results from one systematic review with meta-analysis suggested that, compared to placebo or no codeine, codeine has a moderate benefit for pain and function in patients with osteoarthritis pain of the knee or hip, codeine resulted in a significantly higher risk for withdrawal due to adverse events. Furthermore, findings from one randomized controlled trial suggested a significantly reduced need for rescue pain medications in the codeine controlled-released versus control group, while two randomized controlled trials did not detect significant differences between codeine plus acetaminophen or ibuprofen versus control groups for this outcome. Finally, findings from all three randomized controlled trials suggested higher rates of adverse events (e.g., nausea, constipation) in codeine versus control groups, with significant differences detected in two randomized controlled trials.

Although the systematic reviews were generally well-conducted, the limitations of the included literature (e.g., respiratory depression incidence not reported in systematic reviews and primary studies, co-authors from the drug manufacturer in one primary study, short follow-up durations for all three primary studies) should be considered when interpreting these results. Furthermore, there was a lack of recently conducted primary studies published after 2000, as well as studies comparing codeine with or without acetaminophen or ibuprofen with different opioids or non-steroidal anti-inflammatory drugs other than ibuprofen. Finally, there was a limited quantity of evidence for each of the specific codeine combinations (i.e., codeine alone, codeine plus acetaminophen, codeine plus ibuprofen).

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 and hip or knee osteoarthritis. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published up to November 3, 2020.

Selection Criteria and Methods

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

Table 1: Selection Criteria

Population	Patients (any age) with acute or chronic pain related to osteoarthritis of the knee or hip with or without previous history of orthopedic surgery
Intervention	Q1: Codeine alone Q2: Codeine with acetaminophen and/or an NSAID (e.g., aspirin, ibuprofen, naproxen) as single products or as combination drugs (e.g., codeine-acetaminophen-caffeine combination)
Comparator	Other opioids (e.g., tramadol, oxycodone, morphine, hydromorphone, fentanyl), one or more non-opioid analgesics (e.g., acetaminophen, NSAID), other opioid combinations (e.g., oxycodone with acetaminophen), or placebo
Outcomes	Clinical effectiveness (e.g., pain control, health-related qualify of life, mobility), safety (e.g., overdose-related adverse events such as respiratory depression and liver toxicity, other adverse events such as constipation and risk of falls, dependence/addiction, hospitalizations)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

NSAID = non-steroidal anti-inflammatory drug.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or if they were duplicate publications. Systematic reviews (SRs) in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[11] for SRs and Downs and Black checklist[12] for randomized controlled trials (RCT). Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 609 citations were identified in the literature search. Following screening of titles and abstracts, 597 citations were excluded and 12 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, nine publications were excluded for various reasons, and five publications met the inclusion criteria and were included in this report. These comprised two SRs[1,3] with

meta-analysis (MA) and three RCTs.[13-15] Appendix 1 presents the PRISMA[16] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Two SRs[1,3] with MA and three RCTs[13-15] were identified with relevance to the research questions and inclusion criteria of this report. The two SRs had broader inclusion criteria than the present review. Specifically, one SR[3] included patients with OA of the hand in addition to knee and hip and evaluated various oral opioids (i.e., not just codeine). The other SR[1] evaluated various oral and transdermal opioids. Only primary studies examining relevant population groups and interventions were extracted from these SRs and described in this report. None of the included studies in the SR authored by Fuggle et al.[3] evaluated the intervention of interest for this report. Three RCTs[13-15] included in the SR[1] authored by da Costa et al. were also selected for inclusion in this Rapid Response report because they reported on additional findings that were not captured in the SR. Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Published in 2019[3] and 2014,[1] the two identified SRs included 17[3] and 22[1] randomized controlled trials (RCTs). Of the RCTs included in the SRs, none in the SR by Fuggle et al.[3] and three[13-15] in the SR by da Costa et al.[1] were relevant to this report. While one SR[1] did not have language restrictions, Fuggle et al.[3] limited their search to English or French publications. Timeframes for the literature searches were from inception to June 30, 2017[3] or August 15, 2012.[1]

While two relevant primary studies were double-blind RCTs,[14,15] the primary study conducted by Quiding et al. was a double-blind crossover RCT.[13]

Country of Origin

The first author of the two SRs was from United Kingdom[3] and Switzerland.[1] The first author of the three RCTs was from Canada,[14] Sweden,[13] and Denmark.[15]

Patient Population

The two identified SRs did not specify the age-related inclusion criteria.[1,3] While Fuggle et al.[3] included studies examining patients with OA pain of the knee, hip, or hand (acute or chronic pain not specified), da Costa et al.[1] included patients with chronic OA pain of the knee or hip.

The relevant RCT authored by Peloso et al.[14] recruited 103 participants with OA pain of the knee or hip (acute or chronic pain not specified). The relevant RCT authored by Quiding et al.[13] recruited 26 participants with OA pain of the hip (acute or chronic pain not specified). Finally, the relevant RCT authored by Kjaersgaard-Andersen et al.[15] recruited 158 participants with chronic OA pain of the hip.

Interventions and Comparators

The relevant interventions from the SR authored by da Costa el al.[1] were oral codeine with or without acetaminophen or ibuprofen, while the relevant comparator was placebo. The SR authored by Fuggle et al.[3] did not identify any relevant studies evaluating the use of codeine.

The RCT authored by Peloso et al.[14] compared codeine alone (50mg to 200mg controlled-release tablet) and placebo taken twice daily. When required, participants were given rescue acetaminophen 650mg up to three times daily.[14] The RCT authored by Kjaersgaard-Andersen et al.[15] compared codeine 60mg plus acetaminophen 1000mg and acetaminophen 1000mg alone taken three times daily. When required, participants were given rescue ibuprofen 400mg up to three times daily.[15] The RCT authored by Quiding et al.[13] compared codeine 30mg plus ibuprofen 200mg, ibuprofen 200mg alone, and placebo taken six times in 32 hours. When required, participants were given rescue acetaminophen (dose and maximum frequency not reported).[13]

Outcomes

The relevant outcomes from da Costa et al.[1] included pain, function, adverse events, and withdrawal due to adverse events. Pooled results were presented in the form of standardized mean difference (SMD) for pain and function, and risk ratio for safety outcomes.[1] SMDs of -0.20, -0.50, and -0.80 standard deviation units were considered to be small, moderate, and large differences, respectively, between codeine and control groups.[1] Since no relevant studies assessing codeine were identified in the SR authored by Fuggle et al.,[3] no relevant outcomes were available to summarize for this report.

In the RCT authored by Peloso et al.,[14] additional outcomes not described in the SR authored by da Costa et al.[1] included Western Ontario and McMaster University Osteoarthritis (WOMAC) stiffness, need for sleep medications, trouble falling asleep, pain upon awakening, need for rescue acetaminophen, and rate of adverse events. In the RCT authored by Quiding et al,[13] additional outcomes included need for rescue acetaminophen and rate of adverse events. Finally, in the third RCT authored by Kjaersgaard-Andersen et al.,[15] additional outcomes included need for rescue ibuprofen and rate of adverse events.

Summary of Critical Appraisal

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

Systematic Reviews and Meta-Analyses

As per AMSTAR II criteria,[11] the two included SRs[1,3] with MA were generally well conducted with clearly stated objectives, inclusion criteria, and stated key search terms. The SR authors provided search strategies, searched multiple databases, provided a list of included studies, and evaluated the risk of bias in included primary studies with appropriate techniques. Furthermore, details of study selection were explicitly stated, and data extraction was conducted in duplicate for both SRs, which decreases the risk for inconsistencies. The authors of both SRs performed random-effects MA and used I^2 statistics to assess for heterogeneity. Between-trial heterogeneity as scored by I^2 statistics ranged from 0% to 55% (moderate) for relevant outcomes described in the SR authored by da Costa et al.[1] Both SRs[1,3] were conducted by following an a priori study protocol. Grey literature search was conducted in one SR, which decreases the risk of missing relevant, non-indexed studies.[1] Both SRs reported their funding sources.[1,3] Authors of one SR declared that they have no conflicts of interest.[1]

In terms of methodological limitations, while the exclusion criteria were explicitly stated for both SRs,[1,3] a list of excluded studies and rationale for exclusion was only provided in one SR.[1] The age eligibility criteria were not explicitly stated in the two SRs.[1,3] Justification was not provided for the exclusion of studies published in languages other than English and

French in the SR authored by Fuggle et al.[3] Furthermore, the choice of included study designs was not justified in either SR.[1,3] Publication bias was not assessed in one SR,[3] and when assessed in the other SR,[1] the authors were unable to rule out publication bias. Some co-authors of one SR[3] received grants from pharmaceutical companies (e.g., Merck, Pfizer, Novartis, Takeda, Teva) for other work.

Randomized Controlled Trials

The three RCTs shared some methodological strengths, including: 1) clearly stated objectives, inclusion and exclusion criteria, interventions, outcome measures, and main findings; 2) used double-blinding to help reduce bias; 3) reported estimates of random variability; 4) planned data analyses at the outset of the study; and 5) discussed potential adverse events relating to the interventions. Although statistical tests were appropriately used for all three RCTs,[13-15] statistical tests and P values were not reported for some comparisons in two RCTs.[13,15]

These three RCTs also had some methodological limitations.[13-15] Specifically, the authors of all three RCTs did not specify the time period over which patients were recruited or state if there were any conflicts of interest.[13-15] While the authors of two RCTs did not disclose their funding sources,[13,15] the Canadian RCT[14] was funded by Purdue Frederick, which is the maker of the drug that was evaluated. Furthermore, two co-authors of the Canadian RCT were affiliated with Purdue Frederick.[14]

Summary of Findings

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

Pain and Function

In the SR authored by da Costa et al.,[1] primary study results from three[13-15] and two[14,15] RCTs were pooled for pain and function outcomes, respectively. The interventions evaluated in the three RCTs were codeine controlled-release tablet,[14] codeine plus ibuprofen,[13] and codeine plus acetaminophen.[15] The outcomes were extracted at four weeks for two RCTs[14,15] and at one week for the third RCT.[13] Compared to control (i.e., placebo or no codeine), pooled results suggested that codeine has a moderate benefit for pain (SMD, -0.51; 95% CI, -1.01 to -0.01) and function (SMD, -0.42; 95% CI, -0.74 to -0.10).[1]

Stiffness and Sleep Outcomes

One relevant RCT[14] compared the clinical effectiveness of codeine alone (50mg to 200mg controlled-release) and placebo taken twice daily in patients with OA pain of the knee and/or hip. After 4 weeks, participants in the codeine controlled-release arm exhibited significantly greater improvements from baseline in WOMAC stiffness scores (47.7% improvement) compared to those in the placebo arm (17.0% improvement) (P = 0.003).[14] Furthermore, compared to the placebo arm, participants in the codeine controlled-release arm exhibited significantly less need for sleep medications, less trouble falling asleep, and less pain upon awakening.

Rescue Medication Requirement

All three relevant RCTs reported requirements for rescue pain medications.[13-15] In the RCT authored by Peloso et al.,[14] compared to the placebo arm, participants in the codeine controlled-release arm required significantly fewer doses of rescue with acetaminophen.[14]

The RCT authored by Quiding et al.[13] compared the clinical effectiveness of codeine 30mg plus ibuprofen 200mg, ibuprofen 200mg alone, and placebo taken six times in 32 hours in patients with OA pain of the hip. In this one-week trial, rescue acetaminophen was required by one and six participants in the codeine plus ibuprofen and placebo arms, respectively, with no significant difference.[13] The RCT authored by Kjaersgaard-Andersen et al.[15] compared the clinical effectiveness of codeine 60mg plus acetaminophen 1000mg and acetaminophen 1000mg alone taken three times daily in patients with OA pain of the hip over four weeks. At week 1, compared to the acetaminophen alone group, significantly fewer participants in the codeine plus acetaminophen arm required more than one rescue ibuprofen tablet on average per day.[15] However, no significant differences were detected between the two groups at weeks 2, 3, and 4.[15]

Adverse Events

All three relevant RCTs reported rates of adverse events.[13-15] In the first RCT, while no significant difference was reported in the incidence of nausea between the two groups, there were significantly more incidences of overall adverse events, constipation, somnolence, and dizziness in the codeine controlled-release compared to the placebo arm .[14] In the second RCT, numerically more participants in the codeine plus ibuprofen arm experienced an adverse event, most commonly nausea, compared to those in the placebo arm (statistical analysis not reported).[13] In the third RCT, at weeks 1, 2, 3, and 4, compared to the acetaminophen alone group, significantly more participants in the codeine plus acetaminophen arm experienced at least one adverse event.[15] Overall, nausea, vomiting, dizziness, constipation, and somnolence were predominant adverse events in the codeine plus acetaminophen arm, while nausea, constipation, somnolence, and diarrhea were predominant adverse events in the acetaminophen alone arm (statistical comparisons for specific adverse events were not reported).[15]

Withdrawal Due to Adverse Events

In the SR authored by da Costa et al.,[1] primary study results from the three RCTs[13-15] were pooled for withdrawal due to adverse events. The risk ratio for withdrawal due to adverse events was significantly higher (RR, 3.67; 95% CI, 2.16 to 6.24) in codeine treatment groups compared to control groups (i.e., placebo or no codeine).[1]

Limitations

Of the two identified SRs,[1,3] the SR authored by Fuggle et al.[3] did not include any literature regarding the clinical effectiveness of codeine or codeine with acetaminophen and/or an NSAID for patients with OA of the knee or hip. Overall, no literature compared the clinical effectiveness of codeine with or without acetaminophen or ibuprofen with different opioids or NSAIDs other than ibuprofen. Furthermore, while the two SRs were published recently in 2019[3] and 2014,[1] the three relevant RCTs date back to 1990,[15] 1992,[13] and 2000.[14] The lack of recent primary studies is not unexpected due to interpatient variability in the ability to metabolize codeine to its active metabolite (i.e., morphine), which may result in inadequate pain control or increased risk of adverse events such as respiratory depression.[17] This may have resulted in more cautious use of and fewer recent studies evaluating codeine for OA pain. Despite warnings from health organizations against codeine use in certain populations due to respiratory depression,[18] none of the identified SRs[1,3] or relevant primary studies[13-15] reported this safety outcome. The three primary studies reported up to four weeks of follow up; it is unclear if these study results would be generalizable to longer-term codeine

use. Finally, there was a limited quantity of evidence for each of the specific codeine combinations (i.e., codeine alone, codeine plus acetaminophen, codeine plus ibuprofen).

Conclusions and Implications for Decision or Policy Making

This report was comprised of two SRs[1,3] with MA and three RCTs[13-15] regarding the clinical effectiveness of codeine with or without acetaminophen or ibuprofen for patients with pain related to OA of the knee or hip. While none of the included studies in the SR authored by Fuggle et al.[3] were relevant for this report, the three relevant RCTs[13-15] were included in the SR authored by da Costa et al.[1]

The SR with MA authored by da Costa et al.[1] pooled results from three primary studies,[13-15] which suggested that codeine has a moderate benefit for pain and function in patients with OA pain of the knee or hip compared to control (i.e., placebo or no codeine). However, there was a significantly higher risk for withdrawal due to adverse events in those treated with codeine compared to control.[1]

Additional outcomes not included in the SR[1] with MA were described in the three RCTs.[13-15] Patients taking codeine controlled-release tablets experienced significantly greater improvements in stiffness, less need for sleep medications, less trouble falling asleep, and less pain upon awakening compared to placebo.[14] However, although one RCT[14] suggested significantly less need for rescue pain medications in patients taking codeine controlled-released tablets, two RCTs[13,15] did not detect significant differences in the need for rescue pain medications in the codeine plus ibuprofen and codeine plus acetaminophen groups compared to controls at the end of the trials. Furthermore, findings from all three RCTs[13-15] suggested greater incidence of adverse events (e.g., nausea, constipation) in codeine versus control groups, with significant differences detected in two RCTs.[14,15]

Overall, there was a paucity of recently published primary studies evaluating the use of codeine for patients with OA pain of the knee or hip. Although the identified SRs[1,3] were published within the past six years, the three relevant RCTs date back to 1990,[15] 1992,[13] and 2000.[14] Additionally, no literature comparing codeine with or without acetaminophen or ibuprofen with different opioids or NSAIDs other than ibuprofen were identified. There was also a limited quantity of evidence for each of the specific codeine combinations (i.e., codeine alone, codeine plus acetaminophen, codeine plus ibuprofen). The limitations of the included literature (e.g., respiratory depression incidence not reported in SRs and primary studies, co-authors from the drug manufacturer in one RCT,[14] relatively short follow-up durations for all three RCTs[13-15]) should be considered when interpreting the findings of this report.

Further research investigating the clinical effectiveness of codeine, particularly controlled clinical trials with extended follow-up durations past four weeks, would provide clinicians with additional knowledge base regarding long-term pain control and risks of substance dependence in patients living with OA pain of the hip or knee.

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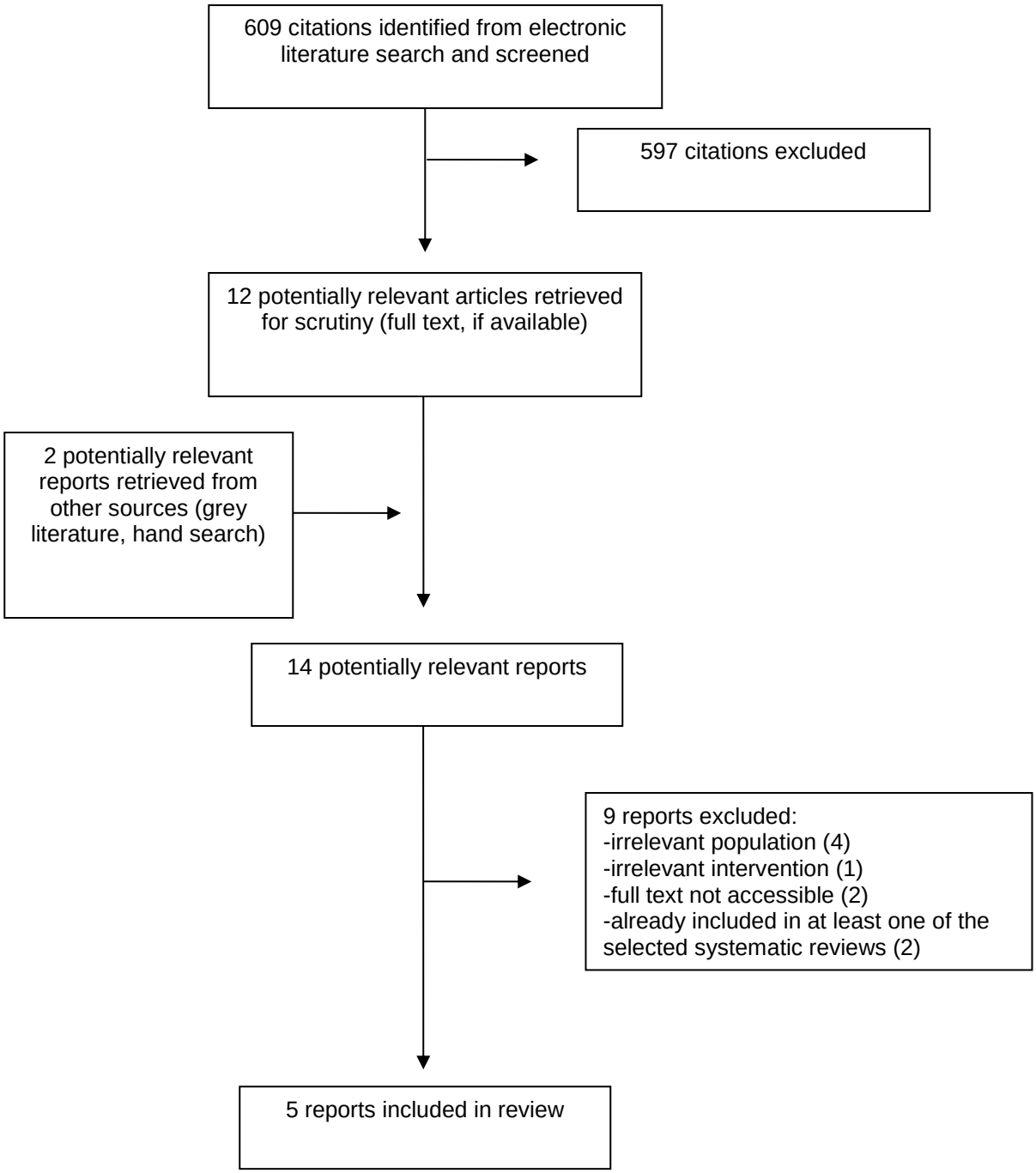
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Fuggle et al., 2019[3] **United Kingdom** **Funding Source:** European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases	**Objective:** To evaluate the safety of opioids **Study design:** SR with MA of double-blind RCTs **Literature search strategy:** The search was conducted in MEDLINE, Cochrane Central Register of Controlled Trials, and Scopus for English or French literature published from inception to June 30, 2017. Grey literature search was not conducted. **Number of studies included:** Of 17 identified studies, no study was relevant to this report **Quality assessment tool:** GRADE	Patients (age-related inclusion criteria NR) with OA of the knee, hip, or hand)	**Interventions**: Oral opioids **Comparator**: Other oral analgesics or placebo	**Outcomes**: - No relevant outcomes were described for patients taking codeine **Follow-up**: Follow-up up to 16 weeks
da Costa et al., 2014[1] **Switzerland** **Funding Sources:** University of Bern, Swiss National Science Foundation, Marie Curie Intra-European Fellowship	**Objective:** To evaluate the effects of opioids on pain, function, safety, and addiction **Study design:** SR with MA of randomized or quasi-randomized controlled trials **Literature search strategy:** The search was conducted in Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and CINAHL for literature published up to August 15, 2012 with no language	Patients (age-related inclusion criteria NR) with OA of the knee or hip	**Interventions**: Oral or transdermal opioids; oral codeine is relevant to this report **Comparator**: Placebo or no treatment; placebo is relevant to this report	**Outcomes**: - Primary outcomes: pain, function - Secondary outcomes: adverse events, withdrawal due to adverse events **Follow-up**: Median follow-up of up to 16 weeks

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	restrictions. Grey literature including conference proceedings and references lists were also searched. **Number of studies included:** Of 22 identified studies, three RCTs were relevant to this report **Quality assessment tool:** GRADE			

CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulated Index to Nursing and Allied Health Literature; EMBASE = Excerpta Medica Database; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; MA = meta-analysis; NR = not reported; OA = osteoarthritis; RCT = randomized controlled trial; SR = systematic review.

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Peloso et al., 2000[14] Canada Funding Source: Purdue Frederick	**Study design:** RCT **Setting:** Four Canadian clinical sites **Objective:** To assess the clinical effectiveness of codeine controlled-released tablet for OA pain	Adult patients (> 35 years) with OA pain of the knee or hip (acute or chronic pain NR) **Number of patients:** N = 103 (51 codeine vs 52 placebo) **Mean age:** 62 years **% female:** 62%	**Intervention:** - Codeine controlled-release tablet (50mg to 200mg taken twice daily) **Comparator:** - Placebo taken twice daily Participants also received rescue acetaminophen 650mg up to three times daily when required.	**Relevant Outcomes:** - WOMAC pain, stiffness, physical function - Need for sleep medications, trouble falling asleep, pain upon awakening, need for rescue acetaminophen - Adverse events, withdrawal due to adverse events **Follow-up:** - Four weeks
Quiding et al., 1992[13] Sweden Funding Source: NR	**Study design:** Crossover RCT **Setting:** Hospital in Stockholm **Objective:** To assess the clinical effectiveness of codeine plus ibuprofen for OA pain	Adult patients (age eligibility criteria NR) with OA pain of the hip (acute or chronic pain NR) **Number of patients:** N = 26 **Mean age:** 53 years **% female:** 85%	**Intervention:** - Codeine 30mg plus ibuprofen 200mg taken 6 times in 32 hours **Comparator:** - Placebo taken 6 times in 32 hours Participants also received rescue acetaminophen (dose	**Relevant Outcomes:** - Pain, need for rescue acetaminophen - Adverse events, withdrawal due to adverse events **Follow-up:** - One week

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
			and maximum frequency NR) when required.	
Kjaersgaard-Andersen et al., 1990[15] Denmark Funding Source: NR	**Study design:** RCT **Setting:** Multiple clinics across Denmark **Objective:** To assess the clinical effectiveness of codeine plus acetaminophen for OA pain	Adult patients (> 18 years) with chronic OA pain of the hip **Number of patients:** N = 158 (83 codeine plus acetaminophen vs 75 acetaminophen) **Mean age:** 66 years **% female:** 46%	**Intervention:** - Codeine 60mg plus acetaminophen 1000mg taken 3 times daily **Comparator:** - Acetaminophen 1000mg taken 3 times daily Participants also received rescue ibuprofen 400mg up to three times daily when required.	**Relevant Outcomes:** - Pain, need for rescue ibuprofen - Adverse events, withdrawal due to adverse events **Follow-up:** - Four weeks

NR = not reported; OA = osteoarthritis; RCT = randomized controlled trial; vs = versus; WOMAC = Western Ontario and McMaster University Osteoarthritis.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews Using AMSTAR 2[11]

Strengths	Limitations
Fuggle et al., 2019[3]	
• The objectives and inclusion/exclusion criteria were clearly stated, and timeframe for follow-up was stipulated • Multiple databases were searched (MEDLINE, Cochrane Central Register of Controlled Trials, Scopus) • Search terms and time frame were provided (inception to June 30, 2017) • An a priori study protocol was followed • The details of study selection and extraction were explicitly reported and performed by two reviewers • A list of included studies was provided, and the characteristics of included studies were described in detail • The quality of included studies was assessed using GRADE • Conducted a random effects meta-analysis • Assessed for heterogeneity using I^2 statistics • The authors disclosed their funding source	• Grey literature search was not conducted • The participant age eligibility criteria were NR • The exclusion of non-English and non-French publications was not justified • The choice of included study designs was not justified • Apart from listing the exclusion criteria, a list of excluded studies was not provided • The assessment of publication bias was NR • Financial conflicts of interested were reported, with some authors receiving grants from pharmaceutical companies (e.g., Merck, Pfizer, Novartis, Takeda, Teva) for other work
da Costa et al., 2014[1]	
• The objectives and inclusion/exclusion criteria were clearly stated, and timeframe for follow-up was stipulated • Multiple databases were searched (Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and CINAHL) • Grey literature search was conducted • Search terms and time frame were provided (inception to August 15, 2012) • An a priori study protocol was followed • No language restriction was applied • The details of study selection and extraction were explicitly reported and performed by two reviewers • A list of included studies was provided, and the characteristics of included studies were described in detail • A list of excluded studies and rationale for exclusion was provided • The quality of evidence was assessed using GRADE • Conducted a random-effects meta-analysis • Assessed for heterogeneity using I^2 statistics • Publication bias was assessed using funnel plots • The authors assessed funding and conflicts of interest in the included studies • The authors disclosed their funding sources and declared that they have no conflicts of interest	• The choice of included study designs was not justified • The participant age eligibility criteria were NR

CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulated Index to Nursing and Allied Health Literature; EMBASE = Excerpta Medica Database; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; NR = not reported.

Table 5: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[12]

Strengths	Limitations
Peloso et al., 2000[14]	
• The study's objective, intervention, and main findings were clearly stated • The main outcomes to be measured were clearly described in the Methods section, and were valid and reliable • The inclusion and exclusion criteria were clearly described • Authors used a double-blind RCT approach • Estimates of random variability were reported • The statistical tests used to assess the main outcomes were described and appropriate • A sample size calculation was conducted • Data analyses were planned at the outset of the study • Potential adverse events relating to the interventions were discussed	• The time period over which patients were recruited was not specified • The authors did not disclose if there were any conflicts of interest • Funding support for this study was reported (i.e., Purdue Frederick), which was the maker of the drug being studied
Quiding et al., 1992[13]	
• The study's objective, intervention, and main findings were clearly stated • The main outcomes to be measured were clearly described in the Methods section, and were valid and reliable • The inclusion and exclusion criteria were clearly described • Authors used a double-blind RCT approach • Estimates of random variability were reported • The statistical tests used to assess the main outcomes were described and appropriate • Data analyses were planned at the outset of the study • Potential adverse events relating to the interventions were discussed	• The time period over which patients were recruited was not specified • A sample size calculation was NR • Statistical tests and P values were NR for some comparisons • The authors did not disclose their funding sources and if there were any conflicts of interest
Kjaersgaard-Andersen et al., 1990[15]	
• The study's objective, intervention, and main findings were clearly stated • The main outcomes to be measured were clearly described in the Methods section, and were valid and reliable • The inclusion and exclusion criteria were clearly described • Authors used a double-blind RCT approach • Estimates of random variability were reported • The statistical tests used to assess the main outcomes were described and appropriate • A sample size calculation was conducted • Data analyses were planned at the outset of the study • Potential adverse events relating to the interventions were discussed	• The time period over which patients were recruited was not specified • Statistical tests and P values were NR for some comparisons • The authors did not disclose their funding sources and if there were any conflicts of interest

NR = not reported; RCT = randomized controlled trial.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings of Included Systematic Review

Main study findings	Authors' conclusion
da Costa et al., 2014[1]	
Pain - Pain outcomes from three RCTs[13-15] were pooled - Moderate benefit for codeine (SMD, -0.51; 95% CI, -1.01 to -0.01) compared to control (i.e., placebo or no codeine) **Function** - Function outcomes from two RCTs[14,15] were pooled - Moderate benefit for codeine (SMD, -0.42; 95% CI, -0.74 to -0.10) compared to control (i.e., placebo or no codeine) **Withdrawal due to Adverse Events** - Withdrawal due to adverse events from three RCTs[13-15] were pooled - The risk ratio for withdrawal due to adverse events was significantly higher (RR, 3.67; 95% CI, 2.16 to 6.24) in the codeine treatment arm compared to control (i.e., placebo or no codeine)	Pain: "Benefits were moderate for codeine (SMD -0.51, 95% CI -1.01 to -0.01; 3 trials) (*p13*)."[1] Function: "We found a moderate benefit for codeine (SMD -0.42, 95% CI -0.74 to -0.10; 2 trials) (*p17*)."[1]

CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio; SMD = standardized mean difference.

Table 7: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Peloso et al., 2000[14]	
Stiffness and sleep outcomes (% improvement from baseline): Outcome / Codeine (N = 51) (%) / Placebo (N = 52) (%) / P value WOMAC stiffness / 47.7 / 17.0 / 0.003 Less need for medications to sleep / 73.3 / 10.4 / 0.0039 Less trouble falling asleep / 72.5 / 37.7 / 0.0220 Less pain upon awakening / 76.4 / 22.8 / 0.0231 **Rescue acetaminophen administration:** - Patients in the codeine arm needed less acetaminophen (4.2±5.8 rescue administrations/day) vs the placebo arm (9.2±8.1 rescue administrations/day) (P = 0.005) **Adverse events:** Adverse event / Codeine (N = 51) (%) / Placebo (N = 52) (%) / P value Constipation / 49 / 11 / < 0.01 Somnolence / 39 / 10 / < 0.01	"All variables in the efficacy analysis indicated superiority of controlled release codeine over placebo. The WOMAC pain scale showed an improvement of 44.8% over baseline in the controlled release codeine group compared with 12.3% taking placebo (p = 0.0004). For the WOMAC stiffness and physical function scales the improvements over baseline on controlled release codeine were 47.7% and 49.3%, respectively compared with 17.0% and 17.0%, respectively, with placebo (p = 0.003; p = 0.0007). Controlled release codeine was also significantly better than placebo on measures of sleep quality and requirement for supplemental acetaminophen (*p764*)."[14]

Main study findings	Authors' conclusion
<table><tr><td>Dizziness</td><td>33</td><td>8</td><td>< 0.01</td></tr><tr><td>Overall</td><td>82</td><td>58</td><td>< 0.01</td></tr><tr><td>Nausea</td><td>NR</td><td>NR</td><td>0.091</td></tr></table>	
Quiding et al., 1992[13]	
Rescue acetaminophen administration: - Rescue acetaminophen was needed by 1 (codeine plus ibuprofen), 4 (ibuprofen), 6 (placebo) patients - No significant difference between codeine plus ibuprofen vs placebo (P = 0.06) - Statistical analysis NR for other comparisons **Adverse events:** - 11 patients in the codeine plus ibuprofen arm reported adverse events, with nausea (6) being most common - 5 patients in the ibuprofen arm reported adverse events, with nausea (3) being most common - 6 patients in the placebo arm reported adverse events, with nausea (2) being the most common - Statistical analysis NR	"After the 1st dose the 8-h mean pain intensity values were 25, 27, and 26 mm after ibuprofen plus codeine, ibuprofen, and placebo, respectively. Following another 5 doses every 4 h the corresponding values were 10, 17 and 29 mm. Repeated administration of both active drugs reduced the pain intensity significantly. The analgesic efficacy of ibuprofen plus codeine was significantly superior to that of ibuprofen which was, in turn, superior to that of placebo. In conclusion, analgesic efficacy was better differentiated after repeated-dose than after single-dose administration (*p303*)."[13]
Kjaersgaard-Andersen et al., 1990[15]	
Rescue ibuprofen administration: - Week 1: 5% and 21% of patients taking codeine plus acetaminophen and acetaminophen alone, respectively, needed > 1 rescue ibuprofen tablet on average per day (P = 0.003) - Week 2: 21% and 20% of patients taking codeine plus acetaminophen and acetaminophen alone, respectively, needed > 1 rescue ibuprofen tablet on average per day (ns) - Week 3: 15% and 26% of patients taking codeine plus acetaminophen and acetaminophen alone, respectively, needed > 1 rescue ibuprofen tablet on average per day (ns) - Week 4: 28% and 26% of patients taking codeine plus acetaminophen and acetaminophen alone, respectively, needed > 1 rescue ibuprofen tablet on average per day (ns) **Adverse events:** - Week 1: 87% and 38% of patients taking codeine plus acetaminophen and acetaminophen alone, respectively, experienced ≥ 1 adverse event(s) (P < 0.01) - Week 2: 64% and 31% of patients taking codeine plus acetaminophen and acetaminophen alone, respectively, experienced ≥ 1 adverse event(s) (P < 0.01) - Week 3: 61% and 22% of patients taking codeine plus acetaminophen and acetaminophen alone, respectively, experienced ≥ 1 adverse event(s) (P < 0.01) - Week 4: 52% and 29% of patients taking codeine plus acetaminophen and acetaminophen alone, respectively, experienced ≥ 1 adverse event(s) (P < 0.01) - Overall, nausea, vomiting, dizziness, and constipation were predominant adverse events in the codeine plus acetaminophen arm (statistical analysis NR)	"Over weeks 1-4, 87%, 64%, 61% and 52% of patients in the codeine plus paracetamol group, and 38%, 31%, 22% and 29% of patients in the paracetamol group had one or more adverse drug reactions. Significantly more patients in the codeine plus paracetamol group had adverse drug reactions in each of the 4 weeks. Nausea, dizziness, vomiting and constipation were predominant adverse reactions in the codeine plus paracetamol group. During the first week of treatment, 30 patients (36%) in the codeine plus paracetamol group and 9 (12%) in the paracetamol group dropped out. As evaluated from patients completing the first week of treatment, the pain intensity during that week compared to their baseline pain was significantly lower in the codeine plus paracetamol group than in the paracetamol group. Moreover, during the first week the paracetamol group received rescue medicine significantly more frequently. In conclusion, when evaluated after 7 days of treatment, the daily addition of codeine 180 mg to paracetamol 3 g significantly reduced the intensity of chronic pain due to osteoarthritis of the hip joint. However, several adverse drug reactions, mainly of the gastrointestinal tract, and the larger number of patients withdrawing from treatment means that the addition of such doses of codeine cannot be recommended for longer-term treatment of chronic pain in elderly patients (*p309*)."[15]

NR = not reported; ns = not significant; vs = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Appendix 5: Further Information

Previous CADTH Reports

Codeine for acute pain: a synopsis of the evidence; Ottawa (ON): CADTH; 2019 Dec. https://cadth.ca/sites/default/files/pdf/htis/codeine_actute_pain_evidence_synopsis.pdf Accessed 2020 Dec 02.

Li KX, Ford C. Codeine for pediatric patients with acute pain: a review of clinical effectiveness [*CADTH rapid response report: summary with critical appraisal*]. Ottawa (ON): CADTH; 2019 Nov: https://cadth.ca/sites/default/files/pdf/htis/2019/RC1200%20Codeine%20for%20Pediatric%20Patients%20Final.pdf Accessed 2020 Dec 02.

Marchand DK, Ford C. Codeine for acute pain for urological or general surgery patients: a review of clinical effectiveness [*CADTH rapid response report: summary with critical appraisal*]. Ottawa (ON): CADTH; 2019 Dec: https://cadth.ca/sites/default/files/pdf/htis/2019/RC1201%20Codeine%20for%20Urological%20Pts%20Final.pdf Accessed 2020 Dec 02.

Marchand DK, McCormack S. Codeine for Acute Pain in Patients Undergoing Orthopedic Surgery: A Review of Clinical Effectiveness [*CADTH rapid response report: summary with critical appraisal*]. Ottawa (ON): CADTH; 2019 Oct: https://cadth.ca/sites/default/files/pdf/htis/2019/RC1199%20Codeine%20for%20Orthopaedic%20Pts%20Final.pdf Accessed 2020 Dec 02.

CADTH. Codeine and acetaminophen for pain relief: a review of the clinical efficacy [*CADTH rapid response report: summary with critical appraisal*]. Ottawa (ON): CADTH; 2012 Apr: https://www.cadth.ca/media/pdf/htis/april-2012/RC0344%20Pain%20Medication%20Dosing%20Final.pdf Accessed 2020 Dec 02.

Health Technology Assessment – Alternative Intervention (Topical Analgesics)

McQuay HJ, Moore RA, Eccleston C, Morley S, Williams AC. Systematic review of outpatient services for chronic pain control. *Health Technol Assess*. 1997;1(6):i-iv, 1-135. PubMed: PM9483161

Systematic Reviews – Relevant Studies Captured by Other Systematic Review

Welsch P, Petzke F, Klose P, et al. Opioids for chronic osteoarthritis pain: an updated systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks double-blind duration. *Eur J Pain*. 2020 Apr;24(4):1-19. PubMed : PM31876347

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 10;35(10):836-843. PubMed: PM31318725

Randomized Controlled Trial – Mixed Population

Mullican WS, Lacy JR, Group T-A-S. Tramadol/acetaminophen combination tablets and codeine/acetaminophen combination capsules for the management of chronic pain: a comparative trial. *Clin Ther*. 2001 Sep;23(9):1429-1445.
PubMed: PM11589258

Non-Randomized Studies – Alternative or Mixed Population

Wei J, Wood MJ, Dubreuil M, et al. Association of tramadol with risk of myocardial infarction among patients with osteoarthritis. *Osteoarthritis Cartilage*. 2020 02;28(2):137-145.
PubMed: PM31629022

Vannacci A, Lombardi N, Simonetti M, et al. Regular use of acetaminophen or acetaminophen-codeine combinations and prescription of rescue therapy with non-steroidal anti-inflammatory drugs: a population-based study in primary care. *Curr Med Res Opin*. 2017 06;33(6):1141-1148.
PubMed: PM28318320

Roberto G, Simonetti M, Piccinni C, et al. Risk of acute cerebrovascular and cardiovascular events among users of acetaminophen or an acetaminophen-codeine combination in a cohort of patients with osteoarthritis: a nested case-control study. *Pharmacotherapy*. 2015 Oct;35(10):899-909.
PubMed: PM26497476