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Non-prescription Analgesic and Antitussive Medications Containing Codeine: A Review of Clinical Effectiveness and Safety

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Context and Policy Issues

Codeine

Codeine is an opioid analgesic that is often used to control acute conditions such as migraine, mild-to-moderate pain and cough.[1-3] Codeine is also used for the long-term treatment of more chronic conditions, i.e. for more than one year.[2,4] It can be administered both as scheduled, around-the-clock dosing and as-needed dosing.[4]

About 20% of codeine can be metabolized to its active metabolite, morphine and morphine-6-glucuronide, with large between-individual variability in the metabolism dependent on cytochrome CYP2D6.[5-8] In general, 30 milligrams (mg) of codeine is considered equivalent to 3 mg of morphine.[8] However, age, sex, race, and genetic polymorphism are associated with the variability in metabolism.[6] For those who are rapid metabolizers, a large amount of morphine can be formed, increasing the risk of adverse effects.[7]

The adverse effects of codeine include respiratory depression, nausea and vomiting, constipation, and increased pain sensitivity.[1] With long term use, addiction and withdrawals may develop.[1] The use of products containing codeine is generally not recommended for young children (aged six months to five years.[9] Additionally, codeine is not recommended for children undergoing anesthesia in the USA or for children undergoing tonsillectomy in Europe.[7]

Regulation on the use of codeine in Canada

In Canada, the use of opioids, including codeine, is currently regulated by the Controlled Drugs and Substances Act. Due to the potential of developing dependence among users, most codeine products are available by prescription only.[5] Low-dose codeine (doses lower than or equal to 30 mg per tablet or 2 mg per milliliter [mL]), however, can be sold without a prescription if used in combination with at least two other medications.[5] These are available as 'over the counter' (OTC) medications, but are usually stored behind the pharmacy counter.[5] In Manitoba, low-dose codeine products are available only by prescription.[5]

Due to the risk of dependence and overdose, several European countries are considering regulating the use of low-dose codeine products.[5] Requiring a prescription for all codeine products may help to restrict the access and monitor use, however, a concern is that those who abuse codeine may end up seeking out other narcotics as a substitute.[5]

Because OTC low-dose codeine products are paired with other medications, the dependence on low-dose codeine products can lead to excessive intake of not only codeine, but also the other medication, particularly acetaminophen and acetylsalicylic acid (ASA).[5]

Previous CADTH reports

The effectiveness of codeine in combination with other medications for pain relief among pediatric patients and those experiencing tonsillectomy or adenoidectomy has been reviewed by the Canadian Agency for Drugs and Technologies in Health (CADTH).[10,11] However, there were no trials on the combination of codeine and acetylsalicylic acid (ASA)

for the pain control after tonsillectomy or adenoidectomy at that time.[10] There were two non-randomized studies comparing codeine with other opioids for the pain relief in paediatric patients identified.[11] Caution was recommended in prescribing opioids for children with compromised oxygen levels due to the adverse effect of respiratory suppression.[11] The other study found no significant difference in pain control between morphine and the combination of codeine and acetaminophen, but noticed significantly more episodes of nausea in the morphine group the day after surgery.[11]

It has been suggested the access to codeine to be limited to avoid undesirable consequences.[5] This requires a review of the benefits and harms associated with codeine use, particularly the low-dose formulations that are currently available over the counter. This report aims to review the literature on the safety and effectiveness of low-dose codeine-containing products for the treatment of pain and cough.

Research Question

1. What is the clinical effectiveness of non-prescription medications containing codeine for the treatment of pain?
2. What is the safety of non-prescription medications containing codeine for the treatment of pain?
3. What is the clinical effectiveness of non-prescription medications containing codeine for the treatment of cough?
4. What is the safety of non-prescription medications containing codeine for the treatment of cough?

Key Findings

There were 12 systematic reviews, 13 randomized controlled trials, and four non-randomized studies included in the review. Three of the systematic reviews examined cough; specifically chronic cough, cough in children, and cough in cancer. The others studied the effects of codeine containing medication on pain, such as pain after dental procedures, cancer pain and chronic non-cancer pain.

There is some evidence to show that low-dose codeine alone or combined with other non-opioid analgesics are effective to treat specific types of pain, compared to placebo, non-opioid analgesics, or opioid drugs. Codeine alone seems to be effective to treat chronic cough and cough in cancer. The adverse effects were not assessed in most studies and the most common were drowsiness, nausea, and constipation. There were several limitations to this review. Most importantly, codeine dose was not well-reported. Most of the SRs and RCTs focused on specific types of pain for codeine treatment. The outcomes and interventions were clinically heterogeneous, making it difficult to synthesize the results from different studies. There was a lack of long-term follow-up and it was therefore difficult to determine whether codeine dependence developed among those using codeine for pain or cough.

It remains unclear whether the benefits to pain and cough control outweigh the adverse effects. Due to the varying doses and combinations with other pain-control medications, it also remains unclear whether there is an optimal dose or combination. Further research

regarding the long-term consequences of low-dose codeine may reduce some of the uncertainty.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2013 and May 17, 2018.

Selection Criteria and Methods

One reviewers 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	Individuals of any age with pain or cough symptoms
Intervention	Q1-2: Analgesic medications containing ≤30 mg codeine per tablet or <2mg/mL codeine in liquid products in combination with additional non-narcotic medicinal ingredients Q3-4: Antitussive medications containing ≤30 mg codeine per tablet or <2mg/mL codeine in liquid products in combination with additional non-narcotic medicinal ingredients
Comparator	Placebo, non-codeine/non-opioid medications, treatment as usual
Outcomes	Q1,3: Clinical effectiveness Q2,4: Safety
Study Designs	Health technology assessments, systematic reviews/meta-analyses, randomized controlled trials, non-randomized studies

AGC = atypical glandular cell, AIS = adenocarcinoma in situ, CIN = cervical intraepithelial neoplasia, DOR = diagnostic odds ratio, HPV = human papillomavirus, HSIL = high-grade squamous intraepithelial lesion, NLR = negative likelihood ratio, NPV = negative predictive value, PLR = positive likelihood ratio, PPV = positive predictive value

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Studies included in a selected systematic review were also excluded.

Critical Appraisal of Individual Studies

The included systematic reviews (SR) were critically appraised using the AMSTAR 2 tool.[12] The quality of randomized clinical trials (RCTs) was assessed using the Cochrane Risk of Bias Tool.[13] The quality of non-randomized studies was assessed using the Newcastle-

Ottawa scale.[14] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations assessed in each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 567 citations were identified in the literature search. Following screening of titles and abstracts, 511 citations were excluded and 56 potentially relevant reports from the electronic search were retrieved for full-text review. Ten potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 37 publications were excluded for various reasons, while 29 publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection. Additional references of potential interest are included in Appendix 5.

Summary of Study Characteristics

Additional details describing the characteristics of the included studies are reported in Appendix 2.

Study Design

Ten SRs were identified for inclusion in this report.[2,8,15-22] Seven SRs examined outcomes related to pain[8,15,16,18-21] and three related to cough.[2,17,22] The numbers of primary studies that evaluated relevant codeine doses in the SRs ranged from zero to 15. [2,8,15-22] The SRs included or aimed to include only RCTs.[8,15,16,18-21]

There were 13 RCTs[23-35] and four non-randomized studies included.[36-39] All RCTs were double-blinded, except for two.[23,31] The non-randomized studies included two prospective cohort studies,[36,39] one nested case-control study,[37] and one retrospective case series.[38]

Year of Publication and Country of origin

The SRs were published in 2013,[22] 2014,[14,20,21] 2015,[17-19] 2016,[2,8] 2017.[15,16] The corresponding authors of the SRs were based in Australia,[2] Hong Kong,[17] the UK,[8,15,16,18] South Africa,[19] Germany,[20] Switzerland,[21] and the USA.[22]

The RCTs were published in 2013,[34,35] 2014,[33] 2015,[31,32] 2016,[30] 2017,[24,25,27-29] 2018.[23,26] The RCTs were conducted in the USA,[23,24,32,33] Brasil,[25,28] Turkey,[26,31] Iran,[27,34] Italy,[29] Australia,[30] and Canada.[35] The prospective cohort studies were published in 2013[39] and 2017[36] from France[39] and Poland respectively.[36] The nested case-control study was published in 2015 and conducted in Italy.[37] The retrospective case series were conducted in the USA and published in 2014.[38]

Study population

The inclusion criteria for the SRs depended on the types of pain[8,15,16,18-21] or cough.[2,17,22] Two SRs focused on children aged 17 years or younger while[15,16] the others included adults or all age groups.[2,8,17-22] The SR by Cooper et al. aimed to include individuals with chronic non-cancer pain.[15] Wiffen et al. aimed to include children aged 17 years or less with cancer pain,[16] while Straube et al. included patients of all ages with cancer pain.[27] Derry, Karlin, and Moore evaluated patients experiencing acute postoperative pain.[18] Mkontwana and Novikova studied individuals with post-caesarian pain.[19] da Costa et al. included patients with osteoarthritis of the knee or hip.[21]

The sample sizes of the RCTs ranged from 20 to 411.[23-35] Childress et al. included those who were pregnant and who were experiencing headaches.[23] Le May et al. recruited children aged 18 years or younger.[35] Six RCTs focused on patients that experienced or were scheduled for surgeries or diagnostic procedures.[26-29,31,34] Four RCTs studied patients visiting the emergency department for pain.[24,30,32,35] Other RCTs recruited patients with pain or conditions associated with pain.[23,25,33,39] The prospective cohort studies recruited individuals with persistent pain[39] and those waiting for diagnostic tests.[36] The nested case-control study used data from a database of Italian patients and selected those diagnosed with osteoarthritis.[37] The retrospective study included children undergoing tonsillectomy.[38]

Interventions and Comparators

All included studies aimed to include medications containing codeine as intervention.[8,15,16,18-21,23-39] Specifically, three SRs aimed to examine multiple codeine doses, but did not find any primary studies for inclusion.[2,15,16] The doses of codeine were not clearly described in two SRs, but codeine were used in combination with other non-opioid analgesics and were considered likely relevant for this review[17,22] The nested case-control study could not retrieve codeine dose in the database, but codeine was used with acetaminophen as intervention and compared with acetaminophen.[37] This comparison was likely relevant to this review.[37] The RCT[35] and the retrospective study[38] that recruited children, calculated the codeine doses based on body weight, but did not report final dosage. To treat pain, codeine 30 mg alone was examined in one SR,[20] and one RCT.[23] A codeine-acetaminophen combination at a dose of 10 mg/325 mg was studied in one RCT.[34]. A codeine-acetaminophen combination at a dose of 25 mg/300 mg was studied in one prospective cohort study.[39]. A codeine-acetaminophen combination at a dose of 20 mg/300 mg was studied in one RCT.[27] A codeine-acetaminophen combination at a dose of 30 mg/200 mg was studied in one SR.[21]. A codeine-acetaminophen combination at a dose of 30 mg/300 mg was studied in six RCTs.[24,26-28,32,33] A codeine-acetaminophen combination at a dose of 30 mg/500 mg was studied in four RCTs[25,28-30] and one prospective cohort study.[36] A codeine-naproxen combination at a dose of 30 mg/550 mg was tested in two RCTs.[26,31] A codeine-ibuprofen combination at a dose of 15 mg/200 mg and other dosages was reviewed in one SRs.[18]

Codeine-phenyltoloxamine combination to treat cough was reviewed in the SR by Malossiotis et al.[17] There was no primary studies included in the SR by Gardiner et al.[2] Various codeine dose to treat cough in the SR by McCrory et al. were reported: 7.5, 15, 30, and 60 mg.[22]

The comparators varied across studies. Codeine was compared to other opioids or placebo in one SR,[15] other opioids in five RCTs and one prospective cohort study,[25,30,32-34,39] other opioids or non-opioid analgesics or placebo in seven SRs and one RCT,[8,16,17,19-22,24] non-opioid analgesics or placebo in one SR, four RCTs, one retrospective study and one nested case-control study,[18,23,26,27,35,37,38] placebo only in one SR and three RCTs,[2,28,29,31] and no treatment in a historical cohort in one cohort study.[36]

Outcomes

Studies that evaluated pain and cough related outcomes were eligible for inclusion. There were three SRs investigating the effectiveness of codeine on cough.[2,17,22] The other seven SRs,[8,15,16,18-21] 13 RCTs[23-35] and three non-randomized studies the effectiveness of codeine on pain.[36,38,39]

There were 15 pain related outcomes identified: pain in general in a prospective cohort study,[39] cancer pain in two SRs,[16,20] chronic non-cancer pain in one SR,[15] acute postoperative pain in one SR,[18] post-caesarian pain in one SR,[19] pain among patients with osteoarthritis in one SR and one nested case-control study,[21,37] limb or extremity pain in two RCTs,[24,30] headache in pregnancy in one RCT,[23] pain after dental procedures in three RCTs,[26,27,29] pain after eye procedures in one RCT,[28] acute periradicular abscess pain in one RCT,[25] pain during ultrasound assessment in one prospective cohort study,[36] and pain after tonsillectomy in one retrospective case series.[38] The RCT by Graudins et al. focused on pain caused by injuries.[30] The RCT by Cristalli et al. provided medication with codeine before dental procedures.[29]

Pain was measured by visual analogue scale (VAS) or numeric rating scale (NRS) in two SRs,[20,21] seven RCTs[23-25,27-30] and one non-randomized study.[39] use of rescue medication in two SRs,[18,20] patients with at least 50% pain relief in one SR,[18] days to return to work in one SRs,[40] complete or partial pain relief in one SR,[20] time to perceived pain relief in one RCT,[23] McGIll Pain Questionnaire and Brief Pain Inventory Scales in one RCT,[28] satisfaction with analgesia,[30] incidence of moderate/sever pain in one non-randomized study,[36] and emergency department visits in one non-randomized study.[38]

There were three SRs on cough.[2,17,22] One studied cough in children,[2] another about cough in cancer,[17] and the other about chronic cough.[22] Cough was measured by cough count and cough severity in McCrory et al.[22]

Summary of Critical Appraisal

Additional details describing the critical appraisal of the included studies are reported in Appendix 3.

Two SRs did not have any critical weakness in the critical domains.[2,19] Six SRs did not publish protocol *a priori*.[8,15,16,18,21,22] Four SRs did not include any primary studies and there was no meta-analysis or risk of bias assessment conducted.[2,8,15,16] One SRs did not conduct meta-analysis.[16] Risk of bias in the included studies were not considered while discussing the results in one SR.[21] Publication bias was not investigated in four SRs.[17,18,20,21] All SRs assessed the risk of bias of the included studies with commonly used tools.[2,8,15-22] All SRs conducted comprehensive literature search in electronic databases, selected the studies in duplicate, and provided a list of excluded studies.[2,8,15-22] Based on the AMSTAR 2 checklist, there was high confidence on the results of two SRs[2,19] and low confidence on the other SRs.[8,15-18,20-22]

Thirteen RCTs had low risk of selective outcome reporting.[23-35] The RCTs by Childress et al. and Zvareh et al. did not describe allocation concealment.[23,34] The RCTs by Childress et al. and Polat et al. did not have adequate blinding of the patients or the physicians.[23,31] Patient attrition in Zavareh et al. was not well described.[34]

The four non-randomized studies included comparable cohorts or cases and controls.[36-39] The three cohort studies seemed to have representative patients from the communities with the non-exposed cohorts selected from the same communities, probably enough follow-up, time and adequate follow-up.[36,38,39] However, the pain intensity in Bertin et al. was reported by patients and subject to measurement bias or recall bias.[39] The information on the outcomes and exposures was available at the time of study due to the retrospective study design in Bedwell et al.[38] Ludwin et al. adopted patient-reported outcomes that were subject to measurement bias and recall bias.[36] For the nested case-control study by Roberto et al.,

the cases and controls were selected from a major database in Italy.[37] Roberto et al. used incidence of adverse effects documented by health professionals[37] The controls did were not selected based on the outcome and thus improper matching was avoided.[37] A potential strength was that the exposure to medication was determined by prescription data and the cases and controls were selected based on diagnostic codes.[37]

Summary of Findings

Additional detail regarding study findings is available in Appendix 4.

1. *What is the clinical effectiveness of non-prescription medications containing codeine for the treatment of pain?*

Pain lasting for at least seven days

Bertin et al. evaluated patients with pain lasing for at least seven days and eligible for paracetamol-codeine (300 mg/25 mg or 600 mg/50 mg [number of tablets not reported, therefore the larger dose may be relevant]) or paracetamol-tramadol (325 mg/37.5 mg) combinations in a prospective cohort study.[39] The most common origin of pain was disease or trauma.[39] The origin of pain was associated with the time-course of pain.[39] The patients with trauma-related pain were more likely to feel constant pain and those with disease-related pain were more likely to have intermittent pain.[39] Both medications reduced pain intensity by approximately 75% and were well tolerated.[39]

Cancer pain

The SR by Wiffen et al. that focused on the effectiveness of opioids on cancer pain in children did not find any primary studies and thus did not present results or conclusions.[16]

The SR by Straube et al. that studied the effectiveness of codeine included 15 RCTs with children or adults, six of which were relevant to this review.[20] Compared to placebo, three primary studies using relevant codeine doses were pooled with the three studies using high-dose codeine.[20] It was found that high- or low-dose codeine or codeine-acetaminophen combination provided better pain relief than placebo in terms of group average pain intensity, however the results were not separated based on low- or high-dose.[20] One included study (codeine 30 mg) reported codeine to be superior to placebo in complete or partial pain relief.[20]

Higher proportions of codeine users reported no worse than mild pain than tramadol users in a cross-over study and a parallel study (codeine 30 mg; codeine 150 mg plus acetaminophen 2500 mg daily).[20] Codeine was similarly effective in complete or partial pain relief in one study (codeine 30 mg), compared to codeine plus ibuprofen and tetrahydrocannabinol.[20] However, ketorolac had a lightly longer time to use rescue medication than codeine (daily dose: 240 mg plus paracetamol 2400 mg).[20]

Chronic non-cancer pain

There were no primary studies identified in the SR by Cooper et al. and thus did not present results or conclusions.[15]

Acute postoperative pain

The SR by Derry, Karlin, and Moore included six RCTs.[18] Compared to placebo, a codeine-ibuprofen combination (25.6 to 60 mg/200 or 400 mg) was associated with higher

proportions of patients with at least 50% pain relief based on the results of five primary studies.[18] One included study showed the codeine-ibuprofen combination (26.5 mg/400 mg) was related to longer time to use rescue medication.[18] One primary study also reported that the numbers of patients requiring rescue medication within four to five hours was higher among those taking placebo compared to those taking codeine 30 mg.[18]

Post-caesarian pain

In the SR by Mkontwana and Novikova, one primary study (codeine 60 mg/paracetamol 800 mg, numbers of tablets not described) evaluating the effectiveness of codeine was included and no significant effect was found compared to placebo.[19]

Pain among patients with osteoarthritis

The SR by da Costa et al. included studies on patients with osteoarthritis in the knee or hip.[21] One of the three RCTs that provided data for codeine adopted relevant codeine dose (30 mg plus ibuprofen 200 mg). This study did not identify significant reduction in codeine and knee or hip pain with codeine, compared to placebo.[21]

Headache in pregnancy

Childress et al. compared metoclopramide administered with diphenhydramine (MAD) with codeine 30 mg for the treatment of headache in pregnancy.[23] The difference in the reduction in pain score at certain time points after medication between MAD and codeine: 30 minutes, one hour, and 12 hours.[23] Though the difference was not significant at six hours.[23] The time to perceived headache relief was shorter for MAD and more patients reported full headache relief in the MAD group.[23]

Acute extremity pain

Chang et al. compared a codeine-acetaminophen combination (30 mg/300 mg) with ibuprofen-acetaminophen, oxycodone-acetaminophen, and hydrocodone-acetaminophen combinations.[24] The decrease in mean NRS pain score in the codeine-acetaminophen group was not significantly or clinically different.[24]

Acute periradicular abscess pain

Santini et al. compared a codeine-acetaminophen combination (30 mg/500 mg) with a tramadol-acetaminophen combination (37.5 mg/325 mg) in patients with acute periradicular abscess in a RCT.[25] Significant pain reduction was observed in both groups at certain time points after medication.[25] However, there was no significant difference in pain reduction between two groups six, 12, 24, 48, or 72 hours after medication.[25] The authors considered the codeine-acetaminophen combination more effective due to more adverse reactions and drop-outs in the tramadol-acetaminophen group.[25]

Pain after dental procedures

Two types of dental procedures were studied: impacted third molar and dental implant surgeries in three RCTs.[26,27,29] Medication was given before or after the procedures.[26,27,29] Cigerim et al. found a naproxen-codeine combination (30 mg/550 mg) to be more effective for pain, edema, and trismus than diclofenac and benzydamine administered after impact lower third molar surgery.[26] If administered before impacted molar surgery, a codeine-paracetamol combination (30 mg/500 mg) was associated with lower pain intensity and longer time to use rescue therapy on the first day of surgery than placebo.[29] However, there

was no difference in the number of codeine-paracetamol tablets used after surgery, compared to placebo.[29] If administered after dental implant surgery, codeine-acetaminophen combination (20 mg/300 mg) was associated with less severe pain three, six, and 12 hours after surgery.[27] Codeine was also related to less severe swelling one, two or three days after surgery.[27]

Pain after photorefractive keratectomy

Compared to placebo, a codeine-acetaminophen combination (30 mg/500 mg) was significantly associated with pain scores measured by three questionnaires one, 24, 48, and 72 hours after surgery in a RCT.[28]

Moderate pain from limb injury

In the non-inferiority trial by Graudins et al., codeine-acetaminophen combination (30 mg/500 mg) was related to reductions in pain 30 minutes after medication, mean VAS reduction, and satisfaction with analgesia.[30] However, due to the sample attrition in the emergency department, the authors concluded that codeine was non-inferior to paracetamol-ibuprofen-thiamine combination or oxycodone 30 minutes after medication.[30]

Pain following tonsillectomy

In the retrospective case series by Bedwell et al., the children receiving ibuprofen-acetaminophen combination were younger than those receiving codeine-acetaminophen combination (0.5 to 1 mg/kg body weight) and were less likely to be treated with antibiotics.[38] There were no difference in emergency department visits due to dehydration or other secondary outcomes, such as hemorrhage, reoperation, and feeding tolerance between these two groups.[38]

2. *What is the safety of non-prescription medications containing codeine for the treatment of pain?*

Pain lasting for at least seven days

Bertin et al. concluded that both codeine-paracetamol (25 mg/300 mg or 50 mg/ 600 mg [number of tablets not reported]) and paracetamol-tramadol combinations (37.5 mg/325 mg) were well tolerated.[39]

Cancer pain

The SR by Wiffen et al. that focused on the effectiveness of opioids on cancer pain in children did not include any primary studies.[16]

The SR by Straube et al. found that adverse effects poorly reported.[20] Nausea, vomiting, and constipation were common.[20] Among nine RCTS that reported withdrawals, seven had withdrawal rates less than 10%.[20]

Chronic non-cancer pain

There were no primary studies identified in the SR by Cooper et al., thus no outcomes adverse events are reported.[15]

Acute postoperative pain

In the SR by Derry, Karlin, and Moore, no serious adverse effects or withdrawals were reported in the six included RCTs.[18]

Pain among patients with osteoarthritis

The nested case-control study by Roberto et al. included all patients diagnosed with osteoarthritis in an Italian database.[37] The doses of codeine was not described, but the codeine dose was potentially relevant to this review due to the fact that it was used in combination with acetaminophen.[37] Compared to acetaminophen alone, the acetaminophen-codeine combination was not significantly associated with the incidence of acute cerebrovascular and cardiovascular events.[37]

Acute extremity pain

Chang et al. did not assess adverse effects.[24]

Acute periradicular abscess pain

Compared to the codeine-acetaminophen combination (30 mg/ 500 mg), Santini et al. found that the tramadol-acetaminophen combination (37.5 mg/325 mg) was associated with more adverse reactions and two patients withdrew from the study.[25]

Pain after dental procedures

Cigerim et al. did not observe drug-related side effects of either codeine-naproxen (30 mg/550 mg) combination or diclofenac alone (50 mg).[26]

Pain after photorefractive keratectomy

The most common adverse effects of the codeine-acetaminophen combination (30 mg/500 mg) examined in Pereira et al. included drowsiness (42%), nausea (18%), and constipation (5%).[28]

Moderate pain from limb injury

In the non-inferiority trial by Graudins et al., the incidence of adverse effects due to a non-opioid, codeine, and oxycodone were 3,3% 1.6%, and 16.9%.[30]

Pain following tonsillectomy

In the retrospective case series by Bedwell et al., the children receiving the ibuprofen-acetaminophen combination were younger than those receiving codeine-acetaminophen combination (codeine at 0.5 to 1 mg/kg body weight) and were less likely to be treated with antibiotics.[38] There were no differences in emergency department visits due to dehydration or other secondary outcomes, such as hemorrhage, reoperation, and feeding tolerance between these two groups.[38]

3. *What is the clinical effectiveness of non-prescription medications containing codeine for the treatment of cough?*

Chronic cough

In the SR by McGrory et al., one included study reported a significant reduction in cough count with varying doses of codeine, 7.5, 15, 30, and 60 mg, six hours after treatment.[22] Two included studies found codeine 15 to 17 mg three to four times a day more effective than dextromethorphan 4 to 6 mg of the same frequencies in reducing cough severity.[22] Overall the evidence to treat chronic cough was sparse.[22]

Cough in children

No relevant studies were identified in the SR by Gardiner et al regarding the use of codeine for the treatment of cough in children, thus no results are reported. [2]

Cough in cancer

There were no new trials identified in the SR update by Molassiotis et al. thus no new analyses was performed[17] Two of the nine included studies reviewed the effectiveness of codeine.[17] The conclusion was the same as the previous SR, in which positive effects of codeine were observed.[17]

4. *What is the safety of non-prescription medications containing codeine for the treatment of cough?*

Chronic cough

In the SR by McCrory et al., one included study reported one of the 39 patients discontinued codeine 30 mg for dry mouth and another for nausea.[22] Two other included studies found nausea, constipation, and/or withdrawal occurring more frequently in the group treated with codeine 15 to 17 mg, compared to those treated with dextromethorphan 4 to 6 mg.[22]

Limitations

There are several limitations to this report. First, there is considerable heterogeneity in the study design, codeine dose, comparator, medication used with codeine, outcome of interest, and the clinical settings. Second, the SRs did not conduct subgroup analysis based on codeine dose if they found any relevant primary studies.[18-22] The relevant results are reported narratively in this review, however it remains uncertain whether the conclusions of some of the SRs can be generalized to those using codeine at a dose of 30 mg or less, as some of the conclusions are based on a range of doses that exceed that.[20]

The changes in the diagnostic and therapeutic standards might be a source of heterogeneity. There were no new trials or non-randomized studies on cough published since 2016[2,17,22] and some of the primary studies included in the SRs were published prior to 1990.[17,20]

Three important characteristics of medication dosage: dose, frequency and duration,[41] were not fully disclosed in many primary studies. For example, a retrospective study could not determine the exact dosage of codeine in the database and this study was included because codeine was combined with acetaminophen and the codeine dose was thought likely to be 30 mg or less.[37]There were fewer than six primary studies reported the dose, frequency and duration of the codeine dosages.[25,33,34,36,38]

The concentration of codeine syrup in the included SR was unclear.[35]

Additionally, the primary studies that used placebo as comparison may not be comparable to those using active comparators or opioids as control. Placebo and active comparators were used as control to evaluate the effectiveness of codeine on cancer pain, acute postoperative pain or the pain after impacted third molar surgery.[18,20,26,29] The choices of comparators might need further investigation.

In the included studies, codeine was used and evaluated for relatively short periods, minutes to less than two years of follow up.[27,37] The consequences of long-term use were not investigated, particularly, the development of dependence.[5]

Further, we were unable to assess publication bias. We did not search for trials that were registered and not published. We did not assess whether trials with results favorable to codeine were more likely to be published. Lastly, there is a lack of evidence about the effectiveness of codeine in certain population groups, such as children with cancer and children with cough.[2,14]

Conclusions and Implications for Decision or Policy Making

There is some evidence to show that codeine alone or combined with other non-opioid analgesics are effective to treat types of pain or pain, compared to placebo, non-opioid analgesics, or opioid drugs. Compared to placebo, low-dose codeine seemed more effective in pain control among patients with cancer, those experiencing impacted third molar surgery if used before surgery, those experiencing photorefractive keratectomy, and those receiving ultrasound assessment of the uterine cavity and tubal patency.[20,28,29,36]

Compared to non-opioid analgesics, low-dose codeine containing analgesics seemed to be more effective to control pain developed after surgery in general, dental implant surgery, and extraction of impacted lower third molar.[18,27,29] However, codeine was not more effective than metoclopramide with diphenhydramine (a non-analgesic medication) to treat headache in pregnancy.[23] Codeine-containing analgesics were not as effective as caffeine-containing analgesics to control swelling and caffeine-containing analgesics were recommended for pain developed after dental implant surgery.[27]

Compared to other opioids, especially tramadol (another weak opioid) and oxycodone, codeine was similarly effective for pain control among patients with cancer and patients with acute extremity pain.[20,24] For acute periradicular pain, low-dose codeine could be more effective than tramadol for pain reduction, used in combination with acetaminophen.[25] However, an ibuprofen-acetaminophen combination may be similarly effective as a codeine-acetaminophen combination to control pain after tonsillectomy.[38] Codeine alone seems effective to treat chronic cough and cough in cancer.[17,22] However, all identified evidence was published in or prior to 2016.[22]

The adverse effects were not assessed in most studies and the most commonly reported adverse effects were drowsiness, nausea, and constipation.[20,28] Drowsiness could be as prevalent as 42% among those receiving photorefractive keratectomy.[27] Patients might withdraw from treatment due to the adverse effects.[20] The risk of developing acute cerebrovascular and cardiovascular events was similar for the use of a codeine-acetaminophen combination and acetaminophen alone.[37]

There were several limitations to this review. Some of the studies included in the systematic reviews were published prior to 1990.[20] Most of the SRs and RCTs focused on specific types of pain for codeine treatment.[30,36-38] The codeine doses in the primary studies might not be fully disclosed or could not be recorded.[35,37,39] There was a lack of long-term follow-up, making it difficult to determine whether codeine dependence developed among those using codeine for pain or cough, and publication bias was not assessed.

Overall, there is evidence to show that low-dose codeine can be effective for pain control or chronic cough, especially compared with placebo or non-opioid analgesics. However, the use of codeine can sometimes be less or similarly effective as non-opioid analgesics, while introducing the adverse effects, such as drowsiness, nausea and constipation. Compared to other opioids, particularly tramadol and oxycodone, low-dose codeine seems to be similarly effective to reduce moderate pain.

It remains unclear whether the benefits to pain and cough control outweigh the adverse effects. Due to the varying doses and combinations with other pain-control medications, it also remains unclear whether there is an optimal dose or combination. Further research regarding the long-term consequences of low-dose codeine may reduce some of the uncertainty.

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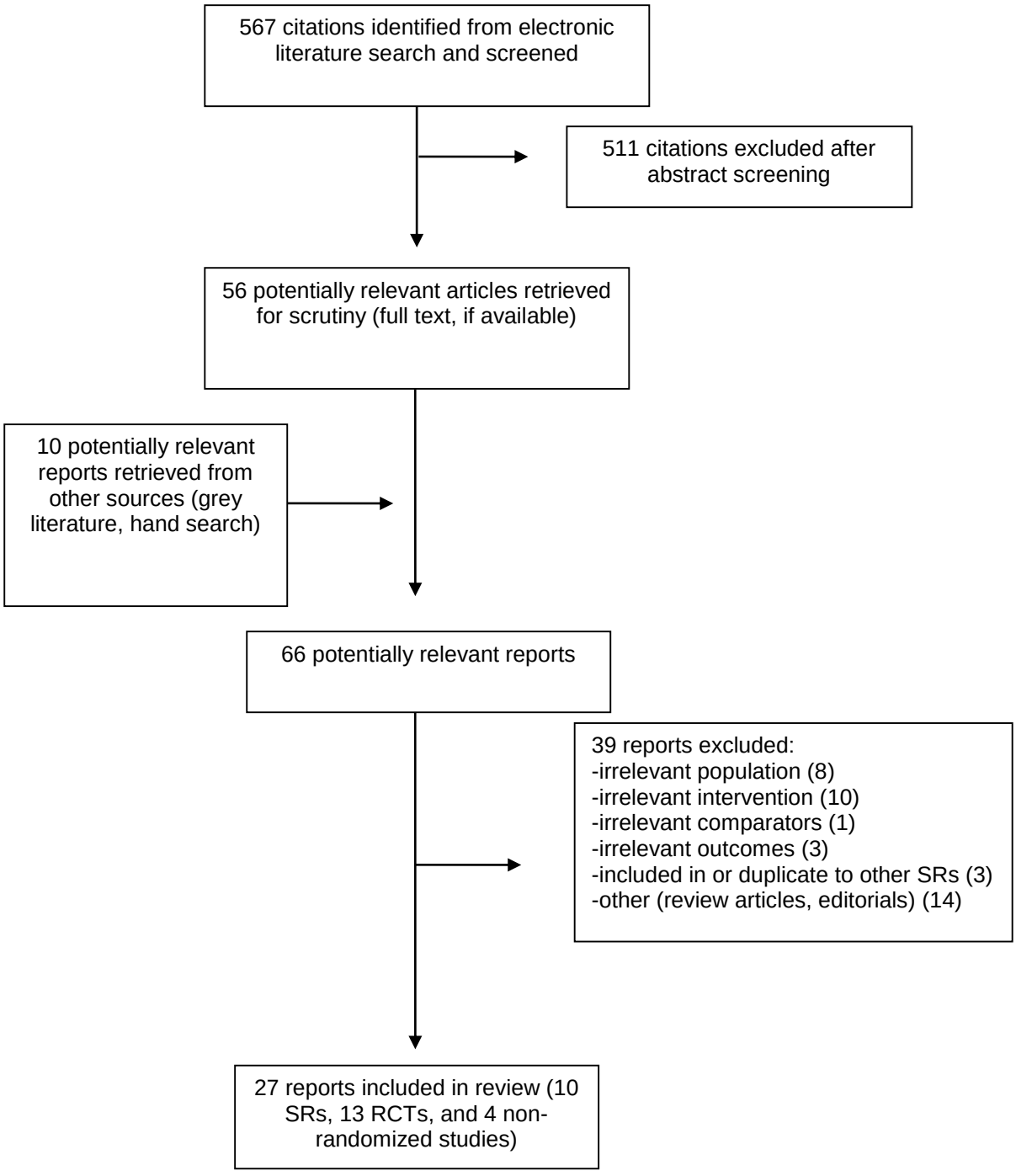
Appendix 1 : Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Pain					
Cooper et al. 2017,[15] UK	None Inclusion criteria: RCTs	Inclusion criteria: "infants, children, and adolescents, aged from birth to 17 years old, with chronic or recurrent pain (lasting for three months or longer), arising from genetic conditions, neuropathy, or other conditions" (p. 4) Exclusion criteria: "perioperative pain, acute pain, cancer pain, headache, migraine, and pain associated with primary disease or its treatment." (p. 5)	Inclusion criteria: Opioids "of any dose and any route" (p. 2) Opioids identified: none	"Opioids with placebo or an active comparator" (p. 2)	Pain relief and related outcomes
Wiffen et al. 2017,[16] UK	None Inclusion criteria: RCTs	Inclusion criteria: infants, children, and adolescents aged from birth to 17 years with cancer-related pain Exclusion criteria: "perioperative pain, short-term infection pain, short-term injury or trauma pain, acute pain, functional abdominal pain, burn pain, and musculoskeletal pains, headache and migraine, sickle cell disease acute crisis pain, mucositis, or any other chronic non-cancer related pain" (p. 5)	Any opioid drugs	Placebo or any active comparator	Pain relief and related outcomes
Wiffen et al. 2016,[8] UK	None Inclusion criteria: RCTs	Inclusion criteria: "adults aged 18 years and above with one or more chronic neuropathic	"Oral paracetamol with or without codeine or dihydrocodeine, at any dose, administered for the relief of neuropathic pain"	Placebo or any active comparator	Pain intensity or relief

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		pain conditions"	(p. 8)		
Derry Karlin and Moore 2015,[18] UK	6 studies Inclusion criteria: double-blinded RCTs with at least 10 participants	1,342 participants (mean age between 20 to 26 years, female majority ranging from 50% to 100% in primary studies) Inclusion criteria: individuals aged 15 years and over with "established postoperative pain of moderate-to-severe intensity following day or in-patient surgery" (p. 7)	"Ibuprofen plus codeine, administered as a single oral dose" (p. 7) Codeine doses ranging from 15 to 60 mg	"placebo or the same dose of ibuprofen alone" (p. 7)	Postoperative pain Primary outcomes: "achieving at least 50% pain relief over four to six hours" (p. 7) Secondary outcomes: time to use rescue medication, use of rescue medication, adverse effects, and withdrawals
Mkontwana et al. 2015,[19] South Africa	13 studies for qualitative synthesis, 8 of which eligible for meta-analysis 1 study studied a combination drug with acetaminophen 300 mg, caffeine 15 mg and codeine 30mg (Angle 2002) The other studied one with paracetamol 800 mg + codeine 60 mg (Bjune 1996; number of tablets not reported) Inclusion criteria: RCTs, cluster RCTs	962 women in 13 studies Inclusion criteria: "women requiring pain relief in the early postpartum period following caesarean section" (p. 5)	"oral medication given to women for post-caesarean pain relief" including opioid and non-opioid analgesics (p. 5)	Placebo or active comparators	Primary outcomes: adequate pain relief; need for additional pain control Secondary outcomes: adverse effects, hospitalization days, rehospitalization, full breastfeeding, etc.
Straube et al. 2014,[20] Germany	15 included in qualitative synthesis, none of which eligible for meta-analysis 6 RCTs using potentially relevant doses (see findings table) Inclusion criteria: RCTs	721 participants in total, but one with Paget's disease and one study included adults with chronic pathologic pain Inclusion criteria: "children or adults with cancer pain" (p. 6)	Inclusion criteria: "codeine, alone or in combination with paracetamol, using any formulation, dosage regimen, and route of administration" (p. 6)	"placebo or an alternative active treatment" (p. 6)	Primary outcomes: "at least 50% reduction in pain" or "pain intensity below 30/100 mm on the visual analogue scale (VAS) or 3/10 on the numeric rating scale (NRS)" or "Global Impression of Change" (p. 6) Secondary outcomes: pain intensity, functioning, withdrawals, and deaths

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
da Costa et al. 2014,[21] Switzerland	22 RCTs, 3 of which comparing codeine with placebo Inclusion criteria: RCTs	Median = 344 in RCTs (27 to 10301) Inclusion criteria: "At least 75% of participants with clinically or radiologically confirmed osteoarthritis of the knee or hip" (p. 7)	"Any type of opioid except tramadol" (p. 6) 1 RCT using relevant codeine dose: 30 mg plus ibuprofen 200 mg	Placebo or active comparators	Primary outcomes: pain and function Secondary outcomes: adverse effects and withdrawals
Cough					
Gardiner et al. 2016,[2] Australia	No included studies Inclusion criteria: RCTs, quasi- RCTs, and stratified RCTs	Inclusion criteria: "children aged 18 years or younger with a diagnosis of chronic cough (cough lasting four or more weeks)" (p. 4)	"medications that contained codeine or codeine derivatives" (p. 4)	Placebo	Numbers of children with cough, cough severity, and adverse effects
Molassiotis et al. 2015,[17] Hong Kong	17 studies, one of which compared morphine and codeine Inclusion criteria: RCTs, quasi-experimental trials and trials without randomization	1390 participants, 1231 or which were cancer patients, mostly lung cancer (median = 68, range = 9 to 342) Inclusion criteria: Adults aged 18 years and over "with malignant disease and experiencing cough or coughing, dry cough, nocturnal wet cough, or wet cough in participants too weak to expectorate properly due to (primary or metastatic) lung cancer or other malignancies, including cough after insertion of a bronchial stent, in any clinical setting" Exclusion criteria: "malignant disease who had cough due to chest infections" (p. 3)	Brachytherapy, laser therapy and photodynamic therapy; pharmacological treatments Inclusion criteria: "Pharmacological and non-pharmacological interventions excluding chemotherapy and external beam radiotherapy." (p. 3)	Placebo or active comparators	Primary outcomes: "subjective or objective improvement in cough frequency or severity, or alleviation of distress" (p. 4) Secondary outcomes: quality of life or symptom scores
McCrory et al. 2013,[22] USA	KQ 2: 48, including 33 parallel-group RCTs and 12 randomized cross-over	KQ 2: 2923 participants (8 to 214 in studies) with	KQ 2: symptomatic treatment for cough including codeine	KQ 2: placebo or active comparators	KQ 2: cough symptoms, cough frequency, cough

First Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
	studies Inclusion criteria: primary and systematic review articles KQ1 not relevant to this review	follow-up time from 1 hour to 115 days Inclusion criteria: KQ 1: patients with cough KQ 2: patients with chronic cough			severity, complications, function, health-related quality of life, health care utilization and cost, and adverse effects

ACP = American College of Physicians; APS = American Pain Society; KQ = key question; NRS = numeric rating scale; RCT = randomized controlled trial; UK = United Kingdom; USA = United States of America; VAS = visual analogue scale

Table 3: Characteristics of included primary studies

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Pain					
Childress et al. 2018,[23] USA	RCT, single-center, no blinding	70 patients, 32 and 33 available for analysis in the codeine and the other group Inclusion criteria: "Normotensive women in the second or third trimester of pregnancy who had symptoms of a primary headache", "which was not relieved by 650 to 1,000 mg of acetaminophen" Exclusion criteria: "first trimester, less than 16 years of age, had received a headache treatment medication other than acetaminophen in the previous 24 hours, had an allergy to one of the study medications, had abnormal intracranial anatomy or suspicion of a secondary cause of headache, if their systolic blood pressure was ≥140 or diastolic blood pressure was ≥90, or were in active labor"	30 mg of oral codeine alone, repeated at 1 hour if no adequate pain control	"10 mg of IV metoclopramide and 25 mg of IV diphenhydramine (administered by IV push over 2 minutes)", repeated at 1 hour if no adequate pain control	Primary outcomes: reduction in pain score Secondary outcomes: headache scores at the other time assessments, additional doses of the study medication or another non-study drug, headache recurrence, side effects, and other subjective assessments of patient experience 24-hour follow-up
Chang et al. 2017,[24] USA	RCT, double-blinded, single-center	411 eligible for analysis, 48% female, 60% Latino, and 31% black Inclusion criteria: 21 to 64 years, presented to the ED for management of acute extremity pain (see article for definition), clinical indication for radiological imaging	30mg of codeine and 300mg of acetaminophen	Three comparisons: 400mg of ibuprofen and 1000mg of acetaminophen; 5 mg of oxycodone and 325 mg of acetaminophen; 5 mg of hydrocodone and 300 mg of acetaminophen	Primary outcomes: pain intensity by an 11-point NRS Secondary outcomes: mean NRS scores at 1 hour and responses to a 4-point Likert scale rating pain as none, mild, moderate, or severe. Other outcomes: "proportion of patients receiving rescue

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
					analgesics, the total amount of analgesics in morphine equivalent units, and an analysis of patients with either documented fractures or a pain score of 10" (p. 1663)
Santini et al. 2017,[25] Brazil	RCT, double-blinded, single-center	N = 20, 10, and 8 (codeine and comparator) analyzed Inclusion criteria: 18+ years-old, diagnosis of APA, spontaneous pain greater than 40 mm as measured in the 0-100 mm Visual Analogue Scale (VAS) (moderate to severe pain)	"oral tablet containing codeine/acetaminophen (30 mg/500 mg) every 4 hours for 3 days" (p. 553)	"tramadol/acetaminophen (37.5 mg/325 mg) every 4 hours for 3 days" (p. 553)	Primary outcomes: pain scores Secondary outcomes: frequency of additional medication use and adverse reactions
Cigerim et al. 2018,[26] Turkey	RCT, double-blinded, single-centre	N = 90 for 1 lower third molar extraction. 46 women Mean age = 24.03 ± 4.82 years (range = 18 and 39) Inclusion criteria: absence of any systemic disease (ASA, American Society of Anesthesiologists Class 1), no history of allergy, non-pregnant patients, and no medication intake for the week leading up to surgery	Naproxen sodium, 550 mg, and codeine phosphate, 30 mg orally	Diclofenac potassium, 50 mg	Postoperative pain, based on "a visual analog scale (VAS) was used on days 2, 3, 5, and 7 at hours 1, 2, 3, 6, 8, 10, 12, 18, and 24." (p. 497)
Samieirad et al. 2017,[27] Iran	RCT, triple-blinded	N = 80 "edentulous in the posterior region of the mandible" Mean age = 40.50 ± 4.80 and 41.5 ± 5.3 years in the caffeine and codeine groups respectively Inclusion criteria: "systemically healthy (ASA Class I or II for physical status classification) (Alissa et al., 2009) from	acetaminophen, 300 mg plus codeine, 20 mg orally	acetaminophen, 300 mg plus anhydrous caffeine, 20 mg	Preoperative and postoperative pain: a visual analog scale (VAS), in such a way that pain was recorded from 0, representing no pain, to 10, representing severe pain

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		any gender or race, with an age range of 35 to 55 years. All the patients had the same surgical difficulty, and proper width and height of bone in their records." (p. 1615)			30 min, 3 h, 6 h, and 12 h after the operation
Pereira et al. 2017,[28] Brazil	RCT, double-blind, add-on, paired-eye, single-center	N = 40 with 80 eyes Inclusion criteria: 20 years of age or above, scheduled for myopic excimer laser PRK (Photorefractive keratectomy)	Usual care therapy plus 30 mg of codeine and 500 mg of acetaminophen orally	Usual care with placebo	Primary outcomes: the difference in pain intensity between the treatment and control eyes, measured on a 0-to-10 pain VAS obtained 24 hours after surgery Secondary outcomes: pain measured at 1, 24, 48, and 72 hours, adverse events (AEs) and clinical assessment of corneal wound healing.
Cristalli et al. 2017,[29] Italy	RCT, split-mouth, double-blinded, single-center	N = 32 with 64 sites 17 female patients Mean ages =22.65 ± 2.74 years (range = 20 to 29) Inclusion criteria: 20 and 29 years, elective surgical removal of bilateral symmetrical impacted mandibular third molars under local anaesthesia	500 mg paracetamol + 30 mg codeine orally	Placebo	Primary outcomes: postoperative pain measured by the Numerical Rating Scale-11 (NRS-11) at 1:00, 6:00, and 11:00 pm during the operative day and at 8:00 am, 1:00, 6:00, and 11:00 pm during the next two days. Secondary outcomes: "number of patients using rescue therapy, the time elapsed from the end of surgery until the first intake of

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
					analgesic medication, and the total number of paracetamol-codeine tablets with the same formulation taken by the patient in relation to the pain symptoms" (p. 3)
Ludwin et al. 2017,[36] Poland	Prospective cohort study, single-center, compared with a historical cohort	N = 300, 175 treated with paracetamol + codeine Inclusion criteria: "women aged 18 to 41 years with unknown tubal patency status trying to conceive without achieving clinical pregnancy for R12 months" (p. 600) See article for the exclusion criteria	Intervention before ultrasound assessment: paracetamol 500 mg and codeine phosphate 30 mg orally approximately 1 hour before the procedure	No treatment in a historical cohort	Pain after ultrasound assessment measured by a VAS
Graudins et al. 2016,[30] Australia	RCT, double-blind, 3-arm, non-inferiority trial	N = 182 61 (33.5%), 62 (34.1%) and 59 (32.4%) randomised to the non-opioid, codeine and oxycodone groups Mean age = 35, 31, and 32 years Male = 42%, 40%, and 44% Inclusion criteria: "age 18 to 75 years; acute limb injury (previous 48 h); moderate pain on arrival (numerical rating 4 to 7 on a 0 to 10 scale); oral analgesia deemed suitable" (p. 668)	Two × codeine 30 mg with Two × paracetamol 500 mg and Two × ibuprofen 200 mg	Two × oxycodone 5 mg with Two × paracetamol 500 mg and Two × ibuprofen 200 mg	Primary outcomes: difference in mean VAS change between groups at 30 min. Secondary outcomes: change in pain, proportions of patients at 30 min with improvement, number of patients requiring additional analgesia, satisfaction with initial analgesia, symptom improvement, and adverse effects
Roberto et al. 2015,[37] Italy	Nested case-control study, based on the Health Search IMS Health	N = 12,483 patients with osteoarthritis (2,182 cases and 10,301 matched controls)	Acetaminophen-codeine combination from this list of acetaminophen-containing medicines (ATC codes N02BE01, N02BE51,	Acetaminophen	Primary outcomes: risk of ACCEs Secondary

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
	Longitudinal Patient Database (HS IMS Health LPD)	Mean ages = 73.0 and 72.4 for cases and controls respectively Female = 58.4% and 59.4% respectively Cases = "patients who had diagnoses of the following ACCEs that occurred during the follow-up period were considered as cases: acute myocardial infarction (ICD-9-CM code 410*, 411*), angina pectoris (ICD-9-CM code 413*), ischemic stroke (ICD-9-CM code 342*, 433*, 434*, 436*, 438*), transient ischemic attack (ICD-9-CM code 435*), or hemorrhagic stroke (ICD-9-CM code 430, 431, 432*)." Controls = "up to five controls were randomly selected within each risk set. Controls (i.e., person-times) who were alive and event free on the index date were matched to their respective cases on age (5 yrs), sex, month and year of cohort entry, and duration of follow-up" (p. 901)	N02BE71, N02AA59) filled during follow-up Although codeine could not be retrieved from the database, the codeine dose was likely to be relevant for the use in combination with acetaminophen .		outcomes:
Polat et al. 2015,[31] Turkey	RCT, single-center, blinding status unclear	N = 60, 20 in each group Mean age = 44.95±10.08, 45.05±9.68, and 43.10±10.82 respectively Female participants = 10, 9, 8 respectively Inclusion criteria: age 18 to 65 years, ASA Physical Status I or II, general anesthesia for an elective single level unilateral microsurgical lumbar discectomy	Oral naproxen sodium + codeine phosphate (550 mg + 30 mg) Oral paracetamol + codeine phosphate (300 mg + 30 mg	Placebo	Pain at 0 hours, 1 hour, 2 hours, 6 hours, 12 hours, and 24 hours postoperatively
Chang et al. 2015,[32] USA	RCT, double-blinded	N = 215 (104 and 111 in two groups) adult ED patients presenting with acute musculoskeletal	codeine/acetaminophen (30 mg/300 mg)	oxycodone/acetaminophen (5 mg/325 mg)	Pain measured in NRS Primary

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		extremity pain Mean age = 38 and 39 years Female participants = 56%			outcomes: between-group difference in improvement in mean NRS pain score, at 2 hours following the most recent ingestion of the study drug Secondary outcomes: between-group differences in proportion of patients with >50% pain reduction, frequency of pre-specified side effects, and overall patient satisfaction
Bedwell 2014,[38] USA	Retrospective case series with chart review	N = 666 consecutive patients who underwent tonsillectomy with or without adenoidectomy using monopolar electrocautery 177 treated with acetaminophen and codeine Mean age = 6.2 vs 8.1 years (ibuprofen/acetaminophen vs codeine/acetaminophen)	Acetaminophen with codeine dosed at 0.5 to 1 mg/kg of codeine every 6 hours. Codeine dose given according to body weight	Acetaminophen dosed at 10 to 15 mg/kg every 6 hours plus Ibuprofen dosed at 5 mg/kg every 6 hours	Primary outcomes: proportion of patients requiring ED visits or inpatient admission for inadequate pain control and/or dehydration Secondary outcomes: postoperative hemorrhage, need for return to the operating room, and oral feeding tolerance on postoperative day 1
Chang et al. 2014,[33] USA	RCT, double-blinded, single-center	N = 181, 93, and 88 in the treatment and control groups respectively Female = 52% and 43% Mean age = 37±11 and 34±12 (significantly younger) years	codeine/acetaminophen (30 mg/300 mg), every 4 hours if needed for 3 days	hydrocodone/acetaminophen (5 mg/500 mg)	Primary outcomes: was the between-group difference in improvement in mean NRS pain scores, at 2 hours following the

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		Inclusion criteria: 21 to 64 years of age, acute extremity pain, and for whom the provider planned to discharge with a short course of oral opioids for outpatient pain management			most recent ingestion of the study drug Secondary outcomes: incidence of pre-specified side effects and overall patient satisfaction
Zavareh et al. 2013,[34] Iran	RCT, double-blinded, single-center	N = 131 ASA I and II patients aged 18‑60 years, scheduled for open cholecystectomy under general anaesthesia Mean age = 39.1±8.9 vs 37.2±9.4 for acetaminophen-codeine and tramadol respectively	Oral acetaminophen-codeine (325/10 mg) with 50 cc water 1 hour before surgery	Oral tramadol (50 mg capsule)	Postoperative pain assessed using at 2, 4, 8, 16 and 24 hr after surgery Side effects, and complications
Bertin et al. 2013,[39] France	Prospective cohort study, national, multicenter	N = 980 Female = 44% Mean age = 50 (SD = 15.8) years Patients with pain lasting "at least 7 days and for which the physician intended to prescribe a Level 2 analgesic treatment, either combined paracetamol–codeine or paracetamol– tramadol" (p. 654)	paracetamol– codeine (300 mg/25 mg or 600 mg/50 mg; number of tablets not reported) Exact frequencies and duration unknown	paracetamol–tramadol (325 mg/37.5 mg)	pain intensity, type of pain, quality of life, and tolerability of the analgesic treatment 7 days
Le May et al. 2013,[35] Canada	RCT, double-blinded, single-center	81 children presented to the ED with musculoskeletal trauma Inclusion criteria: ages of 7 and 18 years, presenting to the emergency department, a musculoskeletal injury to a limb within the past 72 h, a pain score > 3 on the 0–10 visual analog scale (VAS) at triage, speaking French or English, and limb trauma showing bony tenderness, swelling, limited range of motion, or an angulation below 30 degrees	Codeine syrup at 1 mg/kg (max 60 mg). Syrup concentration not reported, but the dose potentially achievable with syrup with less than 2 mg/ml	Ibuprofen caplets dosed at 10 mg/kg (max 600 mg)	Primary outcomes: difference in mean pain score between 90 min and triage Secondary outcomes: differences in mean pain intensity between 60 min and triage and between 120 min and triage; incidence of side effects at

First Author, Publication Year, Country	Study design	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
		See article for exclusion criteria			60, 90, and 120 min.

ACP = American College of Physicians; APS = American Pain Society; ASA = American Society of Anesthesiologists; ATC = Anatomical Therapeutic Chemical; ED = emergency department; IV = intravenous; kg = kilogram; KQ = key question; mg = milligram; min = minute; NRS = numeric rating scale; RCT = randomized controlled trial; SD = standard deviation; UK = United Kingdom; USA = United States of America; VAS = visual analogue scale

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[12]

Strengths	Limitations
Cooper et al. 2017[15]	
• PICO components included in the research questions or study inclusion criteria • Study selection rationale described and explained • Reasons for study exclusion listed in the flowchart • Comprehensive search with Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library, MEDLINE via Ovid, and Embase via Ovid • Study selection in duplicate • Data extraction in duplicate • A list of excluded studies provided • Potential studies in all languages screened • Risk of bias assessment planned • Conflict of interest declared	• Protocol not established *a priori* • No studies included
Wiffen et al. 2017[16]	
• PICO components included in the research questions or study inclusion criteria • Study selection rationale described and explained • Reasons for study exclusion listed in the flowchart • Comprehensive search with Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library, MEDLINE via Ovid, and Embase via Ovid • Study selection in duplicate • Data extraction in duplicate • A list of excluded studies provided • Potential studies in all languages screened • Risk of bias assessment planned • Conflict of interest declared	• Protocol not established *a priori* • No studies included
Wiffen et al. 2017[8]	
• PICO components included in the research questions or study inclusion criteria • Study selection rationale described and explained • Reasons for study exclusion listed in the flowchart • Comprehensive search with Cochrane Central Register of Controlled Trials (CENTRAL; via CRSO), MEDLINE (via Ovid), Embase (via Ovid) and Oxford Pain Relief Database • Study selection in duplicate • Data extraction in duplicate • A list of excluded studies provided • Potential studies in all languages screened • Risk of bias assessment planned • Conflict of interest declared	• Protocol not established *a priori* • No studies included
Gardiner et al. 2016[2]	

Strengths	Limitations
• PICO components included in the research questions or study inclusion criteria • Protocol established *a priori* • Study selection rationale described and explained • Reasons for study exclusion listed in the flowchart • Comprehensive search with Cochrane Airways Group Register of Trials (via the Cochrane Register of Studies), Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online, MEDLINE (Ovid), EMBASE (Ovid), Trials registries (ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)) • Study selection in duplicate • Data extraction in duplicate • A list of excluded studies provided • Potential studies in all languages screened • Risk of bias assessment planned • Conflict of interest declared	• No studies included
Molassiotis et al. 2015[17]	
• PICO components included in the research questions or study inclusion criteria • Protocol established *a priori* • Study selection rationale described and explained • Reasons for study exclusion listed in the flowchart • Comprehensive search with the Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), the Database of Abstracts of Reviews of Effectiveness (DARE), MEDLINE, EMBASE, CINAHL, PsycINFO, AMED, SIGLE (renamed as Open Grey), British Nursing Index, and CancerLit • Study selection in duplicate • Data extraction in duplicate • A list of excluded studies provided • Potential studies in all languages screened • Included studies appraised • Risk of bias in individual studies discussed regarding the result interpretation • Sources of heterogeneity discussed • Included studies described • Potential studies in all languages screened • Conflict of interest declared	• Funding sources of the included studies not mentioned • No meta-analysis • Publication bias not assessed
Derry et al. 2015[18]	
• PICO components included in the research questions or study inclusion criteria • Study selection rationale described and explained • Reasons for study exclusion listed in the flowchart • Comprehensive search with the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE (via Ovid), EMBASE (via Ovid), and the Oxford Pain Relief Database • Study selection in duplicate	• Protocol not established *a priori* • Funding sources of the included studies not mentioned

Strengths	Limitations
• Data extraction in duplicate • A list of excluded studies provided • Potential studies in all languages screened • Included studies described and appraised • Meta-analysis conducted with statistical methods • Risk of bias considered in meta-analysis • Risk of bias in individual studies discussed regarding the result interpretation • Sources of heterogeneity discussed • Publication bias assessed	
Mkontwana et al. 2015[19]	
• PICO components included in the research questions or study inclusion criteria • Protocol established *a priori* • Study selection rationale described and explained • Reasons for study exclusion listed in the flowchart • Comprehensive search with CENTRAL, MEDLINE and Embase • Study selection in duplicate • Data extraction in duplicate • A list of excluded studies provided • Potential studies in all languages screened • Included studies described and appraised • Meta-analysis conducted with statistical methods • Risk of bias considered in meta-analysis • Risk of bias in individual studies discussed regarding the result interpretation • Sources of heterogeneity discussed • Conflict of interest declared	• Funding sources of the included studies not mentioned • Publication bias not assessed
Straube et al. 2014[20]	
• PICO components included in the research questions or study inclusion criteria • Protocol established *a priori* • Study selection rationale described and explained • Reasons for study exclusion listed in the flowchart • Comprehensive search with Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE • Study selection in duplicate • Data extraction in duplicate • A list of excluded studies provided • Potential studies in all languages screened • Included studies described and appraised • Funding sources of the included studies mentioned • Meta-analysis conducted with statistical methods • Risk of bias considered in meta-analysis • Risk of bias in individual studies discussed regarding the result interpretation • Sources of heterogeneity discussed • Conflict of interest declared	• Publication bias not assessed
McCrory et al. 2013[22]	

Strengths	Limitations
• PICO components included in the research questions or study inclusion criteria • Study selection rationale described and explained • Reasons for study exclusion listed in the flowchart • Comprehensive search with Ovid MEDLINE, Scopus, and the Cochrane Libraries • Study selection in duplicate • Data extraction in duplicate • A list of excluded studies provided • Potential studies in all languages screened • Included studies described and appraised • Funding sources of the included studies described • Meta-analysis conducted with statistical methods • Risk of bias in individual studies discussed regarding the result interpretation • Sources of heterogeneity discussed • Funding source declared, AHRQ	• Protocol not established *a priori* • Risk of bias not considered in meta-analysis • Publication bias not assessed

AHRQ = Agency for Healthcare Research and Quality; WHO = World Health Organization

Table 5: Strengths and Limitations of RCTs using the Cochrane Risk of Bias checklist[13]

Strengths	Limitations
Childress et al. 2018[23]	
• Randomization method described • Attrition reported in Figure 1 • Complete cases for analysis • Selective outcome reporting not likely • Codeine dose clearly described	• Allocation concealment unclear • No blinding
Chang et al. 2017[24]	
• Randomization method described • Allocation concealed • Double blinding • Attrition reported in Results • Complete cases for analysis • Selective outcome reporting not likely	• Frequency and duration of codeine dosage not clear
Santini et al. 2017[25]	
• Randomization method described • Allocation concealed • Double blinding • No attrition • Complete cases for analysis • Selective outcome reporting not likely • Codeine dose clearly described	
Samieirad et al. 2017[27]	
• Randomization method described • Allocation concealed • Triple blinding • No attrition • Complete cases for analysis • Selective outcome reporting not likely	• Frequency and duration of codeine dosage not described
Pereira et al. 2017[28]	
• Randomization method described • Allocation concealed • Double blinding • Attrition reported in Figure 1 • Complete cases for analysis • Selective outcome reporting not likely	• Frequency and duration of codeine dosage not described
Cristalli et al. 2017[29]	
• Randomization method described • Allocation concealed • Double blinding • Attrition reported in Figure 1 • Complete cases for analysis • Selective outcome reporting not likely	• Frequency and duration of codeine dosage not described
Graudins et al. 2016[30]	

Strengths	Limitations
• Randomization method described • Allocation concealed • Double blinding • No attrition reported • Complete cases for analysis • Selective outcome reporting not likely	• Frequency and duration of codeine dosage not described
Polat et al. 2015[31]	
• Randomization method described • Allocation concealed • Attrition reported in Results • Complete cases for analysis • Selective outcome reporting not likely	• Anesthesiologists blinded, blinding status of others unknown • Frequency and duration of codeine dosage not described
Chang et al. 2015[32]	
• Randomization method described • Allocation concealed • Double blinding • Attrition reported in Figure 1 • Complete cases for analysis • Selective outcome reporting not likely	• Frequency and duration of codeine dosage not described
Chang et al. 2014[33]	
• Randomization method described • Allocation concealed • Double blinding • Attrition reported in Figure 1 • Complete cases for analysis • Selective outcome reporting not likely	• Frequency and duration of codeine dosage not described
Zavareh et al. 2013[34]	
• Randomization method described • Double blinding • Selective outcome reporting not likely	• Allocation concealment unclear • Conflicting sample sizes in the texts: 131 or 136 • Incomplete outcome reporting possible • Frequency and duration of codeine dosage not described
Le May et al. 2013[35]	
• Randomization method described • Allocation concealed • Double blinding • Attrition reported in Figure 1 • Complete cases for analysis • Selective outcome reporting not likely	• Frequency and duration of codeine dosage not described

Table 6: Strengths and Limitations of non-randomized studies using Newcastle-Ottawa scale[14]

Strengths	Limitations
Ludwin et al. 2017[36]	
• Representing the patients in the community • Comparison group from the same population, different time points • Exposure based on the time periods • Outcome of interest not presenting at the start of the study • Control cohort sampled in the same source of care • Follow-up time enough for short-term outcomes • Follow-up adequate for the assessment of test acceptance	• Outcomes reported by patients, recall and measurement bias possible • Frequency and duration of codeine dosage not described
Roberto et al. 2015[37]	
• Case definition adequate • Consecutive series of cases • Controls sampled from the same database • Controls not presenting the outcome of interest • Cases and controls matched for sex, age, month and year of cohort entry, and duration of follow-up • Outcomes documented in a database • Exposure ascertainment method the same for the cases and controls • Similar non-response among cases and controls	• Nested case-control study • Dose, frequency and duration of codeine dosage not described
Bedwell et al. 2014[38]	
• Representing the patients in the community • Comparison group from the same population, different time points • Exposure based on chart review • Control cohort sampled in the same source of care • Outcomes documented in charts • Follow-up time probably enough for the outcome, emergency room use • Follow-up adequate for the assessment of test acceptance	• Outcome of interest presenting at the start of the study due to the retrospective study design • Duration of codeine dosage not described
Bertin et al. 2013[39]	
• Representing the patients in the community • Comparison group from the same population, different time points • Control cohort sampled in the same source of care • Outcome of interest not presenting at the start of the study • Follow-up time enough for short-term outcome • Follow-up adequate for the assessment of test acceptance	• Exposure reported by patients • Outcomes reported by patients

Appendix 4: Main Study Findings and Authors' Conclusions

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Chronic non-cancer pain	
Cooper et al., 2017[15]	
No studies met the eligibility criteria for the review.	*"There was no evidence from randomised controlled trials to support or refute the use of opioids to treat chronic non-cancer pain in children and adolescents. We are unable to comment about efficacy or harm from the use of opioids to treat chronic non-cancer pain in children and adolescents."*(p.2)[15]
Cancer pain, for those aged 17 years or younger	
Wiffen et al., 2017[16]	
No studies met the eligibility criteria for the review.	"*No conclusions can be drawn about efficacy or harm in the use of opioids to treat cancer-related pain in children and adolescents. As a result, there is no RCT evidence to support or refute the use of opioids to treat cancer-related pain in children and adolescents."*(p.2)[16]
Cancer pain, children or adults	
Straube et al., 2016 [20]	
• 15 RCTs (n = 721) included in the SR; no meta-analysis performed due to insufficient data • Dose of codeine in included studies ranged from 30mg to 120mg • 6 studies with probably relevant codeine doses: Chen 2003 (30 mg), Rico 2000 (Mean 200 mg daily + paracetamol 2000 mg daily, 7 days), Rodriguez 2007 (150 mg daily + paracetamol 2500 mg daily, 21 days), Capretti 1970 (30, 60 mg), Carlson 1990 (240 mg + paracetamol 2400 mg daily, 7 days), Staquet 1971 (30 mg) **Codeine and codeine + paracetamol vs. Placebo:** <u>Participants with VAS pain intensity below 30/100mm (no worse than mild pain):</u> No included study reported data on this outcome <u>Treatment group average pain intensity or pain relief, substantial pain relief and use of rescue medication:</u> Data from 6 included studies (3 of them with relevant doses): codeine or codeine + paracetamol provided greater pain relief over placebo <u>Treatment group average pain intensity or pain relief</u> o Data from 10 included studies (3 of them with relevant doses): o Codeine superior to placebo (p. 13) <u>Complete or partial pain relief (Chen 2003 with relevant dose)</u>	*"The available evidence indicates that codeine is more effective against cancer pain than placebo, but with increased risk of nausea, vomiting, and constipation. Uncertainty remains as to the magnitude and time-course of the analgesic effect and the safety and tolerability in longer-term use. There were no data for children."*(p.2)[20]

Main Study Findings	Authors' Conclusion
○ Codeine superior to placebo (p. 13) Patient Global Impression of Change: No included study provided data for this outcome. **Codeine and codeine + paracetamol vs. Active comparators:** Participants with VAS pain intensity below 30/100mm (no worse than mild pain): ○ One cross-over study (Rico 2000 with relevant dose: in the first period 52%(11/21) in the codeine 30mg VS 39% (9/23) in the tramadol 40 mg group reported no worse mild pain; in the second period 56% (9/16) in the codeine group and 60% (6/12) in the tramadol group reported no pain ○ In a parallel study (Rodriguez 2007 with relevant dose): no worse than mild pain in 41/59 participants (69%) with codeine 150 mg plus paracetamol 2500 mg daily, 40/56 (71%) with tramadol 200 mg daily, and 45/62 (73%) with hydrocodone 25 mg plus paracetamol 2500 mg daily. Treatment group average pain intensity or pain relief ○ Data from 10 included studies (3 of them with relevant doses): ○ codeine or codeine + paracetamol provided comparable levels of pain control as oxycodone, morphine, alclofenac, ciramadol, ketorolac, piroxicam, piroxicam plus codeine, tramadol, delta-9-tetrahydrocannabinol, NIB (a synthetic nitrogen analogue of tetrahydrocannabinol), and an experimental drug Z 424 (p. 14) Complete or partial pain relief (Chen 2003 with relevant dose) ○ "Codeine gave similar results to codeine plus ibuprofen and tetrahydrocannabinol, and was numerically superior to benzopyranoperidine (p.14) Time to use rescue medication (Carlson 1990 with relevant dose) ○ Codeine superior to placebo (p. 13) ○ Ketorolac had a slightly longer time to use of rescue medication than codeine, while fewer participants used rescue medication with codeine than with benzopyranoperidine, and similar numbers with ciramadol and codeine. (p. 14) Patient Global Impression of Change: No included study provided data for this outcome. **AEs, withdrawals, deaths:** • AEs poorly reported across all included studies ○ Nausea, vomiting and constipation most common AEs • 9 included studies reported withdrawals; 7/9 included studies had withdrawal rates < 10%	

Main Study Findings	Authors' Conclusion
• One included study reported serious AEs; 3 deaths were reported in the study but attributable to underlying malignant diseases	
Acute postoperative pain	
Derry, Karlin, and Moore, 2015[18]	
• 6 (n=1342) studies included in the SR **Participants with at least 50% pain relief:** <u>Ibuprofen 200mg + codeine vs. placebo:</u> • One included study ibuprofen 200mg + codeine 15 mg (medium dose) vs. placebo: 18/36 vs. 10/26 reported at least 50% pain relief <u>Ibuprofen 400mg + codeine vs. placebo:</u> • 4 studies (n=443) included comparisons of 400mg ibuprofen + codeine 25.6mg to 60mg vs. placebo ○ Proportion with at least 50% pain relief: ibuprofen + codeine vs. placebo: 64% (178/276) vs. 18% (30/167); RR 4.1(95%CI, 2.8 to 5.9), I^2 = 86%; NNT = 2.2 (95% CI, 1.8 to 2.6) **Time to use of rescue medication:** • One included study (n=224) ibuprofen 400mg + codeine 26.5mg vs. placebo: 8.1 hours vs. 1.7 hours **Participants using rescue medication:** • 1 included study reported the numbers of participants requiring rescue medications within 4 to 5 hours of 30 mg codeine; greater number of participants in placebo required rescue medication; additional details NR **Serious AEs:** • No serious AEs reported in any of the included studies **Withdrawals:** • No adverse event withdrawals were reported	*"The combination of ibuprofen 400 mg plus codeine 25.6 mg to 60 mg demonstrates good analgesic efficacy. Very limited data suggest that the combination is better than the same dose of either drug alone, and that similar numbers of people experience adverse events with the combination as with placebo."*(p.2)[18]
Post-caesarian pain	
Mkontwana and Novikova, 2015[19]	
• Among eight included studies, one used codeine for intervention, Bjune 1996 (Paracetamol 800 mg + codeine 60 mg [number of tablets not reported]) Combination versus placebo, Outcome = Maternal drug effects: • Not significant in Bjune 1996	Authors' conclusion not specific to codeine
Pain among patients with osteoarthritis of the knee or hip	
da Costa et al., 2014[21]	
• Among 3 RCTS that provided data for codeine; dose ranged	The only one trial with codeine of eligible dose did not indicate

Main Study Findings	Authors' Conclusion
from 30mg to 100mg, one with relevant doses (Quiding 1992, 30 mg plus ibuprofen 200 mg, 6 times in 32 hours) **Knee or hip pain :** ○ Moderate benefit for codeine (SMD -0.51, 95% CI -1.01 to -0.01; 3 RCTs); but insignificant results in Quiding 1992	significantly difference in knee or hip pain. However, if trials with higher-dose codeine included, a moderate benefit was observed with codeine for osteoarthritis of the knee or hip with regards to pain and function.
Chronic cough	
McCrory et al., 2016[22]	
Cough count: • One included study found a statistically significant reduction in the 6-hr posttreatment cough count in with varying doses of codeine (7.5mg vs. 15mg. vs. 30mg. vs.60mg) : 29% vs. 42% vs. 56% vs. 67%; *P* < 0.005 **Cough severity:** • Two included studies found codeine 15 to 17mg 3 to 4 times a day more effective than low dose dextromethorphan 4 to 6mg 3 to 4 times a day in reducing cough severity **Adverse events:** • In one included study, 2/39 patients in the codeine 30mg group discontinued medication due to reported dry mouth and asthenia in one patient and nausea in the second patient • Two included studies found the frequency of side effects of nausea, constipation, and/or drowsiness was greater in the codeine 15 to 17mg group compared to the dextromethorphan 4 to 6mg	*"Although the evidence is sparse, the opioid and certain nonopioid/nonanesthetic antitussives most frequently demonstrated efficacy for managing the symptom of chronic cough in adults."* (p.vii)[22]
Cough in children	
Gardiner et al., 2016[2]	
No studies met the eligibility criteria for the review.	*"This review has highlighted the absence of any randomised controlled trials evaluating codeine-based medications in the treatment of childhood chronic cough."*(p.2)[2] *"Given the lack of supporting trials, the findings from trials of acute cough in children, and the known harmful side effects, we have concluded that codeine-based medications cannot be recommended in children with chronic cough."*(p.2-3)[2]
Cough in cancer	
Molassiotis et al., 2016[17]	
• No new trials met the inclusion criteria for the update of the 2010 Cochrane SR on Interventions for cough in cancer • Conclusions from 2010 SR remain unchanged • Among nine primary studies included, two using codeine:	Conclusions from 2010 SR: *"Some indication of positive effect was observed with morphine, codeine, dihydrocodeine, levodropropizine, sodiumcromoglycate*

Main Study Findings	Authors' Conclusion
Dotti 1970 (n = 41, 30 mg codeine and 10 mg phenyltoloxamine), Kleibel 1982 (n = 31, unclear dose)	*and butamirate citrate linctus (cough syrup), although all studies had significant risk of bias."*(p.2)[17]

AE: adverse effect; CI = confidence interval; hr = hour; mg = milligram; RCT = randomized controlled trial; SMD = standardized mean difference

Table 8: Summary of Findings of RCTs

Main Study Findings	Author's Conclusions
Headache in pregnancy	
Childress et al. 2018[23]	
• Metoclopramide administered with diphenhydramine (MAD) Headache Study Reduction in pain score by at least two points 6 hours after medication • No difference between MAD and codeine • "MAD pain scores lower at 30 minutes (3 ± 2.8 versus 5.8 ± 2.3, p < 0.001), 1 hour (2.2 ± 2.3 vs. 4.1 ± 3; p < 0.01), and 12 hours (1.3 ± 2.5 vs. 2.7 ± 3; p < 0.05), but not at 6 hours"(p. 1) Time to perceived headache relief • "Shorter for MAD than for codeine (20.2 ± 13.4 vs. 62.4 ± 62.2 minutes; p < 0.001)" • "More patients in the MAD group reported full headache relief within 24 hours (76.5% vs. 37.5%; p < 0.01)" (p. 1)	• MAD as effective as codeine for the headache that acetaminophen failed to treat in pregnant women
Acute extremity pain	
Chang et al. 2017[24]	
At 2 hours, the mean NRS pain score decrease: • 4.3 (95%CI, 3.6 to 4.9) in the ibuprofen and acetaminophen group • 4.4 (95%CI, 3.7 to 5.0) in the oxycodone and acetaminophen group • 3.5 (95%CI, 2.9 to 4.2) in the hydrocodone and acetaminophen group • 3.9 (95%CI, 3.2 to 4.5) in the codeine and acetaminophen group (P = .053) The largest difference: • Between the oxycodone and acetaminophen group and the hydrocodone and acetaminophen group (0.9; 99.2%CI, −0.1 to 1.8 • Less than the minimum clinically important difference in NRS pain score of 1.3. Adverse events not assessed	• "For patients presenting to the ED with acute extremity pain, there were no statistically significant or clinically important differences in pain reduction at 2 hours among single-dose treatment with ibuprofen and acetaminophen or with 3 different opioid and acetaminophen combination analgesics." • "Further research to assess adverse events and other dosing may be warranted." (p. 1661)
Acute periradicular abscess pain	
Santini et al. 2017[25]	
Pain reduction in both groups over time • Codeine-acetaminophen group: a significant reduction in the scores 12, 24, 48, and 72 hours after treatment (P<0.05).	• "The combination of codeine and acetaminophen is more effective to control moderate to severe pain from acute periradicular abscesses" (p. 551)

Main Study Findings	Author's Conclusions
• Tramadol-acetaminophen group: pain scores significantly decreased over time from time point 6 h (P<0.05). Between-group comparison • At each time point, not significantly different (P>0.05) • Both treatments effective in controlling pain caused by acute periradicular abscess Adverse reactions • combination of tramadol-acetaminophen more adverse reactions and two patients stopped	
Pain after dental procedures	
Pain, edema, and trismus after extraction of impacted lower third molar	
Cigerim et al. 2018[26]	
• "Naproxen sodium-codeine phosphate more effective for pain, edema, and trismus than diclofenac potassium and benzydamine hydrochloride (P < .05)" • "Benzydamine hydrochloride yielded similar clinical responses to diclofenac potassium (P > .05)" • "No drug-related side effects observed" (p. 495)	• "Naproxen sodium-codeine phosphate constitutes the drug of choice after the extraction of a patient's impacted lower third molar" • "Benzydamine hydrochloride has similar efficacy to diclofenac potassium, and it can be used as a nonsteroidal anti-inflammatory analgesic drug" (p. 495)
Pain and swelling management after dental implant surgeries	
Samieirad et al. 2017[27]	
Pain severities • Codeine group: significantly less than those in the caffeine group at 3-, 6-, and 12-h postoperative intervals (p = 0.001). • In both groups, pain within the moderate pain severity range (VAS = 3 to 7) • Pain at its maximum severity at the 6-h postoperative interval • Pain at its minimum at the 1-week interval Severity of swelling • Significantly less in the caffeine group at 1-, 2-, and 3-day postoperative intervals (p = 0.018)	• "The codeine-containing analgesics are significantly more effective than caffeine-containing ones in reducing postoperative pain" • "Caffeine-containing analgesics are significantly more effective than codeine-containing ones in reducing postoperative swelling, which was reported to be significantly less within the first 3-days in the caffeine group" • "Caffeine-containing analgesics are effective and acceptable in reducing both postoperative pain and swelling." (p. 1614)
Pain following impacted mandibular third molar surgery (drug use before surgery)	
Cristalli et al. 2017[29]	
Pain intensity score on the first day • Significantly lower in the analgesic group than in the placebo group (p < 0.001) Time to using rescue therapy • Significantly longer in the analgesic group than in the placebo group (p = 0.004) Number of paracetamol-codeine tablets used postoperatively • No difference between the analgesic and placebo groups (***P***= 0.104)	• "Preoperative paracetamol-codeine is effective in providing immediate postoperative pain control after third molar surgery and in delaying the initial onset of pain" (p. 1)
Pain after photorefractive keratectomy	
Pereira et al. 2017[28]	
Pain scores: • Measured by VAS, McGill Pain Questionnaire, and Brief Pain Inventory scales • For three measures: "statistically and clinically lower during	• "When added to the usual care therapy, the oral combination of codeine/acetaminophen was safe and significantly superior to the placebo for pain control after photorefractive keratectomy." (p. 1206)

Main Study Findings	Author's Conclusions
treatment with codeine/acetaminophen compared with the placebo: 1 hour: 4 (interquartile range = 2 to 4) versus 6 (3 to 6), P < 0.001; 24 hours: 4 (3 to 6) versus 7 (6 to 9), P < 0.001; 48 hours: 1 (0 to 2) versus 3 (2 to 5), P < 0.001; and 72 hours: 0 (0 to 0) versus 0 (0 to 2), P = 0.001" Adverse events • Most common with codeine/acetaminophen: drowsiness (42%), nausea (18%), and constipation (5%)	
Moderate pain from limb injury	
Graudins et al. 2016[30]	
• Large sample attrition from 30 to 90 minutes (n = 61, 62, and 59 per group to 32, 30, and 32 per group) Differences (95% CI) in pain between groups at 30 min • Non-opioid VS codeine: 2.6 (8.8 to 3.6); non-opioid versus oxycodone 2.7 (9.3 to 3.9); codeine versus oxycodone 0.1 (6.6 to 6.4). Mean VAS reductions • Non-opioid, codeine and oxycodone were 13.5, 16.1 and 16.2 mm, respectively. Satisfaction with analgesia • 77.6% (64.7–87.5), 81.0% (67.2–89.0) and 73.6% (59.7–84.7) Adverse events • 3.3% (0.4–11.3), 1.6% (0.4–8.7) and 16.9% (8.4–29.0), respectively. Mean VAS reductions at 60 and 90 min • 23.2 and 18.7 mm for non-opioid; 30.7 and 33.3 mm for codeine; and 26.1 and 31.7 mm for oxycodone	• "At 30 min, analgesic effects of non-opioid, codeine and oxycodone groups were non-inferior" (p. 666)

MAD = metoclopramide administered with diphenhydramine; NRS = numeric rating scale; VAS = visual analogue scale

Table 9: Summary of Findings of Non-Randomized Studies

Main Study Findings	Author's Conclusions
Pain during ultrasound assessment of uterine cavity and tubal patency	
Ludwin et al. 2017[36]	
• incidence of moderate/severe pain: significantly lower in women using painkillers considering any moment of the procedure (relative risk = 0.54; 95% CI = 0.40 to 0.72; *P* = 0.001, number needed to treat = 4) • "Less women presented with moderate/severe pain during air and saline compared with foam infusion" (relative risk = 0.41, 95% CI = 0.28 to 0.61) (p. 599)	• "using paracetamol1codeine before the procedure reduces the pain level, but randomized controlled trials are required" (p. 599)
Pain among patients with osteoarthritis	
Roberto et al. 2015[37]	
• Incidence rate of acute cerebrovascular and cardiovascular events (ACCEs): 117.6 per 10,000 person-years • ACCEs not significantly associated with acetaminophen-containing medications among current (OR 1.22, 95% CI 0.96-1.55), recent (OR 1.12, 95% CI 0.80-1.55), or past users (OR 1.13, 95% CI 0.86-1.48) • **ACCEs not significantly associated with acetaminophen-codeine combination therapy.**	• "No association can be made between the use of acetaminophen and/or an acetaminophen-codeine combination and the occurrence of ACCEs. This information contributes to support clinicians in the choice of acetaminophen therapy for osteoarthritis-related pain, especially in those patients presenting with cerebrovascular and cardiovascular morbidities or related risk factors" (p. 899)
Pain following tonsillectomy	
Bedwell et al. 2014[38]	
• "Patients in the ibuprofen/acetaminophen group were younger than those in the codeine/acetaminophen group (6.2 vs 8.1 years, P < 0.05)" • "Patients in the codeine/acetaminophen group were more likely to use antibiotics in the postoperative period (50.3% vs 5.9%, P < 0.05)" • ED visits for dehydration: proportions not significantly different between the groups (5.1% for codeine, 2.7% for ibuprofen, P = 0.12) • No difference in ED visits or admission for dehydration after controlling for age and antibiotic use (P = .09) • "No difference between the groups for any of the secondary measures" (p. 963)	• "Ibuprofen with acetaminophen represents a safe and acceptable analgesic alternative to codeine and acetaminophen in patients undergoing pediatric tonsillectomy" (p. 96)
Pain lasting for at least seven days	
Bertin et al. 2013[39]	
• Origin of pain: most commonly disease or trauma • Mean baseline pain intensity: 7 (SD 1.3; 0–10 numerical rating scale), similar regardless of the origin • "Time-course of pain differed according to its origin: more than two-thirds of patients with trauma/work accident related pain described it as being constant, whereas 43% of those with disease-related pain described it as recurrent/intermittent." • Origin of pain influencing quality of life: "trauma/work accident related pain led to functional and/or professional temporary incapacity in 77% and 83% of patients (vs 63% for disease-	• "Acute pain should not be understood as a single entity but as multiple entities with specific characteristics related to its underlying origin" • "Level 2 analgesia provides effective relief of acute pain in 'real life' conditions" (p. 653)

Main Study Findings	Author's Conclusions
related pain), while disease related pain led to a change in mood and/or feeling of anxiety in 79% of patients (vs 47% [trauma] and 58% [work accident related])" • "Both paracetamol–codeine and paracetamol–tramadol reduced pain intensity by approximately 75% and were well tolerated" (p. 653)	

ACCE = acute cerebrovascular cardiovascular event; ED = emergency department; OR = odds ratio

Appendix 5: Additional References of Potential Interest

Guidelines

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