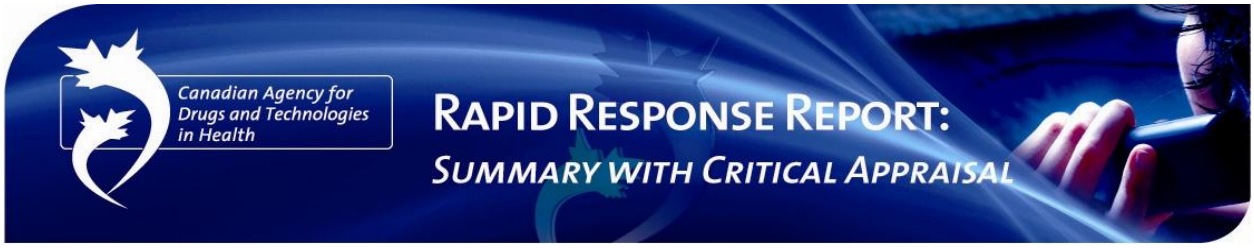

TITLE: Codeine and Acetaminophen for Pain Relief: A Review of the Clinical Efficacy and Safety

DATE: 12 April 2012

CONTEXT AND POLICY ISSUES

Pain has been defined as “an unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage."[1] Pain can be classified as being either acute or chronic. The distinction between acute and chronic pain is usually based on a subjective interval of time since pain onset, the two most commonly used intervals being 3 months and 6 months since onset.[2] Acute pain may be caused by various events as surgery, dental work, bone fractures and burns and cuts.[3] Common types of chronic pain are lower back pain, cancer related pain, arthritis pain, neurogenic pain and psychogenic pain.[3]

In a national telephone survey about postoperative pain 80% of patients rated acute pain as moderate to severe in the first hours to days following surgery.[4] Chronic pain is a common reason for patients to seek medical care. Chronic pain has been reported by twenty to fifty percent of patients seen in primary care.[5]

Pain can be treated by both pharmacological and non-pharmacological means. Major categories of medications for treatment of pain include non-opioid analgesics, opioids, alpha-2 adrenergic agonists, antidepressants, antiepileptic drugs, muscle relaxants, N-methyl-d-aspartate (NMDS) receptor agonists and topical analgesic agents.[6]

Codeine is an opioid used to treat mild to moderately severe pain.[7] Codeine can be habit forming and can cause serious side effects such as slow heart rate, weak pulse, confusion, hallucinations, seizure and problems with urination.[7] Less severe side effects include dizziness, nausea, vomiting, stomach pain, constipation, sweating and mild rash.

The most commonly used over the counter oral non-opioid analgesic is acetaminophen.[6] Acetaminophen is commonly used for the treatment of knee or hip osteoarthritis. The safety of long term use of acetaminophen has been questioned. The use of acetaminophen has is the most common cause of acute liver failure in the United States.[8]

Acetaminophen and codeine combination products are used to relieve mild to moderate pain.[7] Acetaminophen/codeine products work in certain areas of the brain and nervous system to decrease pain. The combination of acetaminophen/codeine may provide better pain relief than

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either medicine alone.[7] The combination drug can have similar side effects as the individual medications.

This review evaluates the evidence on the effectiveness of codeine and acetaminophen/codeine combination products used for the treatment of chronic pain as well as dosing safety of acetaminophen, codeine and acetaminophen/codeine in the treatment of acute and chronic pain.

RESEARCH QUESTIONS

1. What is the clinical efficacy of codeine for chronic pain relief?

2. What is the clinical efficacy of codeine in combination with acetaminophen for chronic pain relief?

3. What is the clinical evidence on patient safety associated with different doses of codeine?

4. What is the clinical evidence on patient safety associated with different doses of acetaminophen?

5. What is the clinical evidence on patient safety associated with different doses of codeine/acetaminophen combination products?

KEY MESSAGE

Based on this review, both codeine and acetaminophen/codeine provide better chronic pain relief than placebo. Chronic use of acetaminophen at doses higher than 2000 mg per day may be associated with increased risk of gastrointestinal events, liver toxicity, and renal dysfunction or failure. This review found evidence of increased risk of adverse events for patients treated with codeine or acetaminophen/codeine combination products compared to placebo. Acetaminophen/codeine treatment for post-operative pain was found to be associated with a higher risk of adverse events compared to placebo. No evidence was found on relative safety of different doses of either codeine or acetaminophen/codeine combination products.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, EMBASE, The Cochrane Library (2012, Issue 1 of 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of 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 and randomized controlled trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and March 5, 2012.

Selection Criteria and Methods

Two independent reviewers screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance using a predefined checklist. Any discrepancies between reviewers were discussed until consensus was reached. Full texts of any relevant titles or abstracts were retrieved, and assessed by two independent reviewers based on the initial inclusion criteria. Any disagreement between reviewers was discussed until consensus is reached.

Table 1: Selection Criteria

Population	Any age Q1, Q2: Patients being treated for chronic pain, any indication Q3,Q4, Q5: Patients being treated for chronic or acute pain
Intervention	Q1, Q3: Codeine alone Q2, Q5: Codeine with acetaminophen Q4: Acetaminophen
Comparator	Q1, Q2: placebo Q3, Q4, Q5: Any
Outcomes	Clinical efficacy (e.g. pain control, pain measurement on VAS) Safety (e.g. overdose, liver function, hospitalizations, other adverse events)
Study Designs	Health technology assessments (HTAs), systematic reviews and meta-analyses, randomized controlled trials (RCTs)

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria or presented preliminary results in abstract form. Duplicate publications and narrative reviews were also excluded. Because of the large number of RCTs evaluating acetaminophen, safety studies evaluating acetaminophen were limited to systematic reviews.

Critical Appraisal of Individual Studies

The methodological quality of the included systematic reviews and meta-analyses were evaluated using the measurement tool for the "assessment of multiple systematic reviews" (AMSTAR; Appendix 1).[9] AMSTAR is an 11-item checklist that has been developed to ensure reliability and construct validity of systematic reviews.

The quality of randomized controlled trials was evaluated using a modified version of Downs and Black instrument (Appendix 2).[10] This assessment instrument, which has been modified to include the source of funding for studies, has a total score ranging from 0 to 28, with higher scores indicating a higher-quality study. For this review a numeric score was not calculated for each study. Instead, the methodological quality of the included evidence was assessed based on reporting, external and internal validity and risk of confounding, where appropriate, and their strengths and limitations were described. Any disagreements were resolved through discussion until consensus was reached.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 835 potential citations were identified by the search in bibliographic databases, with 796 citations being excluded during the title and abstract review based on irrelevance to the questions of interest. The full text documents of the remaining 39 articles were retrieved. Of these 39 articles, 24 did not meet the eligibility criteria and were excluded, leaving 15 articles for this review.[11-25] A PRISMA diagram demonstrating the study selection process is presented in Appendix 3.

Summary of Study Characteristics

Fifteen articles that addressed at least one of the study questions were included in this review, consisting of three RCTs[11,14,15] and 12 systematic reviews.[12,13,16-25] A summary of study characteristics is provided in Appendix 4.

One systematic review was identified that reported on the effectiveness of codeine compared to placebo for treatment of chronic pain.[18] This systematic review investigated treatments for osteoarthritis of the knee or hip.

One systematic review was identified that reported on the effectiveness of codeine-acetaminophen combination compared to placebo for treatment of chronic pain.[12] This systematic review investigated treatments for rheumatoid arthritis pain.

Two systematic reviews were identified that addressed safety for codeine to treat either chronic or acute pain.[16,18] The study populations for these studies were patients with post-operative pain[16] and patients with osteoarthritis of the knee or hip.[18]

There were eight systematic reviews identified that reported on safety of acetaminophen for treatment of either acute or chronic pain.[13,17,19,21-25] The conditions evaluated in these studies were post-operative pain,[22,23] osteoarthritis,[13,21] acute back pain,[17] and fever or pain.[19] Two of the systematic reviews investigated any therapeutic use of acetaminophen.[24,25] The study population in two of the reviews were children 18 years of age or younger.[19,24]

The safety of acetaminophen/codeine combination products was reported in three RCTs[11,14,15] and two systematic reviews.[12,20] All three RCTs evaluated treatment for post-operative dental pain. The medical conditions evaluated in the two systematic reviews were rheumatoid arthritis and post-operative pain.

Summary of Critical Appraisal

Twelve systematic reviews[12,13,16-25] and three RCTs were identified which addressed the safety or efficacy of codeine, codeine-acetaminophen combinations, or acetaminophen. Specific strengths and limitations are presented in Appendix 5.

Ten[12,16-20,22-25] of the systematic reviews included a list and summary of included studies and an additional ten studies[12,16-22,24,25] included a statement of conflicts or interests. The quality of included studies was assessed in six[16,18-20,22,23] of the systematic reviews and duplicate study selection and data extraction was performed in these same studies, with one additional study

also having performed duplicate selection/abstraction.[12] Five reviews[12,18,22-24] had comprehensive search strategies with no potential omissions in terminology.

All three RCTs[11,14,15] clearly stated the objectives, described patient characteristics, interventions and study outcomes, and were double-blinded. For all the studies, it was unclear if the study participants were representative of the majority of patients. One study[14] used an intent to treat analysis. One study[15] adjusted the effect size for the baseline pain level as a confounding factor. The two other RCTs[11,14] did not take potential confounders into account in their analyses.

Summary of Findings

What is the clinical efficacy of codeine for chronic pain relief?

One systematic review was identified that evaluated the effectiveness of codeine to reduce chronic pain compared to placebo.[18] Nuesch et al.[18] reviewed the efficacy and safety of opioids in patients with confirmed osteoarthritis. The primary analysis pooled all types of opioids but a sub-analysis of the effectiveness of individual opioids, including codeine was provided. The authors included randomized or quasi randomized controlled trials in their review. Various pain scales were reported in the review's included studies. Therefore overall pooled effectiveness was summarized by using standardized mean differences (SMD) in pain scores from baseline. The authors state that -0.20 standardized units can be considered a small difference between treatment groups, -0.50 can be considered a moderate effect while -0.80 can be considered a large difference between treatment groups. Based on four included studies, the authors reported the pooled SMD in pain scores for codeine compared to placebo to be -0.51 (95% confidence interval [CI] -1.01 to -0.01). The authors did not provide conclusions specifically on the effectiveness of codeine on pain reduction.

What is the clinical efficacy of codeine in combination with acetaminophen for chronic pain relief?

One systematic review reported on the effectiveness of acetaminophen/codeine combination products for pain compared to placebo.[12] Whittle et al.[12] reviewed studies investigating the effectiveness and safety of opioids for treatment of rheumatoid arthritis pain. The authors included randomized and quasi randomized controlled studies that compared opioid therapy to another therapy (placebo or active therapy). The one included study that compared codeine/acetaminophen to placebo found the risk ratio for pain relief of 50% or better to be 2.28 (95% CI 0.99 to 5.25) in favour of codeine/acetaminophen. The authors did not provide conclusions specifically on the effectiveness of codeine/acetaminophen on pain reduction

What is the clinical evidence on patient safety associated with different doses of codeine?

Two systematic reviews[16,18] addressed the safety of codeine (Appendix 6). Nuesch et al.[18] evaluated the effectiveness and safety of opioids with placebo or no treatment in patients with osteoarthritis of hip or knee. One of the studies included in this review that compared codeine with placebo found no statistically significant difference between the two groups in terms of any reported adverse events. However, the pooled analysis of data from three included studies showed an increased risk of withdrawal due to adverse events in codeine users (pooled Relative Risk [RR] 3.67, 95% CI 2.16 to 6.24; $P < 0.001$). The dose of codeine was not reported

in this review. Derry et al.[16] pooled the data from 12 studies that reported on adverse events of a single dose of codeine (60 mg) for acute post-operative pain. The pooled results showed no difference between the codeine and placebo groups in terms of reported adverse events.

What is the clinical evidence on patient safety associated with different doses of acetaminophen?

The safety of different doses of acetaminophen was reported in eight systematic reviews.[13,17,19,21-25] The results of these studies are described in Appendix 6. Of the eight systematic reviews, two[19,24] evaluated the safety of acetaminophen for pediatric pain and fever and the remaining six studies included adult populations.[13,17,21-23,25]

Acetaminophen safety in children

Lavonas et al.[24] focused on liver injury after therapeutic doses of acetaminophen (≤75mg/day orally or ≤100mg/day rectally) for at least 24 hours. No deaths or liver transplants were reported in any of the 62 selected studies. The pooled risk of developing major or minor hepatic adverse events was 0.031% (95% CI 0.015% to 0.57%). The highest transaminase level was reported to be 600 IU/L. The review by Southey et al.[19] identified 24 RCTs and 12 observational studies that reported on adverse events of acetaminophen versus ibuprofen or placebo. Meta- analysis of data from RCTs showed no statistically significant difference between acetaminophen, ibuprofen and placebo groups in terms of systemic reactions (e.g. nausea, sweating, rash). Compared with ibuprofen group, patients treated with acetaminophen had a similar rate of withdrawals due to adverse events. However, based on the results of individual observational studies, this review reported significantly higher rates of pediatric asthma (Odds Ratio [OR] 1.5, 95% CI 1.4 to 2.0), and anorexia (OR 5.07 95% CI 1.88 to 13.65) in acetaminophen users, as compared to non-users. Despite these findings, the authors concluded that acetaminophen, ibuprofen and placebo had similar safety profiles.

Acetaminophen safety in adults

The selected systematic reviews included patients with chronic conditions such as osteoarthritis pain,[13,21] conditions requiring analgesic treatment for more than 24 hours,[25] acute low back pain,[17] and post-operative pain.[22,23] The outcome data from these studies are provided in Appendix 6.

The findings of four reviews showed that acetaminophen use at doses higher than 2000mg/day might be associated with increased rates of gastrointestinal events,[13,21] liver toxicity,[13,17,21,25] or renal dysfunction or failure, [17,21] Based on the results of a single trial, one systematic review suggested that regular use of acetaminophen (>22 days/month) might increase the risk of cardiovascular events by 35%.[21] This review also indicated that the risk of gastrointestinal adverse events was 20-60% lower in patients who used high dose acetaminophen (>2.6mg/day) than those who treated with high dose non-steroidal anti-inflammatory drugs.[21]

Of the two systematic reviews of acetaminophen for acute post-operative pain, neither reported a statistically significant difference in experiencing adverse events between acetaminophen and placebo groups.

What is the clinical evidence on patient safety associated with different doses of codeine in combination with acetaminophen?

Two systematic reviews[12,20] and three RCTs[11,14,15] reported on safety of acetaminophen plus codeine.

Systematic reviews

Whittle et al.[12] systematically reviewed the effectiveness and safety of opioids in treatment of rheumatoid arthritis pain. Of the 11 studies included in their review, one compared the combination of acetaminophen and codeine (500mg/30mg), three times daily, with placebo. This study demonstrated no statistically significant difference between the two groups in terms of patient reported outcomes and discontinuation of medication due to adverse events.

Toms et al.[20] compared various doses of acetaminophen plus codeine with placebo and acetaminophen alone, when they were used as a single dose pain treatment after surgery. The pooled analysis of data from 20 studies showed that patients taking acetaminophen plus codeine (all doses) had higher rates of having one or more adverse events than those taking placebo pooled RR 1.37, 95% CI 1.15 to 1.63; P < 0.001). The analysis was repeated for subgroups of patients using three different combinations of acetaminophen and codeine (300mg/30mg, 600-650mg/60mg, and 800-1000mg/60mg). The pooled RR for acetaminophen plus codeine (600-650mg/60mg) was 1.57 (95% CI 1.27 to 1.93; P < 0.001). The corresponding RRs were not reported for the other two doses, and a dose response was not reported. More details are presented on the results of the included systematic reviews in Appendix 6.

RCTs

All of the three RCTs evaluated the effect of single doses of acetaminophen plus codeine in treatment of acute pain after dental surgery in adult population. The results of these RCTs are described in Appendix 7.

Gatoulis et al.[11] reported on the safety of the combination of acetaminophen and codeine (300 mg/30mg) in two separate RCTs of dental pain and acute tension headache. In both trials, the study medication was compared to placebo and aspirin. Neither of the trials showed a statistically significant difference between acetaminophen plus codeine and any of the comparators (placebo or aspirin) in terms of adverse events, including serious adverse events as well as neurologic, gastrointestinal, or dermatologic reactions to the study medication.

In the trial by Daniels et al.[14] acetaminophen plus codeine (500mg/15mg) was compared with placebo, Ibuprofen plus acetaminophen (200mg/500 mg, and 400mg/500mg), and Ibuprofen plus codeine (400mg/12.8 mg) for post-operative dental pain. Any patient reported adverse events were recorded during the course of the study, as well as treatment emergent adverse events (within 12 hours of taking the study medication and severe adverse events) (Appendix 7). The results of this trial showed that the frequency of adverse events was significantly higher in patients using acetaminophen plus codeine than those using ibuprofen plus acetaminophen at doses of 400mg/500mg (P = 0.002) or 200mg/500mg (P = 0.004).

Daniels et al.[15] conducted another RCT in a similar population to compare a higher dose of acetaminophen plus codeine (2400mg/240mg) with placebo, ibuprofen (2400mg) and etoricoxib (90mg and 120 mg). Compared to placebo, acetaminophen plus codeine users experienced

significantly more vomiting (P < 0.001), and dizziness (P < 0.05). The overall incidence of patient-reported adverse events and adverse events leading to withdrawal such as nausea and vomiting was significantly higher in acetaminophen codeine group versus etoricoxib 90mg or 120mg (P < 0.001).

Limitations

There are a number of limitations to this review. None of the included studies directly compared the safety of different doses of codeine or acetaminophen/codeine. This may be attributable to our search being limited to RCTs, systematic reviews and HTAs. The review excluded non-randomized trials in which comparative dosing evidence may be reported more often. Additionally our review was limited to literature published in the last 5 years. There likely would have been more evidence available if this restriction was not used. However, the systematic reviews evaluated in this report did include studies that were published earlier than five years ago.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

There is evidence that codeine and acetaminophen/codeine is effective in the treatment of chronic pain. Higher doses of acetaminophen (2000 mg per day) may be associated with serious long term adverse events. There is often consideration of the trade-off between effectiveness and safety when deciding on treatment and dosing of pharmaceuticals. This review did not find evidence on comparative safety of different doses of codeine or acetaminophen/codeine. This may have been due to the limitations of the review in terms of including only studies published in the last 5 years and not including observational studies.

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Appendix 1: AMSTAR Measurement Tool to Assess Systematic Reviews[9]

Reviewer: **Date:**

Ref ID: **First Author (year):**

1. Was a priori design provided? The research question and inclusion criteria should be established before the conduct of the review.	□ Yes □ No □ Can't answer □ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	□ Yes □ No □ Can't answer □ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	□ Yes □ No □ Can't answer □ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	□ Yes □ No □ Can't answer □ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	□ Yes □ No □ Can't answer □ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	□ Yes □ No □ Can't answer □ Not applicable
7. Was the scientific quality of the included studies assessed and documented? A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	□ Yes □ No □ Can't answer □ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	□ Yes □ No □ Can't answer □ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	□ Yes □ No □ Can't answer □ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	□ Yes □ No □ Can't answer □ Not applicable
11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	□ Yes □ No □ Can't answer □ Not applicable

Appendix 2: Downs and Black Checklist[10]

Reviewer: **Date:**

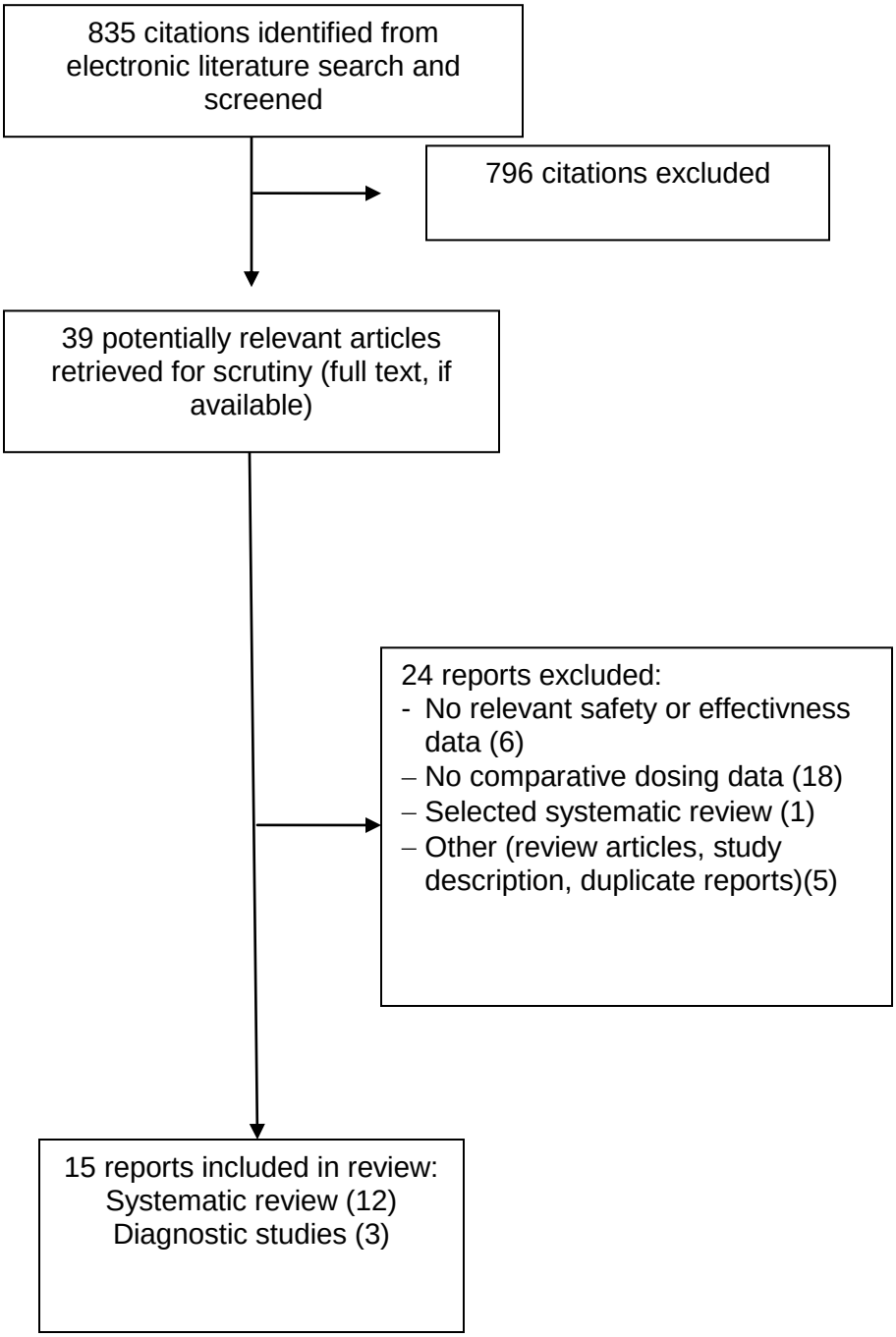
Ref ID: **First Author (year):**

REPORTING	Yes/No/Partially	**Score**
1. Is the objective of the study clear?	Yes=1, No=0	
2. Are the main outcomes clearly described in the Introduction or Methods?	Yes=1, No=0	
3. Are characteristics of the patients included in the study clearly described?	Yes=1, No=0	
4. Are the interventions clearly described?	Yes=1, No=0	
5. Are the distributions of principal confounders in each group of subjects clearly described?	Yes=2, Partially=1, No=0	
6. Are the main findings of the study clearly described?	Yes=1, No=0	
7. Does the study estimate random variability in data for main outcomes?	Yes=1, No=0	
8. Have all the important adverse events consequential to the intervention been reported?	Yes=1, No=0	
9. Have characteristics of patients lost to follow-up been described?	Yes=1, No=0	
10. Have actual probability values been reported for the main outcomes except probability<0.001?	Yes=1, No=0	
11. Is the source of funding clearly stated?*	Yes=1, No=0	
EXTERNAL VALIDITY	Yes/No/Unclear	**Score**
12. Were subjects asked to participate in the study representative of the entire population recruited?	Yes=1, No=0, Unclear=0	
13. Were those subjects who were prepared to participate representative of recruited population?	Yes=1, No=0, Unclear=0	
14. Were staff, places, and facilities where patients were treated representative of treatment most received?	Yes=1, No=0, Unclear=0	
INTERNAL VALIDITY	Yes/No/Unclear	**Score**
15. Was an attempt made to blind study subjects to the intervention?	Yes=1, No=0, Unclear=0	
16. Was an attempt made to blind those measuring the main outcomes?	Yes=1, No=0, Unclear=0	
17. If any of the results of the study were based on data dredging was this made clear?	Yes=1, No=0, Unclear=0	
18. Was time period between intervention and outcome the same for intervention and control groups or adjusted for?	Yes=1, No=0, Unclear=0	
19. Were statistical tests used to assess main outcomes appropriate?	Yes=1, No=0, Unclear=0	
20. Was compliance with the interventions reliable?	Yes=1, No=0, Unclear=0	
21. Were main outcome measures used accurate? (valid and reliable)	Yes=1, No=0, Unclear=0	

INTERNAL VALIDITY-CONFOUNDING (SELECTION BIAS)	Yes/No/Unclear	**Score**
22. Were patients in different intervention groups recruited from the same population?	Yes=1, No=0, Unclear=0	
23. Were study subjects in different intervention groups recruited over the same period of time?	Yes=1, No=0, Unclear=0	
24. Were study subjects randomized to intervention groups?	Yes=1, No=0, Unclear=0	
25. Was the randomized intervention assignment concealed from patients and staff until recruitment was complete?	Yes=1, No=0, Unclear=0	
26. Was there adequate adjustment for confounding in the analyses from which main findings were drawn?	Yes=1, No=0, Unclear=0	
27. Were losses of patients to follow-up taken into account?	Yes=1, No=0, Unclear=0	
Power	Size of smallest intervention group Score 0-5	**Score**
28. Was the study sufficiently powered to detect clinically important effects where probability value for a difference due to chance is <5%?		

*Criteria was added for the current systematic review

APPENDIX 3: Selection of Included Studies



APPENDIX 4: Characteristics of the Included Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes	Safety Outcomes
Systematic reviews						
Di Lorenzo, 2011[13]	Systematic review Inclusion Criteria: Not stated by authors	working patients with osteoarthritis	acetaminophen	placebo		Incidence: dyspepsia. peptic ulcer Risk ratio: upper GI effects, decreased glomerular filtration rate, hypertension
Whittle SL, 2011 [12]	Systematic Review Inclusion Criteria RCTs or quasi randomized controlled trials.	Adult patients with rheumatoid arthritis	Codeine/acetaminophen	placebo	Pain relief of 50% or better	Risk Ratio: Any adverse event, withdrawal due to adverse events
Derry 2010[16]	Systematic review Inclusion Criteria: Double blind trials of single dose codeine compared to placebo	Adults (15 years or older) with moderate or severe post-operative pain	Codeine(60mg)	placebo		Risk ratio: patients with any adverse event
Lavonas 2010 [24]	Systematic review Inclusion criteria: Population based studies(e.g. clinical trials) and case reports	Children 18 years of age or younger receiving a therapeutic dose (≤ 75mg/kg per 24 hour period) of acetaminophen	acetaminophen	none		Number of events: major hepatic AEs Incidence rates: elevated hepatic enzymes/minor hepatic AEs
McCarberg 2010[17]	Systematic review	patients with acute back pain	acetaminophen	none		Increased risk: renal failure, hepatotoxicity/fulminant hepatic failure

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes	Safety Outcomes
	Inclusion criteria Clinical trials evaluating a topical or oral treatment for acute back pain					
Nuesch 2009 [18]	Systematic review Inclusion criteria: Randomized or quasi randomized controlled trials with a control group or no interventions	Patients with clinically or radiologically confirmed osteoarthritis of the knee or hip	Any type of oral or transdermal opioid (including subanalyses for codeine)	placebo	Standardized mean differences (SMD) in pain scores. Various pain measurement scores were included in SMD calculation	Risk ratio and percentage: any AE, withdrawal due to AE
Southey, 2009[19]	Systematic review: Inclusion criteria: RCTs controlled observational studies case series	Children over 18 years of age who have pain or fever	acetaminophen	Ibuprofen, placebo		Odds Ratio: pediatric asthma, anorexia Risk Ratio: AEs leading to discontinuation, systemic reactions
Toms 2009[20]	Systematic review Inlcusion Criteria: Double blind trials of single dose oral acetaminophen with codeine compared placebo or same dose of acetaminophen	Adults (15 years or older) with moderate or severe post-operative pain	Acetaminophen (800mg-1000mg) plus codeine (60mg); Acetaminophen (600mg-650mg) plus codeine (60mg); Acetaminophen (600mg-650mg)	placebo		Risk ratio and percentage: one or more AEs

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes	Safety Outcomes
	alone					
Laine, 2008[21]	Systematic review Inclusion criteria: RCTs systematic reviews, review ofliterature which compared coxibs to acetaminophen or NSAIDS	Patients with osteoarthritis	acetaminophen	placebo, NSAIDS		Risk ratio: GI toxicity, cardiovascular, hypertension, renal dysfunction, Incidence: hepatotoxicity Percentage: hepatic coma, death due to hepatotoxicity
Toms 2008[22]	Systematic review Inclusion criteria: Inclusion Criteria: Double blind trials of single dose compared to placebo	Adults (15 years or older) with moderate or severe post-operative pain	acetaminophen	placebo		Risk ratio and percentage: one or more AEs
Dart 2007 [25]	Systematics review Inclusion criteria: prospective clinical trials and observational studies, retrospective studies	Adults 19 years of age or older receiving a therapeutic dose (≤ 4 g per day) of acetaminophen	acetaminophen	none		Percentage: liver failure, transplantation or death, elevated serum ALT levels, liver failure, liver transplantation or death
Weil 2007[23]	Systematic review Inclusion criteria: randomized control studies	patients having surgical removal a lower wisdom tooth with moderate to severe post removal pain	acetaminophen	placebo		Risk ratio for: patients with any AE

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes	Safety Outcomes
RCTs						
Gatoulis, 2012, United States[11]	Two RCTs: both double blinded, single dose, parallel groups Duration: First RCT: Effectiveness: 6 hours; Safety; 1 week Second RCT: First RCT: Effectiveness: 4 hours; Safety; 1 week	First RCT: n=300 patients aged 15 years or older who had surgical extraction of 2 or more third molars Second RCT: N=487 patients aged 18 years or older with a history of between 2 to 10 tension types headaches per month	First RCT: Acetaminophen(300mg) with codeine phosphate (30mg) First RCT: Acetaminophen(300mg) with codeine phosphate (30mg)	First RCT: placebo, aspirin (1000mg), Second RCT: placebo, aspirin (1000mg),		Both RCTs: any AE, severe AEs, dizziness, headache, nausea, vomiting, dry socket, urticaria
Daniels 2011, United Sates[14]	RCT double blinded, single dose, parallel groups Study duration: 12 hours	n=173 patients aged 16 years or older who had surgical extraction of 3 or more impacted third molars and had a score of 50mm on a 100mm visual analogue scale within 6 hours of surgery	Acetaminophen(100mg) with codeine phosphate (30mg)	placebo; ibuprofen 400 mg with acetaminophen (1000mg); ibuprofen(200mg) with acetaminophen (500mg); ibuprofen (100mg) with codeine (25.6 mg);		One or more AEs, dug related AEs, AEs leading to discontinuation, serious AEs, nausea, vomiting, dizziness, alveolar osteitis, headache, somnolence, hyperhidrosis Any AE, treatment emergent AEs, severe AEs, nausea, vomiting, alveolar osteitis, increased body termeprature, dizziness, headache
Daniels 2011,United States[15]	RCT double blinded, single dose, parallel groups Study duration: 6 hours	n=588 patients aged 16 years or older who had surgical extraction of 2 or more third	Acetaminophen(600mg) with codeine phosphate (60mg)	Placebo, etoricoxib (90 mg); and etoricoxib (120mg); Ibuprofen (600mg)		Any AE, treatment emergent AEs, severe AEs, nausea, vomiting, alveolar osteitis, increased body temperature, dizziness, headache

APPENDIX 5: Critical Appraisal of Individual Studies

First Author, Publication Year	Strengths	Limitations
Systematic Reviews		
Di Lorenzo 2011[13]	• None	• Explicit search strategy from a minimum of 1 database not provided • Summary of study characteristics and list of included and excluded studies not provided • Scientific quality of studies not assessed • Conflict of interest statement not included • Insufficient information about review process provided, so unable to assess most aspects of review quality
Whittle[12] 2011	• Duplicate study selection and data extraction performed • Comprehensive literature search • Summary of study characteristics and list of included and excluded studies provided • Conflict of interest statement included	• Only published studies included (no grey literature) • Scientific quality of studies not assessed
Derry[16] 2010	• Duplicate study selection and data extraction performed • Summary of study characteristics and list of included and excluded studies provided • Scientific quality of studies assessed and documented • Conflict of interest statement included	• Only published studies included (no grey literature)
Lavonas[24] 2010	• Comprehensive literature search • Tables of included study characteristics provided • Financial disclosure statement included	• Duplicate study selection and data extraction not performed • Only published studies included (no grey literature) • List provided for included studies only • Scientific quality of studies not assessed
McCarberg[17] 2010	• Tables of most included study characteristics provided • Conflict of interest statement included	• Literature search not comprehensive • Duplicate study selection and data extraction not performed • Only published studies included (only PubMed and reference list scanning results used) • Scientific quality of studies not assessed
Nüesch[18] 2009	• Duplicate study selection and data extraction performed • Comprehensive literature search • Summary of study characteristics and list of included and excluded studies provided • Scientific quality of studies assessed and documented	• None

First Author, Publication Year	Strengths	Limitations
	• Conflict of interest statement included	
Southey[19] 2009	• Duplicate study selection and data extraction performed • Articles written in English, French, Spanish, Dutch, German or Portuguese included • Summary of study characteristics provided • Scientific quality of studies assessed but not provided • Conflict of interest statement included	• Comprehensive list of resources searched for literature, but potential omissions in search terms used • Only published studies included (no grey literature or additional searching performed) • List provided for included studies only, but reasons for study exclusions included
Toms[20] 2009	• Duplicate study selection and data extraction performed • Summary of study characteristics and list of included and excluded studies provided • Scientific quality of studies assessed and documented • Conflict of interest statement included	• Comprehensive list of resources searched for literature, but potential omissions in search terms used • Only published studies included (no grey literature)
Laine[21] 2008	• Conflict of interest statement included	• Literature search not comprehensive • Summary of study characteristics and list of included and excluded studies not provided • Scientific quality of studies not assessed • Insufficient information about review process provided, so unable to assess most aspects of review quality
Toms[22] 2008	• Duplicate study selection and data extraction performed • Comprehensive literature search • Summary of study characteristics and list of included and excluded studies provided • Scientific quality of studies assessed and documented • Conflict of interest statement included	• Only published studies included (no grey literature)
Dart[25] 2007	• Tables of included study characteristics provided • Articles written in English, French, German, Italian, Japanese, Russian or Spanish included • Conflict of interest statement included	• Explicit search strategy from a minimum of 1 database not provided • Only published studies included (no grey literature or additional searching performed) • List provided for included studies only • Scientific quality of studies not assessed
Weil[23] 2007	• Duplicate study selection and data extraction performed • Comprehensive literature search • Summary of study characteristics and list of included and excluded studies provided • Scientific quality of studies assessed and documented	• Conflicts not known
Randomized Controlled Trials		
Gatoulis, 2012[11]	• Clearly described objectives, interventions, and study	• Did not report characteristics of patients lost to follow-up

First Author, Publication Year	Strengths	Limitations
	outcomes • Included a representative sample of participants • Reported the distribution of principal confounders in study participants • Reported actual probability values • Estimated random variability in data for the study outcomes • Blinded both the study subjects and evaluators to the intervention • Source of funding was stated	• It is not clear if the patients lost to follow-up (if any) were taken into account in the analysis • Did not take into account potential confounding factors in the analysis
Daniels, 2011a[14]	• Clearly described objectives, interventions, and study outcomes • Reported the distribution of principal confounders in study participants • Reported actual probability values • Estimated random variability in data for the study outcomes • Blinded both the study subjects and evaluators to the intervention • Source of funding was stated • The patients lost to follow-up were taken into account in the analysis	• Did not take into account potential confounding factors in the analysis
Daniels, 2011b[15]	• Clearly described objectives, interventions, and study outcomes • Included a representative sample of participants • Reported the distribution of principal confounders in study participants • Reported actual probability values • Estimated random variability in data for the study outcomes • Blinded both the study subjects and evaluators to the intervention • Source of funding was stated • Adjusted for a main confounding factor (baseline pain levels) in the analysis	• Did not report characteristics of patients lost to follow-up • It is not clear if the patients lost to follow-up (if any) were taken into account in the analysis • Did not report actual probability values • No statistical test was performed to compare the intervention of interest in this review (acetaminophen+ codeine) to placebo

APPENDIX 6: Summary of Safety Results from the Included Systematic Reviews and Meta-analyses

Author, year	Intervention (dose)	Comparator (dose)	AEs	No. of studies	AEs in intervention arm (%)	AEs in control arm (%)	Reported measure of harm (95% CI; p-value)	Authors' conclusion
Di Lorenzo, 2011[13]	Acetaminophen (1951-2600 mg/day)	None	dyspepsia	1	-	-	Incidence= 3.37/ patient-year	Acetaminophen is effective and safe at doses ≤2000 mg/day in patients with mild osteoarthritis pain.
	Acetaminophen (2601-3250 mg/day)	None**	dyspepsia	1	-	-	Incidence= 2.78/ patient-year	
	Acetaminophen (2601-3250 mg/day)	None**	Peptic ulcer	1	-	-	Incidence= 1.49/ patient-year	
	Acetaminophen (2000 mg/day)	None**	Upper GI effects	1	-	-	RR=0.9 (0.8, 1.1)	
	Acetaminophen (>2000 mg/day)	None**	Upper GI effects	1	-	-	RR=3.7 (2.6, 5.1)	
	Acetaminophen (4g/day for ≥2 weeks)	Placebo (NA)	Elevated serum ALT levels	1	-	-	Significant elevation (no measures reported)	
	Acetaminophen (>3000 g cumulative)	Acetaminophen (<100g cumulative)	Decreased glomerular filtration rate	1	-	-	RR=2.00 (95%CI not reported)	
	Acetaminophen (continuous use, 6-22 days/month)	No acetaminophen use	Hypertension	3	-	-	RR 1.34–2.00 (p<0.001)	
Whittle, 2011[12]	Acetaminophen (500 mg) plus codeine (30 mg) 3 times daily	Placebo (NA)	Patient-reported AEs	1	-	-	RR=2.33 (0.64, 8.55; p=0.20)	There is insufficient evidence regarding the safety of regular use of opioids in patients with rheumatoid arthritis. No specific conclusion was made by the authors about the safety of acetaminophen plus codeine.
	Acetaminophen (500 mg) plus codeine (30 mg) 3 times daily	Placebo (NA)	Withdrawal due to AEs	1	10	15	RR=0.67 (0.12, 3.57; p=0.64)	
Derry, 2010[16]	Single dose of codeine (60 mg)	Placebo (NA)	One or more AEs	12	20	16	RR*=1.26 (0.94, 1.67; p=0.12)	There was no statistically significant difference between the two groups on terms of AEs.

Author, year	Intervention (dose)	Comparator (dose)	AEs	No. of studies	AEs in intervention arm (%)	AEs in control arm (%)	Reported measure of harm (95% CI; p-value)	Authors' conclusion
Lavonas, 2010[24]	Acetaminophen (≤75mg/kg/day oral, ≤100mg/kg/day rectal)	Not reported	Major hepatic AEs †	59	-	-	No major hepatic AEs were reported	Hepatotoxicity with therapeutic doses of acetaminophen is rarely observed in **pediatric population**. The risk of developing symptomatic hepatotoxicity with these doses of acetaminophen is less than 0.01%.
	Acetaminophen (≤75mg/kg /day, ≤100mg/kg/day rectal)	Not reported	Elevated hepatic enzymes/minor hepatic AEs	59	-	-	Incidence rate= 0.031% (0.015%-0.057%)	
McCarberg, 2010[17]	Acetaminophen (>2-3g/day)	Not reported	Renal failure	1	-	-	Increased risk (no measures reported)	The authors recommended low-level continuous heat treatment over acetaminophen in treatment of acute back pain because it was more effective than acetaminophen with a low risk for systemic adverse events.
	Acetaminophen (>150mg/kg over a period of ≥ 8 hours, or ≥ 4g/day)	None	hepatotoxicity/ fulminant hepatic failure	2	-	-	Increased risk (no measures reported)	
Nuesch, 2010[18]	Codeine (unspecified)	Placebo/ no treatment (NA)	Any AE	1	80	62	RR= 1.28 (0.94, 1.75; p=0.11)	The author did not make any conclusion regarding the safety of codeine in osteoarthritis of knee and hip.
	Codeine (unspecified)	Placebo/ no treatment (NA)	Withdrawal due to AEs	3	38	10	RR*= 3.67 (2.16, 6.24; p<0.001)	
Southey, 2009[19]	Acetaminophen (≥once monthly)	No acetaminophen use	Pediatric asthma (age 2-6)	1	-	-	OR= 1.53 (1.04, 2.0; p<0.007) Adjusted OR= 2.41 (1.50, 3.87)	Acetaminophen has shown similar tolerability and safety to placebo and ibuprofen in treatment of **pediatric** pain and fever, in terms of GI symptoms, asthma and renal

Author, year	Intervention (dose)	Comparator (dose)	AEs	No. of studies	AEs in intervention arm (%)	AEs in control arm (%)	Reported measure of harm (95% CI; p-value)	Authors' conclusion
	Acetaminophen (once monthly [high use] or once per year [medium use])	No acetaminophen use	Pediatric asthma (age 6-7)	1	-	-	OR= 1.46 (1.36, 1.56) $OR_{medium\ use}$= 1.61 (1.46, 1.77) $OR_{high\ use}$= 3.23 (2.91, 3.60)	side effects.
	Acetaminophen (unspecified dose)	No acetaminophen use	Anorexia	1	-	-	OR= 5.07 (1.88, 13.65)	
	Acetaminophen (unspecified dose)	Ibuprofen (unspecified dose)	AEs leading to discontinuation	2	2.2	1.9	RR*=1.85 (0.58, 5.88; p=0.29)	
	Acetaminophen (unspecified dose)	Placebo (NA)	Systemic reactions	4	5.3	3.3	RR*=0.64 (0.30, 1.35; p=0.24)	
	Acetaminophen (unspecified dose)	Ibuprofen (unspecified dose)	Systemic reactions	18	13	14	RR*=0.97 (0.90, 1.02, p=0.27)	
Toms, 2009[20]	Single dose of acetaminophen plus codeine (all doses)	Placebo (NA)	One or more AEs	20	31	19	RR*=1.37 (1.15, 1.63; p<0.001) NNH*= 8.6 (6.4, 13)	The combination of acetaminophen and codeine is effective in postoperative pain with a low incidence of AEs.
	Single dose of acetaminophen (800-1000 mg) plus codeine (60 mg)	Placebo (NA)	One or more AEs	3	27	31	Not reported	
	Single dose of acetaminophen (600-650mg) plus codeine (60 mg)	Placebo (NA)	One or more AEs	14	35	18	RR*=1.57 (1.27, 1.93; p<0.001) NNH*=6.0 (4.6, 8.3)	
	Single dose of acetaminophen (300 mg) plus codeine (30 mg)	Placebo (NA)	One or more AEs	3	15	14	Not reported	

Author, year	Intervention (dose)	Comparator (dose)	AEs	No. of studies	AEs in intervention arm (%)	AEs in control arm (%)	Reported measure of harm (95% CI; p-value)	Authors' conclusion
	Single dose of acetaminophen plus Codeine (all doses)	Acetaminophen (all doses)	One or more AEs	11	27	24	RR*=1.16 (0.87, 1.40; p=0.40)	The addition of codeine to acetaminophen increases the rate of pain relief by over 10%, but increases the proportion of patients experiencing adverse events
	Single dose of acetaminophen (800-1000 mg) plus codeine (60 mg)	Acetaminophen (800-1000 mg)	One or more AEs	4	31	29	Not reported	
	Single dose of acetaminophen (600-650mg) plus codeine (60 mg)	Acetaminophen (600-650mg)	One or more AEs	7	23	20	Not reported	
Laine, 2008[21]	Acetaminophen (<2.6g/day)	NSAIDs (high dose)	GI toxicity	1	-	-	RR= 0.73 (0.67, 0.80)	The likelihood of developing GI toxicity with lower doses of acetaminophen is lower in acetaminophen users than high-dose NSAIDs users. Higher doses of acetaminophen may be associated with increased risk of GI toxicity.
	Acetaminophen (>2.6g/day)	NSAIDs (high dose)	GI toxicity	2	-	-	RR_{study1}= 0.98 (0.85, 1.13) & OR_{study2}= 0.40 (0.33, 0.48)	
	Acetaminophen (unspecified dose)	None**	GI toxicity	1	-	-	RR= 1.30 (1.20, 1.50)	
	Acetaminophen (regular use; >22days/month)	No acetaminophen use	Cardiovascular events	1	-	-	RR= 1.35 (1.14, 1.59)	Acetaminophen use may be associated with an increased risk of cardiovascular events.
	Acetaminophen (unspecified dose)	No acetaminophen use	Hypertension	2	-	-	RR_{nurses}= 2.00 (1.52, 1.62) $RR_{physicians}$=1.20 (0.98, 1.58)	Regular use of acetaminophen may be associated with an increased risk of hypertension or chronic renal failure.
	Acetaminophen (unspecified dose)	No acetaminophen use	Renal dysfunction	2	-	-	$RR_{general}$= 2.50 (1.70, 3.60) $RR_{physicians}$=0.83 (0.50, 1.39)	
	Acetaminophen (high dose)	None	hepatotoxicity	2	-	-	Incidence= 1.6 -1.9 /10^5 person years	Recommended maximum doses of acetaminophen may result in hepatotoxicity

Author, year	Intervention (dose)	Comparator (dose)	AEs	No. of studies	AEs in intervention arm (%)	AEs in control arm (%)	Reported measure of harm (95% CI; p-value)	Authors' conclusion
	Acetaminophen (high dose)	None	Hepatic coma	2	15%-33%	-	Not reported	and elevation of liver enzymes (>3 times).
	Acetaminophen (high dose)	None	Death due to hepatotoxicity	2	15%-19%	-	Not reported	
Toms, 2008[22]	Single dose of acetaminophen (all doses)	Placebo (NA)	One or more AEs	35	16	14	RR*=1.12 (0.97, 1.29; p=0.12)	There was no significant difference between a single dose acetaminophen and placebo in terms of AEs, when it was used in adults with post-operative pain.
	Single dose of acetaminophen (500 mg)	Placebo (NA)	One or more AEs	3	7	6	RR*=0.85 (0.38, 1.90; p=0.70)	
	Single dose of acetaminophen (600-650 mg)	Placebo (NA)	One or more AEs	13	16	14	RR*=1.18 (0.93, 1.50; p=0.16)	
	Single dose of acetaminophen (975-1000 mg)	Placebo (NA)	One or more AEs	19	18	16	RR*=1.10 (0.93, 1.32; p=0.27)	
Dart, 2007[25]	Acetaminophen (4g/day for ≥24hours)	Placebo (NA)	Liver failure, transplantation or death	12	0	Not reported	Not reported	In prospective studies, therapeutic doses of acetaminophen was associated with only small likelihood of increase in liver enzymes and no risk of serious liver injury and death. Retrospective studies showed a higher rate of increased liver enzymes, liver failure or death. A risk-benefit assessment is recommended before any decision to use acetaminophen.
	Acetaminophen (4g/day for ≥24hours)	Placebo (NA)	Elevated serum ALT levels	12	0.4	Not reported	Not reported	
	Acetaminophen (4g/day for ≥24hours)	Placebo (NA)	Elevated serum ALT levels	63	1	Not reported	Not reported	
	Acetaminophen (4g/day for ≥24hours)	Placebo (NA)	Liver failure	63	0.3	Not reported	Not reported	
	Acetaminophen (4g/day for ≥24hours)	Placebo (NA)	Liver transplant or death	63	0.07	Not reported	Not reported	
Weil, 2007[23]	Acetaminophen (all doses)	Placebo (NA)	Any AEs	17	21	18	RR*=1.19 (0.90, 1.57; p=0.23) NNH*= 33 (14.3, infinity)	Acetaminophen is a safe drug for pain relief after surgical removal of lower wisdom teeth.

Author, year	Intervention (dose)	Comparator (dose)	AEs	No. of studies	AEs in intervention arm (%)	AEs in control arm (%)	Reported measure of harm (95% CI; p-value)	Authors' conclusion
	Acetaminophen (≤1000 mg/day)	Placebo (NA)	Any AEs	9	11	8	RR*=1.25 (0.69, 2.25; p=0.46) NNH*= 33 (14.3, infinity)	
	Acetaminophen (>1000 mg/day)	Placebo (NA)	Any AEs	8	27	26	RR*=1.16 (0.84, 1.60; p=0.37) NNH*= 33 (12.5, infinity)	

Abbreviations: AE= adverse event; ALT= alanine transferase; CI= confidence interval; C= control arm; GI= gastrointestinal; I = intervention arm; NA= not applicable); NNH= number needed to harm; NSAIDs= non-steroidal anti-inflammatory drugs; OR= odds ratio; RR= relative risk
*pooled estimates from meta-analyses
** The control group included patients without AEs (case-control study)
† Examples of major hepatic AEs included death due liver failure, liver transplant, elevation of hepatic enzymes 5 times the upper limit of normal, jaundice, etc.

APPENDIX 7: Summary of Safety Results from the Included Randomized Controlled Trials

Author, year	Intervention (dose) [Sample size]	Comparator1 (dose) [Sample size]	Comparator2 (dose) [Sample size]	Comparator3 (dose) [Sample size]	Comparator4 (dose) [Sample size]	AEs	% of AEs					Reported measure of harm (95% CI; p-value)	Authors' conclusion
							I	C1	C2	C3	C4		
Gatoulis, 2012[11] Dental pain study	Acetaminophen (300mg) plus codeine (30 mg) [n= 121]	Placebo (NA) [n= 61]	Aspirin (1000 mg) [n=120]	-	-	Any AE	31	39	28	-	-	No statistically significant difference was reported between the groups.	No specific conclusion was made by the authors regarding safety of acetaminophen plus codeine.
						Severe AEs	22	23	28	-	-		
						Dizziness	1	0	3	-	-		
						Headache	1	1	1	-	-		
						Nausea	11	10	8	-	-		
						vomiting	8	8	6	-	-		
						Dry socket	17	28	16	-	-		
						Urticaria	0	1	0	-	-		
Gatoulis, 2012[11] Tension headache study	Acetaminophen (300mg) plus codeine (30 mg) [n= 233]	Placebo (NA) [n= 103]	Aspirin (1000 mg) [n=223]	-	-	Any AE	24	18	17	-	-	No statistically significant difference was reported between the groups	
						Severe AEs	5	0	0	-	-		
						Dizziness	9	6	5	-	-		
						Dry mouth	2	0	1	-	-		
						Somnolence	10	8	5	-	-		
						Headache	1	0	0	-	-		
						Dyspepsia	0	2	1	-	-		
						Nausea	5	6	2	-	-		
						Urticaria	1	0	0	-	-		
Daniels, 2011 (a)[14]	Acetaminophen (500mg) plus codeine (15 mg) [n= 113]	Placebo (NA) [n= 55]	Ibuprofen (200mg) plus acetaminophen (500 mg) [n=173]	Ibuprofen (400mg*) plus acetaminophen (500 mg) [n=168]	Ibuprofen (400mg*) plus codeine (12.8 mg) [n=169]	Any AE	63.7	63.6	50.9	51.8	57.4	Ibuprofen (400mg) plus acetaminophen and Ibuprofen (200mg) plus acetaminophen had significantly less AEs than acetaminophen plus codeine (p=0.002, and p=0.004, respectively).	No safety concerns were raised by the authors for acetaminophen plus codeine.
						Treatment emergent AEs	39.8	38.2	24.9	18.5	34.9		
						Severe AEs	12.4	7.3	4.0	5.4	7.7		
						Nausea	32.7	32.7	24.9	19.6	29.6		
						vomiting	22.1	23.6	16.8	17.9	20.7		
						Alveolar osteitis	2.7	1.8	4.6	2.4	5.3		
						Increased body temperature	2.7	1.8	1.2	1.8	5.3		
						Dizziness	12.4	5.5	6.9	8.9	13.6		
						Headache	18.6	18.2	11.0	11.3	18.9		

Author, year	Intervention (dose) [Sample size]	Comparator1 (dose) [Sample size]	Comparator2 (dose) [Sample size]	Comparator3 (dose) [Sample size]	Comparator4 (dose) [Sample size]	AEs	% of AEs					Reported measure of harm (95% CI; p-value)	Authors' conclusion
							I	C1	C2	C3	C4		
Daniels, 2011(b)[15]	Acetaminophen (2400mg) plus codeine (240 mg) [n= 62]	Placebo (NA) [n= 46]	Ibuprofen (2400 mg) [n=192]	Etoricoxib (90 mg) [n=191]	Etoricoxib (120 mg) [n=97]	One or more AEs	56.5	26.1	29.7	28.3	28.9	Acetaminophen plus codeine users had higher rates of vomiting (p<0.001), and dizziness (p<0.05), compared with placebo. Acetaminophen plus codeine users had higher rates of reported AEs, drug-related AEs. Nausea and vomiting, as compared with etoricoxib (p<0.001).	Etoricoxib and ibuprofen are superior to acetaminophen plus codeine in terms of tolerability.
						Drug-related AEs	48.4	13.0	9.4	11.0	12.4		
						AEs leading to discontinuation	4.8	0	0.5	0.5	0		
						Serious AEs	0	0	0	0	0		
						Nausea	37.1	6.5	5.2	3.1	4.1		
						vomiting	24.2	2.2	1.0	1.0	1.0		
						Dizziness	16.1	4.3	1.6	2.1	0		
						Alveolar osteitis	1.6	0	4.2	4.2	3.1		
						Headache	14.5	13.0	4.2	5.8	5.2		
						Somnolence	8.1	0	3.1	2.1	2.1		
						Hyperhidrosis	3.2	2.2	0.5	0.5	1.0		

Abbreviations: AE= adverse event; C= comparator; I= intervention; NA= not applicable
*Two single tablets of ibuprofen 200mg plus acetaminophen or codeine.