Acetaminophen with Codeine Safety Concerns

Evidence Summary

Background

Codeine, an opioid analgesic, is indicated for mild to moderate pain. Its analgesic properties come from the conversion of codeine to morphine and morphine-6-glucuronide. Codeine has a 200-fold weaker affinity for µ-opioid receptors than morphine. Pharmacokinetic studies show an increased conversion to morphine in CYP2D6 ultrarapid versus extensive metabolizers compared to poor metabolizers, which can result in toxic systemic concentrations of morphine even at low doses. Codeine and its metabolites are secreted into human breastmilk.

CYP2D6 is a genetic variation that results in the liver changing codeine into morphine more rapidly and completely than compared to those without that genetic variation. CYP2D6 metabolizes approximately 25% of all medications in the human liver. It is estimated that approximately 7 to 10% of Caucasians lack any CYP2D6 activity due to deletions and frameshift or splice-site mutations of the gene. Gene duplications, which can cause ultra-rapid metabolism, have been found in 29% of those of Ethiopian descent, 3.4-6.5% of those of African American descent, 1.2-2% of those of Asian descent, 3.6-6.5% of Caucasian descent, 6% of those with Greek descent, 1.9% of Hungarian descent, and 1-2% of those of Northern European descent. One study suggests that in looking at the population of the world as a whole, 5.5% of the population have a metabolic phenotype of poor metabolizers and 2.1% have an ultrarapid metabolism metabolic phenotype, but there are variations between different geographic regions and in predicted phenotype and metabolic phenotype.

Critically Analyze the Evidence

The GRADE criteria were used to evaluate the quality of evidence presented in research articles reviewed during the development of this guideline. The table below defines how the quality of evidence is rated and how a strong versus a weak recommendation is established.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Type of Evidence</th>
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<tbody>
<tr>
<td>STRONG</td>
<td>Desirable effects clearly outweigh undesirable effects or vice versa</td>
</tr>
<tr>
<td>WEAK</td>
<td>Desirable effects closely balanced with undesirable effects</td>
</tr>
<tr>
<td>Quality</td>
<td>Strong evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies</td>
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<td></td>
<td>Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results)</td>
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<tr>
<td></td>
<td>Evidence for at least 1 critical outcome from observational studies, from RCTs with serious flaws or indirect evidence</td>
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<tr>
<td></td>
<td>Evidence for at least 1 critical outcome from unsystematic clinical observations or very indirect evidence</td>
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PICO Question 1: In pediatric patients, when compared to codeine and combination preparations, are other analgesic medications (i.e., hydrocodone ± acetaminophen, oxycodone ± acetaminophen, ibuprofen ± acetaminophen) more effective for pain control?

Recommendation(s): Strong recommendation with moderate quality evidence to NOT use codeine and codeine combination preparations in pediatric patients. Consider using other equally efficacious pharmacologic methods to manage pain (such as hydrocodone, oxycodone, acetaminophen, and ibuprofen).

Remarks: When balancing the risk of potential CYP2D6 polymorphisms that lead to either ultra-rapid metabolism or no metabolism of codeine with the benefit of analgesia, codeine is not recommended in light of the evidence review that demonstrates that other pharmacologic options have similar efficacy with fewer side effects. Adequate analgesia is an important component of comprehensive patient care. This includes frequent pain assessments as appropriate and tailoring the patient’s plan of care to include both pharmacologic and non-pharmacologic interventions.

Safety Considerations: In 2012, the Food and Drug Administration issued an initial boxed warning on codeine being used due to death and serious adverse events in children who took codeine after a tonsillectomy and adenoidectomy. The FDA’s Adverse Event Reporting System found 13 cases of pediatric death or overdose associated with codeine, with most of the cases reported in the setting of an adenotonsillectomy or respiratory tract infection. Cytochrome P450 2D6 (CYP2D6) metabolizer status was mentioned in seven of the thirteen cases. In February 2013, the FDA issued its strongest boxed warning against using codeine and codeine-containing products to treat postoperative pain in children after tonsillectomy with or without adenoidectomy.
A review of the literature revealed five randomized controlled trials (RCTs) that reviewed pain score differences. [7-11] The studies varied in patient population, type of pain scale, and the medication used to compare analgesic effectiveness to codeine and codeine preparations. One study that compared oxycodone and codeine demonstrated that subjects receiving oxycodone for forearm fractures had a statistically significant greater reduction in pain scores than codeine. [7] Another RCT that compared acetaminophen, ibuprofen, and codeine in children with musculoskeletal injuries, reported that there was no statistically significant difference in reduction in pain score between acetaminophen and codeine groups, but the ibuprofen group demonstrated significantly greater improvement in pain score from 60 minutes post administration and onward. [8] In another RCT that looked at ibuprofen compared to acetaminophen with codeine in outpatient treatment of arm fracture 72 hours after injury, there was no statistically significant difference in pain scores between groups. [9] Friday et al. did a similar study comparing acetaminophen with codeine and ibuprofen in children with acute traumatic extremity pain and found a similar result to Drendel et al. with no statistically significant difference between pain scores after intervention between groups. [10] May et al. compared ibuprofen and ibuprofen plus codeine in children with musculoskeletal injury to an extremity and also found that the groups had no statistically significant differences in pain intensity at any time period. [11]

Six studies (5 RCTs and one observational study) reviewed side effects. [7-12] Charney et al. found no statistically significant differences in side effect occurrences between randomized groups of subjects given oxycodone versus codeine in children with suspected forearm fractures. [7] Clark et al. did not find a statistically significant difference in the number of patients reporting minor adverse events (such as nausea, sleepiness, and constipation) between acetaminophen, ibuprofen, and codeine groups. [8] Drendel et al. found a statistically significant higher report of nausea and vomiting in children who were randomized to receive codeine compared to ibuprofen. [9] Friday et al., May et al., and Bedwell et al. found side effects to be infrequent between comparison groups to codeine. [10-12]

When looking at complications, three observational studies reported post-operative bleeding rates between children post-tonsillectomy who received ibuprofen versus codeine for pain management. [12-14] None of the studies found a statistically significant difference between groups in regard to post-tonsillectomy bleeding. [12-14] Two studies that looked at other risk factors only found age to be statistically significant. [13,14]

Two studies reported return visits to the Emergency Department for treatment for pain or dehydration between patients who received either ibuprofen or codeine after tonsillectomy, and neither study found a statistically significant difference between groups. [12,14]

**PICO Question 2:** In pregnant and/or nursing mothers, when compared to codeine and combination preparations, are other analgesic medications (i.e., hydrocodone ± acetaminophen, oxycodone ± acetaminophen, ibuprofen ± acetaminophen) more effective for pain control?

**Recommendation(s):** Strong recommendation with moderate quality evidence to NOT use codeine and codeine combination preparations in pregnant patients and nursing mothers. Consider using other equally efficacious pharmacologic methods to manage pain (such as hydrocodone, oxycodone, and ibuprofen).

**Remarks:** When balancing the risk of potential CYP2D6 polymorphisms that lead to either ultra-rapid metabolism or no metabolism of codeine, risk to the fetus or breastfeeding neonate with the benefit of analgesia for the mother, codeine is not recommended for pain management given that other pharmacologic options exist with comparative effectiveness and fewer side effects and potential complications. Adequate analgesia is an important component of comprehensive patient care. This includes frequent pain assessments as appropriate and tailoring the patient’s plan of care to include both pharmacologic and non-pharmacologic interventions.

**Safety Considerations:** When looking at safety in pregnant women and nursing mothers, in 2006, there was a case report of neonatal demise secondary to maternal codeine use after a vaginal delivery. [15] In an analysis of data from the National Birth Defects Prevention Study, 464 mothers reported opioid analgesic treatment between one month before and three months after conception, with 34.5% of those women given codeine. Statistically significant associations with maternal opioid use were found among infants with conoventricular septal defect, atrioventricular septal defect, atrial septal defect, hypoplastic left heart syndrome, tetralogy of Fallot, or pulmonary valve stenosis. [16] The authors also found a statistically significant association with spina bifida (but not other neural tube defects), hydrocephaly, glaucoma or anterior chamber eye defects. [16] In a study that compared mothers who called an information center that counsels women about safety of using medications during pregnancy and breastfeeding (Motherisk), 16.7% of mothers who reported taking codeine for pain management during breastfeeding reported neonatal CNS depression when compared with acetaminophen alone (0.5%). [17] Four of 210 infants in the codeine cohort were observed to have “irregular breathing” and were taken to the emergency department for symptoms of lethargy. [17]

In a review of the literature, one Cochrane systematic review and meta-analysis was found that compared effectiveness and safety of analgesia after vaginal birth. [18] They found no statistically significant difference in summed pain intensity difference between fenoprofen (200 mg) and codeine (60 mg). [18] One study reviewed looked at many combinations of NSAIDs with and without codeine and codeine alone and found that NSDIAs were significantly better than opioids with a mean difference in pain score of -0.7 on a 4 point pain scale. [18]

When looking at side effects and complications, one Cochrane systematic review and meta-analysis and retrospective observational study reported those outcomes. [17,18] Deussen et al. found no difference in the number of adverse events between fenoprofen and codeine groups. [19] In a retrospective observational study, Lam et al. found that 20.1% of mothers who were taking oxycodone reported CNS depression in the neonate compared with only 0.5% of those in the acetaminophen group and 16.7% of mothers in the codeine group. [17]
References


6. FDA Drug Safety Communication: Codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death. (2013).


Clinical Standards Preparation
This clinical standard was prepared by the Evidence-Based Outcomes Center (EBOC) team in collaboration with content experts at Texas Children’s Hospital. Development of this clinical standard supports the TCH Quality and Patient Safety Program initiative to promote clinical standards and outcomes that build a culture of quality and safety within the organization.

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No relevant financial or intellectual conflicts to report.

Development Process
This clinical standard was developed using the process outlined in the EBOC Manual. The literature appraisal documents the following steps:

1. Review Preparation
   - PICO questions established
   - Evidence search confirmed with content experts

2. Review of Existing External Guidelines
   - N/A

3. Literature Review of Relevant Evidence
   - Searched: PubMed, EMBASE, CINAHL

4. Critically Analyze the Evidence
   - 1 meta-analysis, 4 randomized controlled trials, and 4 nonrandomized studies

5. Summarize the Evidence
   - Materials used in the development of the clinical standard, literature appraisal, and any order sets are maintained in an Acetaminophen with Codeine Safety Concerns evidence-based review manual within EBOC.

Evaluating the Quality of the Evidence
Published clinical guidelines were evaluated for this review using the AGREE II criteria. The summary of these guidelines are included in the literature appraisal. AGREE II criteria evaluate Guideline Scope and Purpose, Stakeholder Involvement, Rigor of Development, Clarity and Presentation, Applicability, and Editorial Independence using a 4-point Likert scale. The higher the score, the more comprehensive the guideline.

This clinical standard specifically summarizes the evidence in support of or against specific interventions and identifies where evidence is lacking/inconclusive. The following categories describe how research findings provide support for treatment interventions.

“Evidence Supports” provides evidence to support an intervention.

“Evidence Against” provides evidence against an intervention.

“Evidence Lacking/Inconclusive” indicates there is insufficient evidence to support or refute an intervention and no conclusion can be drawn from the evidence.

The GRADE criteria were utilized to evaluate the body of evidence used to make practice recommendations. The table below defines how the quality of the evidence is rated and how a strong versus weak recommendation is established. The literature appraisal reflects the critical points of evidence.

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<thead>
<tr>
<th>Quality</th>
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<td>High</td>
<td>Consistent evidence from well-performed RCTs or exceptionally strong evidence from unbiased observational studies</td>
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<tr>
<td>Moderate</td>
<td>Evidence from RCTs with important limitations (e.g., inconsistent results, methodological flaws, indirect evidence, or imprecise results) or unusually strong evidence from unbiased observational studies</td>
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Recommendations
Practice recommendations were directed by the existing evidence and consensus amongst the content experts. Patient and family preferences were included when possible. The Content Expert Team and EBOC team remain aware of the controversies in the management of acetaminophen with codeine safety concerns in children. When evidence is lacking, options in care are provided in the clinical standard and the accompanying order sets (if applicable).

Approval Process
Clinical standards are reviewed and approved by hospital committees as deemed appropriate for its intended use. Clinical standards are reviewed as necessary within EBOC at Texas Children’s Hospital. Content Expert Teams are involved with every review and update.

Disclaimer
Practice recommendations are based upon the evidence available at the time the clinical standard was developed. Clinical standards (guidelines, summaries, or pathways) do not set out the standard of care and are not intended to be used to dictate a course of care. Each physician/practitioner must use his or her independent judgment in the management of any specific patient and is responsible, in consultation with the patient and/or the patient’s family, to make the ultimate judgment regarding care.

Version History
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<tr>
<th>Date</th>
<th>Action</th>
<th>Comments</th>
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