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CODEINE USE IN CHILDREN

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Abbreviations

APAP, Acetaminophen

CDC, Centers for Disease Control and Prevention

CNS, Central nervous system

CYP2D6, Cytochrome P450 2D6

CYP3A4, Cytochrome P450 3A4

DHHS, Department of Health and Human Services

EM, Extensive metabolizer phenotype

EMA, European Medicines Agency

FAERS, FDA Adverse Event Reporting System

FDA, Food and Drug Administration

M3G, Morphine-3-glucuronide

M6G, Morphine-6-glucuronide

NCCN, National Comprehensive Cancer Network

NeuPSIG IASP, Neuropathic Pain Special Interest Group of the International Association for the Study of Pain

NSAIDs, Nonsteroidal anti-inflammatory drugs

OSA, Obstructive sleep apnea

OSE, Office of Surveillance and Epidemiology—FDA

PM, Poor metabolizer phenotype

RCT, randomized controlled trial

UGT2B7, Uridine diphosphate glucuronyltransferase 2B7

UM, Ultra-rapid metabolizer phenotype

WHO, World Health Organization

Introduction

Over the last couple decades, the safety of codeine-containing products for the pediatric population has been under the microscope of the U.S. Food and Drug Administration (FDA). Momentum for more restrictive labeling perhaps was initially ignited with the 1997 American Academy of Pediatrics' statement regarding the lack of well-controlled studies for the use of cough suppressants such as codeine in children and the potential risk.[1] In 2006, The American College of Chest Physicians' echoed these concerns, advising against the use of cough suppressants for children 14 years of age or younger.[2] By 2012, the World Health Organization had removed codeine from its essential medicines list for children.[3] In subsequent years, agencies such as the European Medicines Agency, Canadian Ministry of Health, and the FDA expanded codeine contraindications to children under 12 years of age for any indication, and in any pediatric patient for the management of pain post tonsillectomy and/or adenoidectomy.[4-9] The most recent US label change occurred in 2018, when the FDA omitted the pediatric dosing and indication for codeine- and hydrocodone-containing cold/cough products; now these are labeled for use in adults only, for symptoms associated with allergies or the common cold, with the aforementioned contraindications continued.[10]

This repot will review the current codeine labeling regarding pediatric patients, FDA safety actions, and relevant guidelines that address the use of codeine as a cough suppressant or for pain management pediatric patients. Medicaid prescription utilization data for codeine products will also be presented along with considerations for prior authorization criteria for the use of codeine in pediatric patients.

The use of codeine in Utah requires a prescription written by a controlled substance-licensed practitioner. Solid, oral dosage forms of codeine are Schedule II controlled substances, while liquid, syrup, and solution formulations of codeine are classified either as Schedule III or V, depending on the product. Certain codeine-containing products have preferred status on Utah Medicaid Preferred Drug List (PDL), as of January 2022: codeine tablets, and codeine/acetaminophen tablets and solution. Any short-acting opioid use in children <18 years of age beyond a 7-day supply requires a prior authorization (ie, Medication Coverage Exemption form submission) to express the clinical rationale. Additional age limits are listed for codeine/guaifenesin cough preparations with use restricted to 12 years and older; and for codeine/butalbital products, restricted to adult use only. There are no stated age restrictions for codeine/promethazine products on the PDL or other lists attached to the PDL.

Methodology

We searched for systematic reviews and guidelines addressing pediatric patients specifically and the use of codeine for the treatment of pain or cough in this population. The following websites were searched directly for policy statements or clinical guidelines:

i. U.S. Food and Drug Administration: https://www.fda.gov/
ii. American Academy of Otolaryngology-Head and Neck Surgery: https://www.entnet.org/quality-practice/quality-products/clinical-practice-guidelines/
iii. American Academy of Pediatrics: https://www.aap.org/en/
iv. American College of Chest Physicians: https://www.chestnet.org/Publications/CHEST-Publications/Guidelines-Consensus-Statements
v. Clinical Pharmacogenetics Implementation Consortium (CPIC): https://cpicpgx.org/

vi. World Health Organization: https://apps.who.int/iris/

Current product labels (ie, package inserts), were obtained from the National Library of Medicine website, DailyMed, which houses product labeling submitted to the FDA: https://dailymed.nlm.nih.gov/dailymed/FDA.
Systematic reviews were searched within the Cochrane Library and Epistemonikos (see **Appendix 1** for search strings).

Background

Codeine Metabolism, Metabolizer Phenotypes, and Drug-Drug Interactions

Agonist action at mu-opioid receptors produces analgesia and euphoria. Additional effects include respiratory depression, decreased gastric motility, abdominal pain, dysphoria, and peripheral vasodilation.[11] Codeine, similar to other opioids, is thought to suppress cough,[12,13] yet the risk/benefit profile of codeine as an antitussive is a topic of debate. Safety issues with codeine in the pediatric population largely relate to population variability in the cytochrome P450 (CYP) **2D6** enzymatic pathway responsible for conversion of codeine, which has minimal affinity at the mu-opioid receptor, into the potent mu-opioid receptor agonist, morphine.[14,15] Morphine is further metabolized into an active metabolite, morphine-6-glucuronide (M6G), and into other less active metabolites.[16,17] Another metabolic pathway involved in codeine metabolism is CYP3A4. Thus, there are safety implications respective to potential drug-drug interactions with strong CYP3A4 inhibitors or inducers. Codeine and its metabolites are primarily excreted through the kidneys.[17] The half-life of codeine and its metabolites is approximately 3 hours. The following bullets provide a breakdown of codeine metabolism, as a percentage of the dosage administered and reflective of what occurs in with normal functioning enzymes:[18]

- About **70%-80%** of the codeine dose undergoes uridine diphosphate glucuronyltransferase **(UGT) 2 B7/B4** conjugation to codeine-6-glucuronide (**C6G**), which has debatable analgesic properties.[18-20] C6G has been proposed to have similar affinity at mu-opioid receptors compared to codeine in animal models,[21] and has been documented to contribute to the analgesic effect in humans[19,22,23] Genetic polymorphisms of the UGT enzyme occur; however, the impact on codeine safety is unclear.[14]
- About **5%-10%** of the codeine dose undergoes **CYP2D6** metabolism to **morphine.** 5-15% of morphine is further metabolized into an active metabolite, morphine-6-glucuronide (**M6G**) and the remainder into metabolites with negligible acivity.[17,24] M6G has similar mu-opioid affinity as morphine, however with higher affinity for delta-opioid receptors.[13]
- About **10%** of the codeine dose undergoes **CYP3A4** metabolism to the inactive metabolite, norcodeine.[11]

Phenotype of CYP2D6 functionality is classified into four categories (ultra-rapid, extensive, intermediate, or poor metabolizer) which is predicted based on genotyping. However, while genotyping is correlated to the phenotype and can predict *to some degree* the level of CYP2D6 activity, it may not always predict the phenotype.[25,26] The extensive metabolizer phenotype is considered to demonstrate normal enzymatic activity. Ultra-rapid metabolizers are patients usually with more than two copies of normal-

function CYP2D6 genes who convert codeine to morphine more quickly than anticipated with empirical dosing. Thus, dosing in the general recommended range can cause toxicity in ultra-rapid metabolizers due to higher than expected concentrations of morphine.[26,27] Authors of a small pharmacokinetic study found the AUC (area under the curve) of morphine in the ultra-rapid metabolizer group was approximately double that of the extensive metabolizer group, post codeine administration.[27] The proportion of the codeine dose converted to morphine has been reported as high as 75% in an ultra-rapid metabolizer compared to 5-10% with normal CYP2D6 function (ie, extensive metabolizer phenotype).[28] Labeling for codeine expresses the estimated prevalence of the ultra-rapid metabolizers as "…1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain ethnic groups (ie, Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican)."[29] In contrast, intermediate or poor CYP2D6 metabolizers may experience diminished or no therapeutic effect from codeine.[30,31] In a 2018 US cohort study in adults, authors reported that "Among the 104,509 patients, 2,329 (2.2%) were predicted to be ultrarapid metabolizers (UMs), 85,021 (81.4%) normal metabolizers (NMs), 11,172 (10.7%) intermediate metabolizers (IMs), and 5,987 (5.7%) poor metabolizers (PMs)."[32] The poor metabolizer phenotype is more prevalent in Caucasian descent, and the intermediate metabolizer phenotype more prevalent in Asian and African descent.[32] The 2020 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline recommends against the use of codeine and tramadol in patients who are poor or ultra-rapid metabolizer predicted phenotypes based on CYP2D6 genotyping.[26] The labeling for codeine-containing products also have a black box warning regarding potential toxicity in ultra-rapid metabolizers.

Drugs that inhibit or induce CYP may produce clinically significant drug-drug interactions. CYP2D6 inducers can lead to higher/toxic levels of the more active codeine metabolites while inhibitors can lead to inadequate analgesic effect. The single CYP2D6 inducer we are aware of is oritavancin.[33] Strong CYP2D6 inhibitors include bupropion, fluoxetine, paroxetine, quinidine, cinacalcet, and possibly amiodarone.[13] According to Lexicomp drug interaction checker, the following additional medications can inhibit CYP2D6: duloxetine, and terbinafine (note this list is not exhaustive but serves as some additional examples).[34]

- While codeine-containing products do not have a warning regarding inducers of CYP2D6, avoidance of concomitant use with documented CYP2D6 inducers is prudent to avoid overproduction of morphine. Labeling does include a *black box warning* to avoid concomitant use CYP2D6 inhibitors since this could result in a reduction of analgesic effect. Additionally, if codeine is up-titrated while on a CYP2D6 inhibitor, but then the inhibitor is later discontinued with the codeine dose kept the same, toxic morphine levels could arise.[13,29,35]
- Codeine containing products also have a *black box warning*, advising to avoid its use in combination with all CYP3A4 inhibitors and CYP3A4 inducers[*], due to the potential for increased toxicity or decreased effect, respectfully.[13,29,35]

Although there are genetic tests used to predict one's metabolizer phenotype, the FDA viewed that mass genetic testing of CYP2D6 was not feasible, due to the costs and possible limited predictive value

[*] Examples of CYP3A4 inhibitors listed in the package insert include macrolide antibiotics, azole antifungal agents, and protease inhibitors; CYP3A4 inducers include rifampin, carbamazepine, and phenytoin

in the post-adenotonsillectomy setting, since some of the serious adverse event pediatric cases were in extensive metabolizers.[36] Nonetheless, some specialists in the pharmacogenomics field may favor a personalized approach based on the patient's genotype if known or attainable.[37,38] Evidence-based guidelines have been published regarding interpretation and decision-making based on CYP2D6 genotype/phenotype.[26,38] Recommendations from the 2020 Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline, as previously mentioned, are incorporated into this report. Attention to potential drug-drug interactions is also a crucial step in the personalized approach to prescribing.

FDA Safety Assessments and Actions

In December 2015, FDA advisory committees, including the Pulmonary Allergy Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee, met to consider utilization and adverse event cases among the FAERS (FDA Adverse Event Reporting System) database related to codeine in the pediatric population.[36] Previously in 2013, the FDA added a contraindication for the use of codeine for postoperative tonsillectomy and/or adenoidectomy pain in pediatric patients, and also required a black box warning describing the risks of respiratory depression in the CYP2D6 ultra-metabolizer phenotype.[8,36] This action followed the FDA's 2012 safety review of codeine when the most well-documented cases of life-threatening respiratory depression were found in the post-tonsillectomy/adenoidectomy (PTA) setting: a total of 8 codeine-associated pediatric deaths post-tonsillectomy/adenoidectomy were identified between 1969 to 2012 among published case reports and adverse-event reporting databases.[39]

- **2015 FDA Review**: National outpatient-pharmacy data captured by the FDA's Office of Surveillance and Epidemiology (OSE) showed that of the **1.9 million pediatric-codeine prescriptions in 2014,** 56% of patients were under 12 years old; 76% received codeine prescriptions for analgesic purposes; and 26% received codeine liquid products for cold/cough symptoms.[36] Data from the FDA Adverse Event Reporting System (FAERS) through May 2015 showed a total of **64** pediatric cases with serious respiratory depression (24 being fatal events) related to codeine use, with the majority of fatalities in patients younger than 12 years of age.[9,30] In cases with known CYP2D6 genotype, both ultra-rapid and extensive metabolizers were identified. FDA reviews concluded that, "a) codeine toxicity at therapeutic doses of codeine may occur in children who are CYP2D6 extensive and ultra-rapid metabolizers and b) codeine toxicity may occur in children taking higher than recommended therapeutic doses (overdosing or concomitant administration of multiple opioid drug products)."[36] Table 1 of **Appendix B** summarizes the FAERS cases at that time. Data from the literature and other adverse event reporting systems such as The National Electronic Injury Surveillance System Cooperative Adverse Drug Event Surveillance (NEISS-CADES) were also reviewed by the panel: 79 pediatric emergency department admissions for a codeine-related adverse drug event were found in the NEISS-CADES database from 2004-2013. In addition, the LexisNexis malpractice claims database showed 18% of death claims and 5% of hypoxic injury claims were related to opioid use following tonsillectomy surgery, with codeine being the opioid most frequently used (case counts not provided).[36,40]
    - Side note: Although the precise incidence of codeine severe adverse respiratory events in the pediatric population could not be estimated, some clinicians speculate that the risk is rather low considering the millions of prescriptions provided for codeine products to the pediatric population over the last 5 decades.[41] The FDA national estimates data showed between 2 and

3 million pediatric patients received a codeine outpatient prescription *per year* from 2010 to 2014; and additionally a downward trend occurring in prescribing of codeine for pediatric patients, decreasing by 40% from 2010 with 3.1 million pediatric patients to 2014 with 1.9 million pediatric patients. The argument has also been made that risk can be mitigated by focusing on the now known risk factors for codeine adverse events and efforts to mitigate the risk, rather than not allowing codeine for any pediatric patient who may benefit, and substituting with other opioids that also have caveats (eg, also not well studied in pediatric patients).[41]

In 2017, the FDA announced additional contraindications and labeled warnings for codeine.[9] Labeling for codeine products now describes the following:

i. **Contraindication** for all children younger than 12 years of age, regardless of intended use as antitussive or analgesic (contraindication added 2017)

ii. **Contraindication** for post-operative pain **in pediatric patients younger than 18 years of age following tonsillectomy and/or adenoidectomy** (continued contraindication from 2013)

- Rationale explained in labeling: "Based upon post-marketing reports, children younger than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultra-rapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect."[11,13,18,29,35]

iii. *Black box warning* to avoid the use in adolescents 12 to 18 years of age who have potential risk factors for respiratory depressant effects of codeine (eg, severe lung disease, postoperative status, obstructive sleep apnea, obesity, neuromuscular disease, and concomitant use of other respiratory depressants) (warning added in 2017)

iv. *Labeled warning* to avoid use during breastfeeding due to the toxicity risk to the baby (warning added in 2017)

In 2018, after further meetings with outside experts regarding codeine as an antitussive, the FDA modified the indicated age for use of codeine- and hydrocodone-containing[†] antitussive *prescription* products. These products are now labeled for use in adults (for relief of cough and upper respiratory symptoms associated with allergy or the common cold) and exclude the previously recommended pediatric dosages. Rationale is provided in the labeling: "Because the benefits of symptomatic treatment of cough associated with allergies or the common cold do not outweigh the risks of use of codeine in pediatric patients, promethazine HCl and codeine phosphate oral solution is not indicated for use in patients younger than 18 years of age."[13] Furthermore, the FDA's safety communication noted that for cases where cough treatment is necessary, alternative medicines are available such as dextromethorphan and benzonatate.[10] **Table 1** lists codeine-containing prescription antitussives that the

[†] Hydrocodone (HC) containing cold/cough products include: HC/guaifenesin (FlowTuss, Obredon); HC/pseudoephedrine/guaifenesin (Hycofenix, Rezira); HD/chlorpheniramine (Tussionex Pennkinetic, Vituz); HC/chlorpheniramine/pseudoephedrine (Zutripro); HC/homatropine (generic)

FDA referred to in their safety announcement. Some states, excluding Utah, may still have codeine-containing cough products available over-the-counter (OTC) with dosing directions for pediatric patients as young as 6 years of age.[10,42-44] This marketing discrepancy likely relates to different routes of regulating prescription and OTC products.

Table 1. Codeine Formulations Used for Cough/Cold Symptoms

Prescription Products Referred to in the FDA's 2018 Safety Communication Regarding Labeling Changes[10]	
Codeine/Chlorpheniramine	Extended Release Suspension: **Tuzistra XR**: 14.7mg-2.8mg/5mL Extended Release Tablet: **Tuxarin ER**: 54.3mg-8mg
Codeine/Promethazine	Syrup (generic): 10mg-6.25mg/5mL
Codeine/Phenylephrine/ Promethazine	Syrup: Promethazine VC and generics: 10mg-5mg-6.25mg/5mL
Codeine/Pseudoephedrine/ Triprolidine	Triacin C: note that this product now appears discontinued, per Micromedex Red Book
Products Regulated as OTC	
Codeine/Phenylephrine/ Triprolidine*	Histex-AC: 10mg-10mg-2.5mg/5mL
Codeine/Guaifenesin*	Coditussin AC 10mg-200mg/5mL; Virtussin AC, Guaiatussin AC, Cheratussin AC, Robafen AC, 10mg-100mg/5mL
Codeine/Guaifenesin/ Pseudoephedrine*	Coditussin DAC: 10mg-200mg-30mg/5mL; Lortuss EX: 10mg-100mg-30mg/5mL; Virtussin DAC: 10mg-100mg-30mg/5mL
*In some states these products may be available over-the-counter. In Utah, they require a prescription. The 2018 FDA labeling changes did not seem to apply to this group.	

The potential for additive toxicity is a concern when promethazine is combined with codeine, since promethazine itself can increase the risk of respiratory depression. Promethazine products have a *black box warning* stating that children may be more sensitive to additive respiratory depressant effects when promethazine is combined with codeine and/or other CNS depressants.[29] Prior to the 2018 label changes, promethazine with codeine was already contraindicated in patients under 6 years of age.[36]

Use of Codeine as an Antitussive in Pediatric Patients

The lack of well-controlled supportive evidence for the use of codeine as an antitussive in the pediatric population has been a concern at least since 1997 when the American Academy of Pediatrics published their position statement highlighting that codeine antitussive dosing had not been optimized for children, but was extrapolated from adult dosing.[1] With case reports of serious adverse events, authors highlighted that further research was needed in children, and that providers should inform parents about unestablished antitussive efficacy in children and potential risks. Authors described that acute cough from respiratory *viral infections* is a short-lived symptom and can be alleviated with fluids and humidity, and that underlying conditions such as asthma may go untreated if patients take an over-the-counter or prescribed cough-suppressant first-line without proper medical evaluation. Impeding clearance of secretions in a productive cough (ie, wet cough) may cause further complications such as pooling of secretions, airway obstruction, secondary infection, and hypoxemia.[1]

Systematic reviews in 2014 and 2016 by Cochrane continued to conclude a lack of randomized controlled evidence for significant benefits of codeine as an antitussive in pediatric patients, either for acute or chronic cough.[45-48] As an alternative option, in a 2018 Cochrane systematic review (SR), authors found that honey likely improves acute cough symptoms "…to a greater extent than no treatment, diphenhydramine, and placebo, but may make little or no difference compared to dextromethorphan."[49]

An expert panel of the **American College of Chest Physicians** (ACCP) recommended against the use of codeine for the treatment of *acute cough* in pediatric patients, in 2017 and 2020.[50,51] For acute cough, authors suggest honey for pediatric patients older than 1 year, with common cold symptoms. Authors restate the Cochrane SR finding that honey may be better than no treatment, diphenhydramine, or placebo, but it is not better than dextromethorphan and further note that dextromethorphan is inappropriate for children < 2 years of age.[50] For *chronic cough*, the panel provided a 2020 guideline for patients 14 and younger.[51] In this guideline, chronic cough is defined as a daily cough lasting > 4 weeks. Children with chronic cough need to be carefully evaluated for underlying respiratory or systemic disease such as "…bronchiectasis, retained foreign body, aspiration lung disease, atypical respiratory infections, cardiac anomalies and interstitial lung disease, among others."[51] The guideline lists many "pointer" symptoms and signs that may indicate a particular underlying etiology of cough (see Table 1 of the guideline). Cough is subdivided into **(a) specific cough,** associated with other symptoms and signs (ie, etiologic pointers) suggestive of an associated or underlying problem, **(b) nonspecific cough**, which is dry and nonproductive, absent of an identifiable respiratory disease and with normal chest radiograph and spirometry, and **(c) expected cough**, due to common upper respiratory viral infections in an otherwise healthy child where the cough duration is usually <2 weeks *but may be longer in a small minority*. The guideline provides algorithms for the management approaches and highlights that children with chronic cough should be followed closely and re-evaluated frequently. Symptomatic treatments for cough are only mentioned when discussing the management of *non-specific cough* (of undetermined cause) where it appears a trial of a medication may be appropriate. Codeine is subtly listed among "possible treatments for non-specific cough", however, with the notation that study evidence is lacking for this medication. Authors state, " …sometimes, a 'trial of therapy' is appropriate and if used, it is imperative that the children are followed up and medications ceased if there is no effect on the cough within an expected timeframe…"[51] A specific medication highlighted further for trial in non-specific cough was beclomethasone: "For children aged ≤14 years with non-specific cough, we suggest when risk factors for asthma are present, a short (2-4 weeks) trial of 400 mg/day of beclomethasone equivalent may be warranted, and these children should always be re-evaluated in 2 to 4 weeks."[51] Treatment with bronchodilators and corticosteroids may be both therapeutic and diagnostic.[52] The ACCP has recommended against the use of OTC cold and cough medicines. This was more clearly expressed in their 2006 recommendations when the panel recommended against the use of OTC cough suppressants, which included codeine, in children 14 years of age or younger with chronic cough. The panel suggested following adult guidelines for the management of chronic cough in adolescents 15 years and older, but that there was no good evidence to define what the exact cut-off age should be.[51] There appears to be limited/insufficient evidence to make recommendations for or against the use of codeine, based on ACCP adult guidelines for unexplained chronic cough or for chronic cough due to stable chronic bronchitis.[53,54]

Guidelines seem to offer little advice regarding scenarios with complications due to cough, or cough in which the child/adolescent experiences ongoing poor or little sleep, considerable limitation of daily

activities (eg, school or extracurricular) due to cough, injury or impeded healing due to cough, or social burdens from cough disturbance to self and others despite the use of non-pharmacologic agents. The provider's judgement with full consideration of the scale of impact on the patient's daily life is necessary to decide if suppression of a dry non-specific cough is appropriate. During an expert roundtable meeting with the FDA in 2017, representatives of key health professional societies highlighted that a cough suppressant may be considered if cough is causing *clinical consequences* including but not limited to consecutive nights of poor sleep, vomiting, rib fractures, or hypoxia.[52] Options for acute irritant cough mentioned were nasal saline, increased humidification, honey, treatment of post-nasal drip if present with antihistamine and physical maneuvers, bronchodilators or corticosteroids which can both be diagnostic and therapeutic, guaifenesin, and antitussives (dextromethorphan or benzonatate).

In 2020, the CHEST Expert Cough Panel published a scoping review to update information and identify gaps in research among the pediatric or adult populations regarding complications that may be associated with coughing.[55] The panel documented diverse serious complications of cough and described that negative effects of cough, especially sustained cough, may be augmented per the patient's scenario, age, and comorbid illnesses. Cough can have a negative impact on those undergoing or recovering from surgery or procedures, and cough may increase risk from the side-effects of medications (eg, corticosteroids or anticoagulants). Authors note that it makes physiologic sense to try to control cough before surgery to avoid wound dehiscence. After summarizing possible complications due to cough, the CHEST panel concluded that "clinicians should not underestimate the impact of coughing to patients due to the potential for serious and life-threatening complications to themselves or to others and the adverse effect on quality of life. It is not an inconsequential problem or concern and should not be trivialized."[55]

Codeine for Analgesia in Pediatric Patients

Codeine is generally used alone or in combination with acetaminophen (APAP) for the treatment of *mild to moderately* severe pain when non-opioid alternatives are either inadequate upon trial, not expected to provide adequate analgesia, not tolerated upon trial, or are not expected to be tolerated.[11,18] Codeine is available as a single-ingredient product, as tablets.[18] The oral solution as a single-ingredient is no longer available in the US. Codeine/APAP is available as both an oral solution and tablets.[11,24] Dosing in pediatric patients has typically been between 0.5 to 1 mg/kg/dose every 4 to 6 hours as needed (and a maximum single dose of 60 mg). Prior to the 2017 labeling changes, pediatric dosing was included in the package insert for codeine/APAP solution for as young as 3 years of age.[56] While labeling for codeine containing-products no longer include pediatric dosing, literature documented doses are provided in LexiComp and past publications.[57-60] The LexiComp monograph for codeine also notes the approach of CYP2D6 genotype testing for the limited pediatric cases that may require and benefit from codeine use.[61]

There may be scenarios in which codeine is preferable or more feasible to prescribe especially for patients that are followed closely and already have their genotype determined and/or response to codeine determined (perhaps while inpatient). Alternative opioids (eg, morphine, oxycodone), which are all schedule II controlled substances (CII), maybe not be as feasible to prescribe depending on the patient's situation since these products come with additional restrictions that may impede prompt access (ie, refills not allowed, inability of some provider systems to issue electronic prescriptions for a schedule II substance).[61] Gammal and colleagues described implementation of a precision-medicine

approach (ie, based on genotyping) for prescribing of codeine for pediatric patients (from 9 months to 18 years) who received care at St. Jude Children's Research Hospital for catastrophic illnesses.[61] Preemptive pharmacogenetic testing results for the patients' *CYP2D6* genotype were incorporated into the electronic health record (EHR) to help inform the prescribing or avoidance of codeine.[61] Despite innovative approaches such as precision medicine via genotyping, weak opioids such as codeine and tramadol are no longer recommended by the World Health Organization (WHO) as options for pediatric pain management; these agents have been removed from the list of essential medicines for children due to the associated unpredictable response to these therapies.[62-64] Due to the limited evidence for pharmacotherapies for pediatric chronic pain, the 2020 WHO guideline provided a generalized recommendation rather than preference for a specific drug class: "In children with chronic pain, appropriate pharmacological management, tailored to specific indications and conditions, may be used (conditional recommendation, low certainty evidence)."[63] For cancer-related moderate to severe pain, in 2018, WHO advised that mild analgesics (APAP and NSAIDs) should not be given alone but instead could be used in combination with an opioid.[65]

Treatment of Pain in Pediatric Patients

In **2019, the DHHS Pain Management Best Practices Inter-Agency Task Force** (DHHS-BPITF) published identified gaps in care and recommendations related to pain management. The lack of FDA-approved treatments specifically for pediatric patients (and for moderate to severe pain in general) leaves off-label use of therapies to accommodate the treatment need, which may be based on observational evidence and is highly reliant on expert experience and consensus.[66,67] Authors of the best-practices report advised that health systems must consider/address the needs of children/youth with unique challenges associated with acute and chronic pain, including individuals with relapsing pain conditions such as sickle cell disease (SCD).[67] Pediatric patients suffering from pain may experience suboptimal care related to (i) a significant shortage of pediatric pain specialists and comprehensive pain service centers, possibly due to reimbursement issues, and (ii) a lack of best practices guidance among some health systems for off-label prescribing of both opioids and non-opioid pharmacologic options. To meet the needs of pediatric patients, the task force recommended developing pediatric pain management guidelines for responsible opioid prescribing[67]—as opposed to eliminating pediatric opioid prescribing completely despite their associated risks and limited evidence. "In the current environment, patients with chronic pain — particularly those being treated with opioids — can be stigmatized."[67] Poor pain management in children may cause harm by subjecting the patient to persistent pain leading to impairment in daily functioning, learning, extracurricular activities; such an adverse experience could perhaps increase the risk of developing psychological conditions such as depression.[68]

Acute Pain

Tonsillectomy and adenoidectomy are common surgical interventions employed to treat recurrent tonsillitis and obstructive sleep apnea (OSA).[69,70] Prior to the 2013 FDA-issued contraindication, codeine was widely prescribed for pediatric post-tonsillectomy pain.[36] With growing rates of obesity and obstructive sleep apnea, tonsil and adenoid surgery remain common procedures.[71] This surgery is often performed as an outpatient procedure with same-day discharge. The risks involved with rapid discharge followed by limited at-home monitoring has been highlighted by several authors. Surgery does not immediately correct respiratory insufficiency related to OSA, which can leave individuals more vulnerable to the respiratory depressant effects of opioids compared to their healthy counterparts.[72,73]

The biological plausibility that children with obstructive sleep apnea are more sensitive to opioids has been taken into consideration by the FDA over the years, thereby arriving at the contraindication for codeine in post-tonsillectomy/adenoidectomy setting.[36,74,75]

Treatment recommendations or practice points made in recent clinical guidelines by the **American Academy of Otolaryngology-Head and Neck Surgery** have included the following:

- Strong recommendation against the use any medication containing codeine following tonsillectomy in children younger than 12 years (2019)[76]
- "Clinicians should advocate for nonopioid medications as first-line management of pain after otolaryngologic surgery." (2021)[77]
    - Acetaminophen as monotherapy has limited ability to control post-tonsillectomy pain; though, it can be used as add-on therapy to NSAIDs (2019)[71]
    - NSAIDs are an option for pain control, as systematic reviews and RCT evidence suggest they are not associated with increased risk of bleeding or readmissions (but ketorolac remains controversial) (2019)[71]
        - Specialists however, still note potential adverse events and uncertainties with NSAIDs regarding bleeding *severity*, an endpoint often not addressed in RCT or systematic review evidence.[78,79] There are case reports and observational evidence suggesting that ibuprofen may increase the severity of bleeding (ie, requirement for transfusion) in those who experience post-tonsillectomy hemorrhage while on ibuprofen. Yet, at least the evidence shows that the risk of hemorrhage (ie, incidence rate) is not increased with postoperative use of ibuprofen.[79]
- If opioids are required, oxycodone and morphine seem the best options rather than selection of codeine, tramadol, or hydrocodone which are significantly metabolized by CYP2D6 (2019).[71] Clinicians should limit opioid therapy to the lowest effective dose and duration possible, and **educate patients to stop opioids when pain is controlled with non-opioids** (2021).[77]

For perioperative acute pain, there is evidence suggesting that NSAIDs can be used first-line for pain management in many cases,[80] otherwise, NSAIDs may be used to reduce opioid requirements as combination therapy.[81] Multimodal approaches are being employed in various settings (eg, post spine deformity surgery, neurosurgery) where NSAIDS, APAP, gabapentin, and neuraxial or regional nerve blocks (ie, anesthetic) may be incorporated to reduce total opioid consumption following operation.[82-84] A 2021 consensus-based guideline by the American Pediatric Surgical Association (APSA) Outcomes and Evidence-based Practice Committee provides a table of surgery types in which an opioid-free recovery (OFR) is recommended for most patients, and surgery types for which an OFR may be possible in some patients.[84] Refer to Table 4 of the guideline for a full list of surgeries in each category; the following bullets list some examples:

- OFR recommended for most patients: central line placement, soft tissue excision, umbilical/epigastric/or inguinal hernia repair
- OFR *may* be possible in some patients: laparoscopic procedures, tonsillectomy/adenoidectomy

At discharge, the APSA consensus statement recommend non-opioid option(s) as first-line; though, authors note that their review "…did not include a search of complications associated with non-opioid

medications, which should be considered when clinically applicable."[84] With respect to codeine, the panel endorses the FDA guidance (ie, warnings and contraindications) concerning pediatric use.[84]

In 2013, the European Medicines Agency reviewed literature regarding pediatric codeine use and concluded that NSAIDs had at least equal or better efficacy vs. acetaminophen/codeine for **musculoskeletal pain/extremity injuries**.[85] Authors of a 2020 systematic review that evaluated ibuprofen vs opioids for musculoskeletal pain in children presenting in the emergency department (ED) concluded that "…there is no straightforward statistically significant evidence of the optimal analgesic agent to be used," but that the favorable pain relief and tolerability profile of ibuprofen make it an initial drug of choice for ***mild-to-moderate*** **musculoskeletal pain**.[86] Regarding *post-discharge* musculoskeletal pain management, a 2021 SR, located 1 RCT comparing oral ibuprofen to oral codeine-products in the pediatric population.[87] This 2009 RCT found "…no significant difference in analgesic failure or pain scores between ibuprofen and acetaminophen/codeine, but children receiving ibuprofen had better functional outcomes."[88] Expert reviewers advise that the evidence so far places ibuprofen as a preferable first-line option for pediatric pain due to extremity musculoskeletal injury, especially for minor sport-related musculoskeletal extremity injury.[89] Nonetheless, 2 of the 5 RCTs in total, of ibuprofen vs. any opioid for management of pediatric musculoskeletal pain reported that only 52% of children treated with ibuprofen in one study[90] and 29.9%[91] in the other study achieved adequate analgesia at 60 min after ibuprofen treatment. Thus, while ibuprofen alone may be sufficient for *some* children with musculoskeletal injury, many may still require rescue therapy.[87] Additionally, there is debate and uncertainties regarding whether NSAIDs impede bone healing, or if NSAID use is associated with wound infections or bleed complications.[92,93]

Chronic Pain

Between 5% to 38% of children and adolescents are estimated to suffer from chronic pain.[67] Chronic pain may stem from a variety of congenital diseases (eg, sickle cell disease) and non-congenital diseases (eg, juvenile idiopathic arthritis, fibromyalgia[94], inflammatory bowel disease, headaches, chronic abdominal pain, chronic musculoskeletal pain, complex regional pain syndrome).[67] Unfortunately, there is a paucity of high quality evidence regarding pharmacologic interventions (opioid and non-opioid options) for chronic pediatric pain.[66,95,96] In 2017, Cochrane systematic reviews reported no RCT evidence for the management of pediatric **non-cancer chronic pain** with respect to opioids (including codeine)[97] or acetaminophen;[98] and low or very low quality of evidence for NSAIDs,[99] antiepileptics, and antidepressants.[100,101] It should also be considered that there is no strong evidence for the use of NSAIDs for certain chronic pain conditions such as neuropathic pain or fibromyalgia in general.[102-104] Similarly, for **chronic cancer pain**, due to the lack of RCTs in children, Cochrane authors were unable to evaluate the harms or benefits of opioids (including codeine).[105-107]

In 2020, the Canadian Agency for Drugs and Technologies in Health commissioned a review of clinical guidelines addressing **chronic pain** treatment in pediatric patients. They found only one evidence-based guideline meeting their inclusion criteria.[108] In this 2018 guideline by the Scottish Government, authors describe limited evidence for pharmacotherapies for the management of pediatric chronic pain.[96] Regarding opioids, authors advised that "Strong opioids should be used with caution and only with specialist advice or assessment," as these are not for routine use but are reserved for when other analgesics are ineffective.[96] Codeine was not recommended in children under the age of 12, or adolescents with respiratory problems or known CYP2D6 rapid metabolizers.[96]

A 2021 consensus statement by the European Pain Federation (EFIC) for the management of **chronic non-cancer pain**, recommends that opioids can be employed for "…exceptional cases and in specialized centres for pain therapy in children and adolescents."[109] Although it may be ideal to have pediatric patients managed by pain specialists, this may not be feasible for all patients, as the DHHS has pointed out a shortage of such specialists.[67]

Further information from guidelines regarding specific pain etiologies or pain types are discussed in the following sections.

Sickle Cell Disease Related Pain

The DHHS-BPITF guidance document expounds upon sickle cell disease (SCD), a condition with unpredictable acute pain episodes, or "pain crises," and chronic severe daily pain affecting about 30% to 40% of patients with SCD.[67] SCD-related pain significantly impairs daily functioning and the majority of patients tend to fail non-opioid medications. Opioid prescribing constrains may not allow for an individualized approach or opioid supply to cover unplanned acute pain crises; such constraints can result in increased healthcare utilization.[67] The panel recommended that access to safe/appropriate use of opioids (with close follow-up and at the lowest effective dose) be protected for patients with SCD and ***consideration be given for exempting patients from restrictions that do not specifically address patients with SCD.*** Experts have advised that "Health care professionals must appreciate the severe nature of the pain and the urgent need for effective pain relief therapies."[110] In a 2019 expert review, authors recommended against the use of codeine for routine SCD pain treatment. When opioids are required, formulations containing morphine, oxycodone, or hydromorphone, are commonly selected since these are not affected by CYP2D6 polymorphisms to the same degree that codeine is.[111]

Neuropathic Pain (NeP)

NeP can occur as a symptom (acute or chronic) in pediatric conditions. For example, 5% of shingles cases occur in children and about 1 in 4 of these pediatric cases develop postherpetic neuralgia, according to the Dallas Children's Medical Center.[112] Moreover, children are not invincible to traumatic injury/accidents that may cause neuropathic damage/pain or other neuropathic pain causes (complex regional pain syndrome, congenital diseases, diabetic peripheral neuropathy[113], metabolic related, cancer, or cancer-treatment related).[114,115] The 2015 NeuPSIG guideline described that research for the treatment of neuropathic pain in children is a neglected area despite the wide treatment need.[103]

In the 2020 French recommendations for neuropathic pain authors describe that due to the lack of high-quality studies, recommendations for the pediatric population were based on expert consensus. Authors recommended gabapentin (10 to 30 mg/kg per day, TID) or amitriptyline (0.3 to 1 mg/kg/day once per day) first-line for neuropathic pain in children. Other options used in adults can be considered such as topical lidocaine, as a first-line option for localized, peripheral neuropathic pain. In the event of insufficient pain relief with these options, a switch in agent or combination regimen with gabapentin/amitriptyline is recommended. Psychological support and/or physiotherapy should be provided as add-on treatments. If the aforementioned approaches fail, the child should be referred to a pediatric chronic pain clinic where other interventions or pharmacotherapies such as opioids can be considered.[116] In a 2019, expert prepared algorithm for pediatric oncology, authors include gabapentinoids, tricyclic antidepressants (TCAs), and methadone as first-line options for pediatric

cancer-related neuropathic pain; and lidocaine 5% patches, ketamine, and other strong opioids as second-line therapy.[117]

For neuropathic pain that is localized and peripheral, the guideline by the 2018 Scottish government recommended considering lidocaine 5% patches, otherwise, gabapentin is a first-line option for neuropathic pain. Low dose amitriptyline or nortriptyline can be selected for certain types of pain such as functional gastrointestinal disorders, chronic daily headache, chronic widespread pain, and mixed nociceptive/neuropathic back pain. For non-malignant, *unspecified pain*, authors recommended considering acetaminophen and/or NSAIDs; though these too, do not have high-level evidence for their long-term use in pediatric chronic pain.[96]

Migraine Pain

Codeine-containing or butalbital-containing products are not among recommended treatment options for migraine in children. Rather, the 2019 guideline by the American Academy of Neurology (AAN) recommends nonprescription oral analgesic options (eg, acetaminophen or ibuprofen) or triptans (eg, almotriptan, sumatriptan/naproxen, and zolmitriptan nasal solution are approved for patients aged 12 years and older; and rizatriptan is approved for patients aged 6 years and older).[118] Other approaches such as biofeedback training should also be considered since this has shown to be beneficial for chronic headache and migraine in children.[67]

- The codeine-butalbital products available on the market are approved for tension headache in adults, and their safety and efficacy have not been established in the pediatric population.[119,120]

Alternative Opioids to Codeine for Analgesia

An opioid analgesic may be required for *moderate to severe pain* when NSAIDs and acetaminophen are in inadequate or inappropriate, or when neuromodulator options are insufficient for neuropathic pain. However, "evidence for the most appropriate dose and type of opioid for rescue analgesia is limited."[121] During the FDA's review of codeine, the FAERS database was also searched in 2012 for adverse events related to pediatric prescribing of hydrocodone, oxycodone, and morphine. There were no identified adverse event cases unconfounded by other factors; identified serious adverse events were either related to drug-drug interactions impairing the metabolism of hydrocodone or confounded by physical obstruction of the airway.[36]

I. The following bullets summarize comments regarding alternative opioids among key guidance reports published in recent years.

- In 2016, the AAP commented that "Data are currently insufficient to unequivocally endorse the widespread use of oxycodone in infants and children."[30]
- In 2019, The American Academy of Otolaryngology-Head and Neck Surgery described that if opioids are required, oxycodone and morphine seem to be the best options rather than selection of codeine, tramadol[‡,122], or hydrocodone which are significantly metabolized by

[‡] Tramadol is contraindicated in children <12 years of age for any use and in children <18 years of age following tonsillectomy and/or adenoidectomy. Product labeling also advises to avoid tramadol in pediatric patients 12 to 18 years of age with considerable risk factors for respiratory depression (eg, obesity, OSA, or severe lung disease).[9] Tramadol undergoes conversion to an active metabolite (O-desmethyl tramadol) primarily by CYP2D6; other CYP

CYP2D6.[71] Clinicians should limit opioid therapy to the lowest effective dose and the shortest duration, and educate patients to stop opioids when pain is controlled with non-opioids.[77]

- The 2020 WHO guideline for pediatric chronic pain includes morphine as an opioid option.[123] The WHO essential medicines list for pediatric patients notes that alternatives to morphine are hydromorphone and oxycodone; and that methadone additionally is an option for the management of cancer pain.[124]
- The 2021 guidance by CPIC, nonspecific to peditric prescribing, does not make recommendations for avoidance of oxycodone based on genotype/phenotype because evidence of is unclear. Data is conflicting, particularly for ultra-rapid metabolizers, from prospective studies regarding the association of CYP2D6 genotype/phenotype and the analgesic or toxicity effects of oxycodone.[26] Studies to optimize oxycodone dosing in pediatric patients are in progress.[125,126] Based on the evidence available, CPIC notes that use of hydrocodone at the age-specific or weight specific dosage can be considered in CYP2D6 normal, intermediate, and poor metabolizer CYP2D6 phenotypes.[26]
- The 2021 Canadian Pediatric Society position statements recommended that "Analgesics should be used in a stepwise manner, beginning with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) before progressing to opioids;"[127] though, authors do not address whether these agents are effective for neuropathic pain. For an alternative opioid to codeine, authors state that oral morphine has the "…strongest evidence base for efficacy and safety."[127]

II. Metabolism considerations for oxycodone, hydrocodone, and morphine

- **Oxycodone** is an active analgesic as the parent molecule; 7% is excreated as the parent molecule through the kidneys.[128] The ***CYP3A4*** enzyme is cited as a major metabolic pathway, by which approximately 50% of the oxycodone dose is N-demethylated to noroxycodone with very little analgesic activity. Noroxycodone is further metabolized to noroxymorphone, a metabolite which may contribute to mu-receptor-related effects.[128-130] CYP3A5 is also reported to play a role in oxycodone N-demethylation.[131] About 18% of the oxycodone dose undergoes keto-reductase to metabolites not known to be active.[128] The remaining 10% of the oxycodone dose is metabolized by ***CYP2D6*** to oxymorphone. It is not clear to what extent a CYP2D6 ultra-rapid phenotype alters the toxicity risk of oxycodone.[26] Oxymorphone seems to contibute to the analgesic effect to a similar extent as the parent compound, oxycodone.[128]
- **Hydrocodone**: **CYP2D6** plays a role in the metabolism of hydrocodone in normal metabolizers: 5% of the dose is converted to the more potent hydromorphone metabolite. An eightfold greater plasma concentration in the active metabolite, hydromorphone, in ultra-rapid metabolizers has been reported.[26,30] **CYP3A4** is the primary metabolic pathyway, by which hydrocodone is converted to norhydrocodone[132,133] a metabolite with unclear effects. The 2021 CPIC guideline includes hydrocodone as an option for patients with CYP2D6 normal, intermediate, and poor

enzymes, 3A4 and 2B6, also metabolize tramadol to a metabolite (N-desmethyl-tramadol) not known to have significant activity.[122]

CYP2D6 metabolizer phenotypes; no recommendation is made for patients who are CYP2D6 ultra-rapid metabolizers due to insufficient evidence on effects.[26]

- **Morphine** is primarily metabolized by uridine 5'-diphosphoglucuronosyltransferase (UGT) isoforms (mainly **UGT2B7**) to an active metabolite, morphine-6-glucuronide (M6G) and to inactive morphine-3-glucuronide (M3G). These metabolites, with M6G thought to be the most problematic, have been documented to accumulate in renal insufficiency with unadjusted dosing.[134-136] Genetic polymorphisms of the UGT enzyme occur; however, the impact on safety is unclear.[14] Although seldomly mentioned in review literature, CYP3A4 may also play a minor role in the metabolism of morphine, converting the drug to normorhine which may have activity.[20,137] The organic cation transporter, OCT1, is responsible for hepatocellular uptake of morphine and polymorphisms of its corresponding gene may increase the risk of adverse effects from morphine or its precursors (ie, codeine).[20] Animal models also suggest that inhibition of P-glycoprotein potentiates opioid effects by increasing the morphine CNS concentration.[138,139] Clinically important drug interactions and adverse effects such as respiratory suppression byway of inhibition of P-glycoprotein have also been demonstrated with other opioids (eg, loperamide).[140,141]

Ultimately, more research is needed to determine the influence of pharmacogenetic factors on the analgesic and toxicity effect of alternative opioids in the pediatric population.[26,41,127]

Abuse/Misuse Consideration

The 2021 consensus-based guideline by the American Pediatric Surgical Association Outcomes and Evidence-based Practice Committee highlights the risk of opioid misuse and abuse in adolescents, as adolescents' own prescription (eg, left over supply) is the 2nd top source for misused opioids in adolescents (the 1st being diverted from sources). Moreover, adolescents are likely to divert their left-over opioid medication if approached.[84] In the 2016 opioid prescribing guideline by the CDC, authors mention survey-based studies finding that 20% of adolescents prescribed an opioid reported abusing them or using them to augment other drugs[142], and that exposure to opioids "…before high school graduation is associated with a 33% increase in the risk of later opioid misuse."[143,144]

- Judicial use of opioids in adolescents, and tracking of a patients' controlled substance prescription history (ie, using the state's controlled substance database) cannot be over emphasized.

Utah Medicaid Drug Utilization

Tables 2 and 3 show the number of paid claims for codeine-containing products (analgesics in one table and cough products in the other) for pediatric patients (age 0 to <18 years) in the fee-for-service (FFS) Utah Medicaid population from 2019 through 2021[§].

- In 2021 there were **34** pediatric patients who used a codeine/APAP product (analgesic formulation), and **20** patients who used a codeine-containing antitussive product.
- There were no pharmacy fills for the single-ingredient codeine product, codeine/butalbital combination products, codeine/carisoprodol products, or the long-acting branded products (Tuzistra, Tuxarin) among pediatric patients during the 2019-2021 period.

Table 2. APAP/Codeine Analgesic Formulations, Pharmacy FFS Claims and Patients

	2019		2020		2021	
	Counts	Patients	Counts	Patients	Counts	Patients
APAP/CODEINE **SOL** 120-12/5	10	10	<5	<5	<5	<5
APAP/CODEINE TAB 300-**15**MG	<5	<5	0	0	0	0
APAP/CODEINE TAB 300-**30**MG	28	26	31	28	36	30
APAP/CODEINE TAB 300-**60**MG	0	0	0	0	<5	<5
Total APAP/Codeine Use	<43	<42	<36	<33	42	**34**

Table 3. Codeine Cough Liquids, Pharmacy FFS Claims and Patients

	2019		2020		2021	
	Counts	Patients	Counts	Patients	Counts	Patients
Guaifenesin-Codeine Liquid 100-10/5ml	37	34	<5	<5	8	7
Promethazine/Codeine SOL 6.25-10/5mL	34	29	17	16	17	13
Total Codeine Antitussive Use	71	63	<22	<21	**25**	**20**

The age distribution of patients receiving codeine-containing products in 2021 is shown in Tables 4 and 5 for the main product types: Codeine/APAP or Codeine Antitussive Liquid.

Table 4. Age Distribution of Pediatric Patients Using Any *APAP/Codeine* Formulation in 2021

Age at time of claim	Patients Count
<12 years	8
12 to <18 years	26

Table 5. Age Distribution of Pediatric Patients Using Any Codeine *Antitussive Liquid* in 2021

Age at time of claim	Patient Count
<12 years	8
12 to <18 years	12

[§] Utilization data was pulled on Jan. 6th, 2022.

The comparison of codeine prescription claim counts in 2016 versus 2021 counts (Table 6) suggests that prescribers are now selecting codeine for the pediatric patients much more judiciously overall, following the 2017/2018 FDA labeling changes. This is true across both categories of codeine products (ie, antitussives and analgesics).

Table 6. Comparison of 2016 and 2021 Pediatric Pharmacy Claims Overall

Year	**2016**	**2021**
Pediatric Claims for **APAP/Codeine**	297	42
Pediatric Claims for **Codeine Cough Liquids**	476	25

Nonetheless, since acute prescribing of codeine occurred in a small number of patients under 12 years of age over the last year, prior authorization criteria could help ensure that these are exceptional scenarios where prescribers have (a) exhausted non-codeine options for cough (for pediatric patients receiving codeine antitussives) with cough having clinical consequence; or (b) have supportive rationale for those receiving codeine/APAP (as further discussed in the next section). It is also worth considering whether non-opioids for cough, such as over-the-counter products (honey, nasal saline, dextromethorphan) are coverable *upon prescription* for Medicaid patients, as these options are not listed among the OTC list of covered products for Utah Medicaid patients, as of January 2022. If there are no covered non-opioid alternatives for patients with cough, then this could be influencing the prescriber's selection of treatment.

Potential Age Restrictions and Prior Authorization Criteria

Additional drug-specific prescribing criteria for codeine may be considered to supplement the already existing criteria in place for short-acting opioids. See Table 7 and Table 8 for a list of codeine-containing products that fall into the categories mentioned in the considerations below.

A. Utah Medicaid currently requires a prior authorization for greater than a 7-day supply of short-acting-opioid use (which encompasses codeine) in children <18 years, to express the clinical rationale.

   - Requirement for a prior authorization even for short-term use (ie, less than a 7 day supply) can be considered for codeine/APAP products in **codeine naive** patients (without *any* history of codeine use) who are 11 years and younger as this opioid is FDA-contraindicated in this age group. Medical necessity may be considered on a case-by-case basis, for instance, in patients who have already received codeine without adverse events while inpatient or in their history (ie, may grandfather in some patients who have a history of use for severe/serious conditions and who have already demonstrated favorable response to codeine, or who have CYP2D6 genotype determined to guide prescribing). Additional considerations/limitations listed in bullet C.1. can be applied to this age group.

B. Age limits are currently in place for Utah Medicaid patients with respect to codeine/guaifenesin cough preparations with use restricted to 12 years and older; and for headache products with codeine/butalbital, restricted to adult use only.

   - The labeled contraindications for codeine prescription products support this age restriction for codeine cough products. The FDA's rationale seemed mainly geared toward the negative risk/benefit profile of codeine for pediatric patients with respect to treating acute cough associated with allergies or viral infections (ie, common cold). In addition, we recommend placing an age restriction on codeine/promethazine products if not already in place. This combination is not mentioned in the PDL, yet paid pediatric claims occurred in 2021 (some for children younger than 12 years of age). An additional concern with this combination is that children may be more sensitive to the additive respiratory depressant effect of promethazine *(black box warning)* when combined with CNS depressants such as codeine. [29]
     - Prior authorization ctieria may aslo be considered for codeine antitussives as referred to in bullet C.2. on the following page.
   - For codeine-butalbital preparations intended for headache, none of these agents appear to have a place in therapy for pediatric migraine based on the recommended therapies among the 2019 AAN guideline.[118] Thus, we recommend continuing the age restriction for that group of products.

C. Potential prior authorization criteria for use in patients 12 years of age or older to ensure prescriber considers potential risk factors, contraindications, warnings, and potential alternative options:

1. For **<u>treatment of pain</u>** in patients 12-17 years of age with codeine single-ingredient tablets or codeine/APAP liquid or tablets, consider having the provider **attest to the following:**
   - Use is not for post-tonsillectomy or adenoidectomy pain **or** for patients with OSA
   - Other potential respiratory risk factors have been considered/addressed by dose adjustment and close monitoring (eg, obesity, additive effects from concomitant CNS depressants, renal insufficiency, p-glycoprotein inhibitors or CYP inhibitors/inducers[**])
   - Other alternatives have been considered as either
     a) Inappropriate, for example with respect age, contraindication, co-morbidities, or potential interaction with concurrent medication, or
     b) Expected to provide inadequate pain relief (or have already been trialed) with respect to pain severity and/or residual pain; or pain type

     Provider to attest that each analgesic option has been considered, indicating the rationale as either a) or b)
     i. NSAIDs and/or APAP
     ii. Other opioid alternatives (eg, morphine, oxycodone)
     iii. For neuropathic pain, topical lidocaine for peripheral/localized pain; or other neuromodulators (eg, TCA or gabapentin)

2. For **treatment of <u>chronic cough</u>** in patients 12-17 years of age with codeine-containing cough syrups/liquids:
   - Treatment of *acute cough* with codeine prescription antitussives (eg, codeine/promethazine) may be restricted to adults, as FDA and experts have advised that they should not be used for pediatric acute cough (eg, for common cold or viral infections) due to the negative risk/benefit profile
   - Case-by-case consideration may be made for pediatric patients (12-17 years of age) for the use of codeine as an antitussive *for non-specific chronic cough* if requested by a specialist (eg, pulmonologist) in addition to provider attesting that
     - Use is not for a patient with OSA, or post-tonsillectomy/adenoidectomy status
     - Other potential respiratory risk factors have been considered/ addressed by dose adjustment and close monitoring (eg, obesity, additive effects from concomitant CNS depressants, renal insufficiency, p-glycoprotein inhibitors or CYP inhibitors/inducers)
     - Other alternatives (eg, inhaled beclomethasone if risk factors for asthma are present[51], honey, hydration, dextromethorphan, benzonatate [††,10,145]) are either
       a) Inappropriate, for example with respect age, contraindication, co-morbidities, or potential interaction with concurrent medication, or
       b) Unavailable or not covered for the patient, or
       c) Were tried and failed

[**] Due to potential to increase codeine conversion to morphine directly or indirectly, codeine is not recommended in combination with inducers or inhibitors of CYP2D6 or CYP3A4. Avoidance with p-glycoprotein inhibitors should also be considered.

[††] Benzonatate is only available as a capsule to be swallowed whole and should not be used in patients less than 10 years of age. The FDA has issued a safety warning regarding overdoses in children below 10 years of age.

D. **Table 7** summarizes the aforementioned considerations based on formulation and summarizes dosing information from package inserts or references such as LexiComp:

Table 7. Codeine Formulations and Restriction Considerations

Codeine Analgesics	
Consider restricting use to patients 12 years of age and older who meet prior authorization criteria • Case-by-case consideration can be made for patients<12 years of age with catastrophic illnesses especially if oral liquid morphine is unavailable or inaccessible, patient is genotyped and/or already has a history of use without adverse events, etc	
Codeine • Tablets 15 mg, 30 mg, 60 mg **Codeine/acetaminophen** • Liquid: 12-120mg/5 mL • Tablets: 15mg-300 mg; 60mg-300 mg	Dose limits may be based on the historical dose of codeine in children: 0.5-1 mg/kg Q4-6hour (max dose of 60 mg).[57-60,146] The maximum dose of APAP should also not be exceeded (ie, the lesser of either 75mg/kg/day or 4,000 mg/day, and no more than 5 daily doses)[147]
Codeine Antitussives	
Consider restricting use of codeine-containing antitussives to patients 12 years of age and older who meet prescribing criteria: use for **chronic** cough in patients 12 or older maybe considered on a case by case based upon prescription from specialist (eg, pulmonologist); use should generally not be for purposes of acute infection, allergy, or asthma mediated. Special considerations may also be made based on severe complications from cough in unique scenarios (eg, wound dehiscence due to cough forces following surgery).[55]	
Codeine/Promethazine • Generic syrup (10mg-6.25mg/5mL) **Codeine/Phenylephrine/ Promethazine** • **Promethazine VC** syrup and generics (10mg-5mg-6.25mg/5mL)	• Due to the potential additive toxicity of promethazine (ie, respiratory depression), codeine/guaifenesin seems more favorable • Prior to the 2018 label changes, dosing for 12 years of age and older was 5 mL every 4 to 6 hours, not to exceed 30 mL per day[148,149]
Other Cough Products • Codeine/Guaifenesin • Codeine/Guaifenesin/ Pseudoephedrine • Codeine/Phenylephrine/ Triprolidine	*Dosages on OTC labeling for 12 years and older*[42-44] • Virtussin AC (Codeine/Guaifenesin): 10mg-100mg/5mL; 10mL every 4 hours, max of 6 doses per 24 hours • Coditussin DAC (Codeine/Guaifenesin/ Pseudoephedrine): 10mg-200mg-30mg/5mL; 10 mL every 4 to 6 hours; no more than 32mL per 24 hours • Histex-AC (Codeine/Phenylephrine/ Triprolidine): 10mg-10mg-2.5mg/5mL; 5 mL Q4hr, max of 20 mL/24 hours

E. There are several codeine-containing formulations, listed in **Table 8**, that do not appear appropriate for pediatric patients. Co-formulated ingredients butalbital and carisoprodol can have additive CNS-depressant effects and their combination with codeine does not appear established for the pediatric population. Moreover aspirin is generally not recommended in pediatric patients due to the potential to cause Reye's syndrome.[120] None of the listed formulations, including the long-acting codeine/chlorpheniramine products in Table 8, have a particular place-in-therapy mentioned among pediatric-specific guidelines reviewed.

Table 8. Formulations for Potential Complete Restriction in Patients 17 years of Age and Younger

Codeine-butalbital combinations products • Codeine/APAP/Butalbital/Caffeine • Codeine/ASA/Butalbital/Caffeine	*Consider restricting use to **adults** only* Codeine or butalbital are not recommended for pediatric migraine; we are not aware of a current guideline that recommends these products in the pediatric population.
Codeine-aspirin combination products • Codeine/ASA/Butalbital/Caffeine • Codeine/ASA/Carisoprodol	*Consider restricting use to **adults** only* Preparations containing aspirin have potential to cause Reye's syndrome in pediatric patients[120]; butalbital and carisoprodol were not identified to have a place-in-therapy among reviewed guidelines
Codeine/Chlorpheniramine • **Tuzistra XR Liquid** and **Tuxarin ER Tablet**	*Consider restricting use to **adults** only* These long-acting cough products are only indicated for adults, and there is not sufficient clinical experience in pediatric patients that we are aware of

Additional Consideration

- Additive toxicity with concurrent CNS depressants; *may consider restiction against pediatric use of codeine in combination with benzodiazepines*
    - Codeine produts include a *black box warning* regarding use in combinaton with other CNS depressants such as benzodiazepines. Additionaly, the toxicity risk may be compound with those cough/cold codeine products that also contain promethazine, as labeling for these also includes a *black box warning* that children may be more sensitive to additive respiratory deppressant effects when promethazine is combined with codeine and/or other CNS depressants.

Example of Other States' Criteria

Table 9 summarizes codeine-specific pediatric restrictions from 6 other state Medicaid programs. For brevity, we focused on extracting restrictions that were specifically developed for codeine use in pediatric patients rather than general opioid prescribing restrictions/limits that many states have in place. As shown in the table, many of the states we reviewed have implemented a blanket pediatric restriction for the codeine-containing products; however, the strictness is variable among the sample, as differing criteria (eg, age or medical conditions) and methods (eg, point-of-sale edits vs prior authorization) are used.

Table 9. Selected State Medicaid[a] Requirements for use of Codeine in Children

Age Restriction	***Additional pediatric-specific criteria located***	***Notes***
California[150]		
≥ 2 y, for codeine/ promethazine/ ±phenylephrine	*None found*	*Uniform quantity limits (not specific to age) are in place for all opioids*
Iowa[151]		
≥ 12 y for codeine	If 12 and 18 years, must also meet these requirements: ▪ Med is *not* for treatment of pain post-tonsil/adenoid surgery ▪ Patient is not obese (BMI < 30 kg/m^2) ▪ Patient does *not* have OSA or severe lung disease	Age-edit override; prior authorization required for <18 years of age
Louisiana[152]		
▪ ≥ 18 y for codeine as *single ingredient* ▪ ≥ 12 y for codeine *combination* products	*None found*	▪ Age restriction implemented as a point of sale edit
Mississippi[153]		
≥ 18 y for codeine products		*No pediatric exemptions for codeine were found*
Oregon[154]		
≥ 13 y for codeine products	If age 13 to 18 y, must also meet these requirements: ▪ Must be for a funded condition[b] ▪ Patient did *not* have a recent tonsillectomy or adenoidectomy Quantity limits for pediatric use of codeine: max daily dose of 240 mg, and up to 3 day supply	Codeine pediatric-specific PA required for age <19 years old
Washington[155]		
For patients age 20 y or younger, a PA is required to describe medical rationale for selecting codeine rather than non-pharmacologic or non-opioid medications		Requests for supply exceeding the specified dispensing limits are considered on a case-

Table 9. Selected State Medicaid[a] Requirements for use of Codeine in Children	
Pediatric-specific dispensing limits apply. If used for acute pain unrelated to cancer, hospice/palliative/or end of life, the limits for short-acting opioids for children (≤20 years) include up to 18 dosages or up to 120 daily MME per prescription, and up to a 42 calendar day supply within a 90 day period. Use for longer duration requires a chronic-use prior authorization.	by-case basis to accommodate medical necessity for unique circumstances supported by clinical judgement and documentation

Abbreviations: APAP, acetaminophen; BMI, body mass index; MME, morphine milligram equivalents; OSA, obstructive sleep apnea; PA, prior authorization; y, years old;
[a] Information from each state's Fee-for-Service (FFS) program (or combined FFS and accountable care organization program)
[b] Funded conditions are not stated on the PA form, but cough and pain are listed as example conditions for use of codeine.

Conclusion

Codeine is a prodrug which produces an analgesic effect by way of its active metabolite, morphine. Conversion to morphine is dependent on CYP2D6 metabolism, which is an enzyme with variable expression (ie, polymorphism) in the general population. Population variation in CYP2D6 metabolism phenotype, and particularly the ultra-rapid metabolizer phenotype, is a main issue resulting in unpredictable safety with codeine in children, while the poor CYP2D6 metabolizer phenotype arises the issue of insufficient efficacy with codeine. If a patient's genotype is unknown and they haven't already demonstrated tolerability and positive response to a prescribed codeine regimen, the effect of codeine has some degree of unpredictability. Potential negative repercussions of any pharmacokinetic/dynamic mechanism elevating active drug levels in the blood or CNS can be further augmented by co-morbidities or clinical factors that increase vulnerability to respiratory depressive effects of the opioid (eg, obstructive sleep apnea, obesity, severe pulmonary disease or hypoventilation conditions, concomitant CNS depressants).

During the FDA's review of codeine use in pediatric patients, the reviewing panel expressed that the risk of CNS-depression with codeine appeared higher in those younger than 12 years of age, or those at any pediatric age when provided for post-op tonsillectomy/adenoidectomy pain; and that the risk to benefit ratio was too high for routine use of codeine as a cough suppressant in pediatric patients. The most recent labeling change in the US took place in 2018, when the FDA shifted the age for indication of codeine-cough prescriptions to adults only (indication is for cough and upper respiratory symptoms associated with allergy or the common cold in patients 18 years of age and older). The risks associated with the use of codeine for cough outweighs the benefits in *most children*—certainly for *acute* cough.[1,51] Pediatric dosing is also removed on newer FDA-labels for codeine analgesic products, but the indication remains generally worded for the treatment of mild to moderate pain where alternatives are insufficient and an opioid is required.

At least it seems promising that codeine is being prescribed much more judiciously, based on the lower counts of pediatric codeine claims in the Utah Medicaid population in 2021 relative to 2016, a year prior to the recent set of labeling changes for codeine.

Prior authorization criteria are proposed (see page 21-24), taking into account FDA contraindications for use in pediatric patients under 12 years of age, or for pediatric post-tonsillectomy/adenoidectomy pain. Criteria regarding attestation of the prescriber's consideration of other pertinent clinical factors or treatment approaches are proposed as a means to mitigate risk while leaving some level of flexibility for provider clinical judgment, rather to eliminate all prescribing of codeine insensitive to unique patient conditions/scenarios, considering that there may be unique cases for which there is not an established optimal treatment for pediatric-pain cases that have insufficient response to NSAIDs or acetaminophen.

Appendix A: Literature Search Strings and Recent Guidelines

Cochrane Library:

((opioid* or opiate* or codeine) AND (child* or pediatric*) AND (pain or analgesi*)):ti,ab,kw

OR

(MeSH descriptor: [Analgesics, Opioid] explode all trees) AND (MeSH descriptor: [Child] explode all trees) AND (MeSH descriptor: [Pain] explode all trees OR MeSH descriptor: [Analgesia] explode all trees)

- Dec. 14th, 2021: 60 Systematic review results

Epistemonikos:

Title/Abstract [(opioid* or opiate* or codeine) AND (child* or pediatric*) AND (pain or analgesi*)]

- Dec. 13th, 2021: 75 results (limited from 2018-2021)

Guidelines for the preparation of this report included the following:

Otolaryngology Setting

1. Clinical Practice Guideline: Opioid Prescribing for Analgesia After Common Otolaryngology Operations Executive Summary (American Academy of Otolaryngology-Head and Neck Surgery, 2021)[39]
2. Clinical Practice Guideline: Tonsillectomy in Children (American Academy of Otolaryngology–Head and Neck Surgery Foundation, 2019)[71]

Pain

3. 2019 Guidance from the Pain Management Best Practices Inter-Agency Task Force of the US DHHS[67]
4. 2018 Scottish government guideline for management of chronic pain in children[96]
5. Recent WHO guidelines:
    - WHO Model List of Essential Medicines for Children - 8th list, 2021[64]
    - Guidelines on the management of chronic pain in children, 2020[123]
    - WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents, 2018[65]
6. Neuropathic pain
    a. 2020 French Recommendations for neuropathic pain[116]
    b. 2019 Neuropathic pain in pediatric oncology[117]
7. Migraine
    a. Acute treatment of migraine in children and adolescents (American Academy of Neurology and the American Headache Society, 2019)

Cough

8. Managing Chronic Cough as a Symptom in Children and Management Algorithms (CHEST Guideline, 2020)[51]
9. Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated With the Common Cold (CHEST, 2017)[50]

Appendix B

Table 1. Serious Outcomes, Codeine Data: FAERS Database from 1969 to May 2015 [36]

- ❖ **64 <u>Total</u> Pediatric (<18 years old) Cases of Serious Respiratory Depression**
  - **24 deaths;** 21 hospitalizations; 16 life-threatening cases
  - 10 cases with documented CYP2D6 genotype: 7 ultra-rapid metabolizer, 3 extensive metabolizers (EMs)
    - Concomitant medication were reported for 1 of these EMs, which included valproate
    - Reasons for codeine use
      - pain management (n=34)
      - cough/cold (n=14)
      - unknown (n=16)
    - Time to event onset from start of therapy (reported for 31 cases)
      - median (5 doses); range (1 to 18 doses)
      - 33 unknown entries
- ❖ **<u>Subgroup of Patients, Age < 12 years</u> (n=50); 21 deaths**
  - Serious cases of respiratory depression with analgesic codeine use (n=26)
  - Serious cases of respiratory depression with codeine for cough/cold (n=14)
    - 10 cases of unknown codeine product type
  - **Indications for use in the cases resulting in death (n=21):** post-op pain following tonsillectomy/adenoidectomy (n=6); cough/cold (n=7); general pain (n=2); postoperative pain (n=2); sore/strep throat pain (n=1); unknown indication (n=3)

The total number of pediatric codeine exposures during the time period of these events is not known; however, is expected to be millions. For example, FDA national estimates just for a 5 year window (2010 through 2014) showed that 2 to 3 million pediatric patients received a codeine outpatient prescription *per year*.

Definitions

<u>Codeine Associated Respiratory Depression</u>: Temporal association following a codeine-containing product administration AND one of the following: naloxone administration, a diagnosis of respiratory depression, signs or symptoms consistent with respiratory depression, such as slow or shallow breathing, difficult or noisy breathing, or unusual sleepiness, death outcome.

Exclusion Criteria: presence of strong alternative explanation(s), suicidality, substance abuse, transplacental exposure or breast feeding exposure, or lack of information for proper assessment

<u>Serious Adverse Drug Event</u>: experiences include outcomes of death, life-threatening events, hospitalization, disability, congenital anomaly, and other serious important medical events.

- Citations for example case reports of serious respiratory depression/or death post codeine ingestion[136,156-158]

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