Background Document
Pediatric Advisory Committee Meeting
September 11, 2017

Benefit/Risk Assessment of Prescription Opioid Antitussive Products for Treatment of Cough in Pediatric Patients

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1. Introduction

Thank you for your participation in the Pediatric Advisory Committee (PAC) meeting to be held on Monday, September 11, 2017.

In February, 2016, FDA leaders, in response to the opioid abuse epidemic, called for a far-reaching action plan to reassess the agency's approach to opioid medications.[1] As FDA assesses the benefits and risks of a product, it must make certain that its decision making is based on all of the available information. Opioids present unique challenges: they have significant benefits when used as prescribed, yet cause enormous harm when misused and abused. Recognizing these challenges, FDA has been taking specific steps to ensure that decisions are science-based and made within a benefit/risk framework that evaluates not only the outcomes of prescription opioids when used as prescribed, but also the public health effects of inappropriate use. For opioid drugs, reviewing all the available information requires extensive additional review—in both pre-approval and post-approval settings—to assess the risk for misuse and abuse. To make certain that FDA is incorporating all relevant viewpoints and expertise into its decision making, the agency has expanded its use of advisory committees. FDA is convening this advisory committee (AC) meeting to discuss the use of prescription opioid antitussive products for treatment of cough in pediatric patients. The main objective of the AC meeting is to obtain advice from the committee members on the benefit/risk assessment for prescription opioid antitussive products in pediatric patients.

Prescription opioid products were approved as antitussives as early as the 1940's. Codeine and hydrocodone are centrally acting opioid antitussives. The currently marketed prescription opioid antitussive products all contain either codeine or hydrocodone; they are available in combination with other medications in prescription products for treatment of cough and symptoms associated with upper respiratory allergies or the common cold. Over-the-counter (OTC) codeine products are marketed through the OTC Drug Monograph.[2] Please note that the focus of this AC meeting is on the prescription opioid cough products and not OTC cough products. Section 2 of this document provides a brief regulatory history for codeine- and hydrocodone-containing prescription cough products.

Both codeine and hydrocodone are associated with respiratory depression and death, particularly in young children. FDA has reviewed these safety issues over the years and has taken numerous regulatory actions. Based upon our reviews, FDA has required revisions to the product labels to describe available data regarding the risk in young children and to restrict use in some younger age groups. Relevant pediatric labeling and the history of these safety issues are described in more detail in section 3. The purpose of this AC meeting is not to discuss in detail these safety issues or a new safety issue, but we are including the background on the safety issues FDA has reviewed over the years to help inform the current benefit/risk discussion.

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[1] FDA Opioids Action Plan [https://www.fda.gov/newsevents/newsroom/factsheets/ucm484714.htm]

[2] Codeine is available through the over-the-counter (OTC) Drug Monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (21 CFR 341.14, 21 CFR 341.74, 21 CFR 341.90) in combination with other medications for cough and cold symptoms.

Additional information pertinent to the consideration of the benefit/risk of opioid-containing prescription cough products is included in this document. National trends in outpatient prescriptions of cough products for pediatric patients are described in section 4. Professional organizations and international regulatory bodies have stated positions regarding the use of opioid-containing cough products in pediatric patients, as described in section 5.

In preparation for this AC meeting, FDA held an Expert Roundtable Meeting on April 24, 2017, with representatives of professional organizations involved in pediatric care. The purpose of this meeting was for FDA to obtain information on the use of cough suppressants in children, particularly opioid cough suppressants, and to understand their experience with prescription opioid cough products. The meeting discussion is described in section 6 of this document, and a summary of the meeting is included in these background materials.

FDA is convening this AC meeting to discuss the use of prescription opioid cough products in children, specifically whether the benefit/risk assessment for the use of these products in pediatric patients remains favorable.

2. Regulatory History of Prescription Opioid Antitussive Products

Codeine

Codeine is an opioid that is a derivative of opium and a selective mu receptor agonist that has been available in the United States since the 1950s. Combinations of codeine with promethazine were first approved in 1952 (NDA 8306), and were later the subject of a Drug Efficacy Study Implementation (DESI) review. In 1962, Congress amended the Federal Food, Drug, and Cosmetic Act to require that a new drug also be proven effective, as well as safe, to obtain FDA approval. This amendment required FDA to conduct a retrospective evaluation of the effectiveness of drug products that FDA had approved as safe between 1938 and 1962 through the new drug approval process. FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of products that were approved only for safety between 1938 and 1962. The Agency reviewed and re-evaluated the findings from the NAS/NRC panels. FDA's administrative implementation of the NAS/NRC reports was called DESI.

Based upon the DESI review process, promethazine and codeine combination products were found effective as an antihistamine-antitussive combination, with or without a decongestant.[3] The basis for approval of codeine as an antitussive through DESI is not the focus of this AC meeting.

Prescription codeine antitussive products are available in combination with other medications for the indication of "relief of cough and symptoms associated with upper respiratory allergies or the common cold." The prescription codeine-containing antitussive products are listed as Drug

[3] FR February 2, 1984, Docket 81N-0393; DESI 6514

Enforcement Agency (DEA) Schedule III drugs. Table 1 shows the available prescription codeine products for this indication and the relevant pediatric labeling.

Table 1 Prescription Codeine Products for Cough/Cold Indications

Application (Company)	Product	Dosage Form	Relevant Pediatric Labeling
NDA 206323 (Spriaso)	Chlorpheniramine maleate, codeine phosphate (Tuxarin ER)	Extended Release Oral Tablet	•Contraindication in children <12 years •Contraindication for postoperative management in children <18 years post tonsillectomy & adenoidectomy (T&A) •Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine •Not indicated for patients <18 years
NDA 207768 (Tris Pharma)	Chlorpheniramine polistirex, codeine polistirex (Tuzistra XR)	Extended Release Oral Suspension	
NDA 8306 ANDA (multiple)	Codeine phosphate, phenylephrine hydrochloride, promethazine hydrochloride	Oral Syrup	•Contraindication in children <12 years •Contraindication for postoperative management in children <18 years post T&A •Boxed Warning regarding respiratory depression in children (promethazine) •Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine •Dosing information for children 12 years and older
	Codeine phosphate, promethazine hydrochloride	Oral Syrup	
ANDA 88704 (Sti Pharma)	Codeine phosphate, pseudoephedrine hydrochloride, triprolidine hydrochloride (Triacin C)	Oral Syrup	•Contraindication in children <12 years •Contraindication for postoperative management in children <18 years post T&A •Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine •Dosing information for children 12 years and older
NDA – New Drug Application; ANDA – Abbreviated New Drug Application; NTE – not to exceed Source: FDA Orange Book search on July 14, 2017			

Prescription codeine cough product labels currently contain a Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine, a contraindication in patients younger than 12 years of age, and a contraindication for postoperative management in children younger than 18 years of age post-tonsillectomy and/or adenoidectomy. The background for this safety labeling is discussed in section 3 of this document.

Approval of New Drug Applications (NDAs) for prescription codeine cough products is based upon the established efficacy and safety of codeine and efficacy and safety of other active pharmaceutical ingredients (APIs) in the OTC cough-cold monograph.[4] The OTC monograph permits "rational" combinations of various categories of cough and cold products, such as antitussives, antihistamines, and decongestants. NDAs are typically based upon a bioequivalence program (i.e., pharmacokinetic studies). Generally, no new clinical safety or efficacy studies are required for the approval of these products.

[4] 21 CFR 341—Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Product for Over-The-Counter Human Use

As shown above in Table 1, some older codeine cough and cold combination products have dosing information for children as young as 12 years of age, whereas the newer approved codeine combination products do not currently have dosing information for children. This is because the new applications for codeine products have post-marketing requirements to conduct studies in pediatric patients (See Pediatric Study Requirements below). Labeling for these products would be updated following completion of these studies and submission of data to the FDA.

Hydrocodone

Like codeine, hydrocodone is a centrally acting opioid antitussive that is available in combination with homatropine or in combination with other cold medications. Hydrocodone (Hycodan, NDA 05213) was first approved in 1943. Under the DESI review process, the FDA found Hycodan to be effective for the symptomatic relief of cough.[5,6] In 2014, DEA reclassified the hydrocodone-containing antitussive products from Schedule III to Schedule II drugs.[7]

[5] 47 FR 23809, June 1, 1982

[6] Hycodan is the only hydrocodone cough product that does not contain an antihistamine or decongestant, so its indication is different. Hycodan's indication is for the relief of cough (without qualifying language that the cough is related to allergies or a cold).

[7] 79 FR 49661, August 22, 2014

Table 2 shows the available prescription hydrocodone products for cough/cold indications.

Table 2 Available Prescription Hydrocodone Products for Cough/Cold Indications

Application (Company)	Active Ingredient (Product)	Dosage Form	Relevant Pediatric Labeling
NDA 22424 (Mission Pharmacal) NDA 205474 (Sovereign Pharmaceuticals)	Hydrocodone bitartrate, guaifenesin (FlowTuss)* (Obredon)*	Oral solution	• Boxed Warning regarding deaths with concomitant use of benzodiazepines or other central nervous system depressants • Not indicated for use in patients <18 years
NDA 22279 (Mission Pharmacal) NDA 22442 (Cypress Pharma)	Hydrocodone bitartrate, pseudoephedrine hydrochloride, guaifenesin, (Hycofenix)* (Rezira)*		
NDA 204307 (Cypress Pharmaceuticals)	Hydrocodone bitartrate, chlorpheniramine maleate (Vituz)*		
NDA 22439 (Cypress Pharmaceuticals)	Hydrocodone bitartrate, chlorpheniramine maleate, pseudoephedrine hydrochloride (Zutripro)*		
Multiple ANDAs	Hydrocodone bitartrate; Homatropine methylbromide[8] (Hycodan generics)	Oral solution	• Boxed Warning regarding deaths with concomitant use of benzodiazepines or other central nervous system depressants • Warning: fatal respiratory depression in children <6 years of age • Dosing information for children ≥6 years • Use with caution in pediatric patients ≥6 years • Safety and effectiveness in pediatric patients under six have not been established
NDA 19111 (UCB, INC)	Chlorpheniramine polistirex; hydrocodone polistirex (Tussionex Pennkinetic)*	Oral suspension, extended release	• Boxed Warning regarding deaths with concomitant use of benzodiazepines or other central nervous system depressants • Contraindicated in children <6 years • Dosing information for children ≥6 years • Use with caution in pediatric patients ≥6 years
Source: FDA Orange Book search on July 18, 2017 * Indicates multiple ANDA products			

[8] A subtherapeutic amount of homatropine methylbromide was added to prevent abuse

Approval of NDAs for hydrocodone combination cough products is based upon the established efficacy and safety of hydrocodone for cough and efficacy and safety of other APIs in the OTC monograph. NDAs are typically based upon a bioequivalence program (i.e., pharmacokinetic studies). Generally, no new clinical safety or efficacy studies are required for the approval of these products.

Prescription hydrocodone cough products have information in the product labeling about respiratory depression in children less than 6 years of age. As shown above, some older hydrocodone cough/cold combination products have dosing information for children as young as 6 years of age, whereas the newer approved hydrocodone combination products do not currently have indications for children. Similar to codeine, newer NDAs for hydrocodone products currently have post-marketing requirements to conduct studies in pediatric patients (See Pediatric Study Requirements below). Labeling for these products would be updated following completion of these studies and submission of data to the FDA.

In January 2017, the Sponsor for Tussionex (UCB, Inc.) submitted a labeling supplement to limit use of Tussionex to adults 18 years of age and older. Specifically UCB, Inc. proposes a limitation of use that Tussionex is not indicated for patients under 18 years of age. UCB noted existing concerns about safety of opioid use in children, the prevalence of abuse of prescription opioid medications, and known serious adverse events with use of opioid antitussives in children. UCB concluded that the benefit/risk assessment for Tussionex is not favorable for the treatment of acute cough in pediatric patients. The feedback from this AC panel may impact the FDA's review of this supplement.

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) has observed an increase in NDAs for prescription hydrocodone cough products in the past decade. In the past, there were many illegally marketed hydrocodone-containing antitussives. Since FDA determined that hydrocodone bitartrate is a new drug, manufacturers must have an approved application before marketing any drug product that contains hydrocodone. On October 1, 2007, FDA published a Federal Register (FR) notice of its intention to take enforcement action against illegally marketed drug products containing hydrocodone.[9] Manufacturers must obtain FDA approval of an NDA or an ANDA to legally market these products. The recent increase in the number of NDAs for prescription hydrocodone cough products is likely because of these efforts to ensure that hydrocodone cough products are marketed legally.

Pediatric Study Requirements for Prescription Opioid Antitussives

As stated above, certain prescription codeine and hydrocodone products are required to conduct pediatric studies. Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred. Currently, FDA may require sponsors who submit a New Drug Application (NDA) for an opioid antitussive to conduct pediatric studies under PREA.

[9] 72 FR 55780 October 1, 2007, 2007N-0353

Currently, there are 6 NDAs for products containing codeine (NDA 206323 [Tuxarin ER]) or hydrocodone (NDA 22279 [Hycofenix], NDA 205474 [Obredon], NDA 22442 [Rezira], NDA 204307 [Vituz], and NDA 22439 [Zutripro]) that have outstanding requirements under PREA. These products are only labeled for adults (18 years and older) pending the results of the required pediatric studies. The required pediatric studies generally consist of information to support labeling of dosing, efficacy, and safety information in pediatric patients, and include the following:

- Single-dose pharmacokinetic (PK) study in children 6 - 17 years of age
- Safety and tolerability study in 400-450 pediatric patients aged 6 - 17 years of age. The study should enroll otherwise healthy children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be appropriate symptomatic treatment.

The single-dose PK study has been required so that pediatric dosing can be established. The objective of the large safety study is to provide sufficient safety information regarding the use of the product in patients 6-17 years of age. Efficacy and safety are based upon the established efficacy and safety of the APIs in the OTC monograph or previously approved products.

3. Safety of Opioid Antitussive Products among Children and Adolescents

Codeine and Risk of Respiratory Depression and Death Due to Ultra-rapid Metabolism

Codeine is a prodrug that is metabolized by the CYP2D6 pathway to the potent metabolite morphine. A high degree of variability exists for CYP2D6-mediated activation of codeine because of underlying genetic differences in CYP2D6 activity. Patients may be classified as having one of four metabolic phenotypes depending on the genotype: ultra-rapid metabolizer (UM), extensive metabolizer, intermediate metabolizer, and poor metabolizer. Patients with CYP2D6 dysfunction may have therapeutic failure secondary to reduced biotransformation of codeine to morphine. Conversely, UMs may be at risk of toxicity because of more rapid and complete conversion to morphine.

The variability in metabolism of codeine and risk of toxicity has been the focus of FDA safety reviews and led to numerous regulatory actions in the United States and in other countries. The following is a brief history of codeine and concerns related to UMs and potential toxicity, including respiratory depression and death.

- Neonatal toxicity related to exposure to high levels of morphine through the breast milk of a UM mother taking codeine
    - A 2006 publication in the Lancet described the death of a nursing infant who was exposed to high levels of morphine via breast milk because the mother, who was taking codeine, was a UM of codeine, a CYP2D6 substrate.[10]

[10] Koren G, Cairns J, Chitayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006; 368(9536):704.

- In 2007, FDA revised codeine labeling to warn of this risk and also issued communications to healthcare providers and the public regarding use of codeine in nursing mothers and the risk to infants exposed to morphine in breast milk from mothers who were UM of codeine.[11]

- Fatal and life-threatening respiratory depression in children following codeine treatment for pain post-adenotonsillectomy who were CYP2D6 UMs
  - Following identification of a case series published in *Pediatrics* in April 2012,[12] FDA embarked on an evaluation of the issue.
  - In August 2012, FDA issued a Drug Safety Communication acknowledging the case series about the risk of death or life-threatening respiratory depression following adenotonsillectomy in some children who received codeine for pain control following surgery, and describing that an evaluation was underway.[13]
  - In February 2013, FDA issued a Safety Labeling Change notification letter for codeine-containing products to require a contraindication for use in children following tonsillectomy and/or adenoidectomy (T&A) and a boxed warning describing the risks of being a UM of codeine.[14]
  - FDA's assessment of this safety issue was published online in April 2013 as a Perspective in the *New England Journal of Medicine* - "New Evidence about an Old Drug — Risk with Codeine after Adenotonsillectomy".[15]
  - The required labeling changes were approved in May 2013 and included the following:
    - Boxed Warning regarding death related to Ultra-Rapid Metabolism of codeine to morphine
    - Contraindication in children post T&A
    - Warning regarding death related to Ultra-Rapid Metabolism of codeine to morphine

  - In October 2012, the European Medicines Agency (EMA) initiated a review of codeine focusing on codeine use in children for pain relief. In June 2013, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) recommended the following, which was endorsed by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh):[16]
    - Codeine-containing medicines should only be used to treat acute (short-lived) moderate pain in children above 12 years of age.
    - Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat

[11] FDA Press Release on Codeine Use by Nursing Mothers [https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048740.htm]
[12] Kelly LE, Rider M, van den Anker J, et al. More Codeine Fatalities After Tonsillectomy in North American Children. *Pediatrics* 2012; 129(5): e-1343-7.
[13] August 15, 2012, FDA Drug Safety Communication [http://www.fda.gov/Drugs/DrugSafety/ucm313631.htm]
[14] February 20, 2013, FDA Drug Safety Communication [https://www.fda.gov/Drugs/DrugSafety/ucm339112.htm]
[15] Racoosin JA, Roberson DW, Pacanowski MA, and Nielsen DR. New Evidence about an Old Drug – Risk with Codeine after Adenotonsillectomy. *N Engl J Medicine 2013;* 368: 2155-2157.
[16] European Medicines Agency: Codeine-containing medicines [Weblink]

obstructive sleep apnoea, as these patients are more susceptible to respiratory problems.
    - The product information of these medicines should carry a warning that children with conditions associated with breathing problems should not use codeine.
    - The risk of side effects with codeine may also apply to adults. Codeine should therefore not be used in people of any age who are known to be UMs nor in breastfeeding mothers (because codeine can pass to the baby through breast milk).

- In June 2013, Health Canada announced that it reviewed the safety of prescription pain and cough medications containing codeine and is no longer recommending their use in children less than 12 years of age. This recommendation was based on very rare cases of serious side effects and deaths in children that have been attributed to codeine, when given directly to a child, or to babies from breast milk.[17]

- In April 2014, the EMA initiated a review of codeine use in children for cough and cold. In March 2015, the PRAC recommended the following which was endorsed by CMDh.[18]
    - Codeine should be contraindicated in children below 12 years.
    - Use of codeine for cough and cold is not recommended in children and adolescents between 12 and 18 years who have problems with breathing.

- Because of the EMA recommendations, FDA initiated a safety review of available data regarding respiratory depression and death with codeine-containing products for cough and analgesia in children.
    - A search of the FAERS database from January 1969 to May 2015 identified 64 worldwide serious cases of respiratory depression in children < 18 years of age, of which the majority of cases were in children under 12 years of age. Of the 64 cases, 24 had an outcome of death. Twenty-one of 24 death cases involved children less than 12 years of age. The reasons for codeine-containing product use in these cases included post-tonsillectomy and/or adenoidectomy pain management, other post-operative pain, general pain, sore or strep throat pain, and cough and cold. The information on CYP2D6 genotyping was limited; however there were death cases that involved patients who were either extensive or UMs of codeine.[19]

- In December 2015, FDA held an AC Meeting to discuss available safety data regarding the use of codeine in children for cough and cold indications. The FDA summary memo from

[17] Health Canada's review recommends codeine only be used in patients aged 12 and over. June 2013 [http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/33915a-eng.php]
[18] European Medicines Agency: Codeine-containing medicinal products for the treatment of cough or cold in paediatric patients [Weblink]
[19] Pham T, Nguyen A, Dormitzer C. Drug utilization and safety review of cough/cold and analgesic codeine-containing products in pediatric population (0-18 years) as background for the 12/10/15 joint PADAC-DSaRM AC meeting. Review finalized November 12, 2015.

this meeting is attached. The majority of the panel recommended contraindication of codeine for both cough and analgesia. The following is a summary of the voting from the panel:

- Expand contraindication for codeine for use for <u>any pain management</u> in children
  - Children < 6 years of age – 2 votes
  - Children < 12 years of age – 6 votes
  - Children < 18 years of age – 20 votes
  - No change – 1 vote
- Expand contraindication for codeine for use for <u>the treatment of cough</u> in children
  - Children < 6 years of age – 1 vote
  - Children < 12 years of age – 5 votes
  - Children < 18 years of age – 20 votes
  - No change – 3 votes
- Remove codeine from FDA monograph for OTC use for the treatment of cough in children
  - Children < 6 years of age – 0 votes
  - Children < 12 years of age – 1 vote
  - Children < 18 years of age – 27 votes
  - No change – 0 votes

- In April 2017, FDA announced new labeling restrictions[20] for prescription codeine products to contraindicate the use of codeine in children less than 12 years of age because the safety data suggested that the youngest children were at highest risk. The labeling includes the following concepts:
  - Contraindication of use of codeine for cough or pain in children < 12 years of age
  - Strengthened Warning that breastfeeding is not recommended when taking codeine
  - Warning regarding use in adolescents between 12 and 18 years who have risk factors (e.g. obesity, obstructive sleep apnea) that may increase the risk of respiratory depression.

Hydrocodone and Risk of Respiratory Depression and Death

There are also risks of respiratory depression and death in children with hydrocodone. In 2007, based upon reports of respiratory depression and death in children, the sponsor proposed adding a contraindication to the Tussionex labeling for children less than 6 years of age. Following review, in February 2008, FDA approved new labeling for Tussionex to add a contraindication in children less than 6 years of age. FDA also released a Public Health Advisory (PHA) and Healthcare Professional sheet at that time.[21] The PHA emphasized the appropriate dosing for Tussionex, which is an extended release product. The reports with Tussionex prompted a safety review for the immediate-release Hycodan product. In 2008, FDA approved updated labeling for Hycodan with a new warning regarding the risk of fatal respiratory depression in children less than 6 years of age. The newer hydrocodone combination product labels have similar warnings.

[20] April 20, 2017 FDA Drug Safety Communication [https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm]
[21] FDA Public Health Advisory March 11, 2008 [Weblink]

While hydrocodone is metabolized in part by the CYP2D6 and CYP3A4 pathways, the variability in CYP2D6 metabolism for hydrocodone has not been identified as a risk factor as it has with codeine. The Office of Surveillance and Epidemiology (OSE) completed a review of the safety of hydrocodone-containing cough and cold products in 2016.[22] OSE identified 38 worldwide serious pediatric cases of respiratory depression with hydrocodone-containing cough and cold products in the FDA Adverse Event Reporting System (FAERS) database from January 1, 1969 to January 12, 2016. Of the 38 serious pediatric cases, 23 had an outcome of death. The majority of cases were in children less than 6 years of age, were reported with the extended-release suspension formulation, and/or associated with inadvertent overdoses (e.g., accidental ingestion, incorrect measurement). All pediatric reports involving the extended-release suspension formulation in the case series were received by FDA prior to issuance of the PHA in March 2008.

Additionally, OSE identified reports of respiratory depression associated with the use of hydrocodone antitussives and concomitant use of CYP3A4 inhibitors. Hydrocodone analgesia products have a Boxed Warning regarding the risk of an increase in plasma concentration of hydrocodone and respiratory depression with concomitant use of CYP3A4 inhibitors. OSE recommended adding the drug interaction with CYP3A4 inhibitors and hydrocodone to the Warnings and Precautions section of the label of all hydrocodone-containing antitussives. This recommendation is currently under consideration.

Risks of misuse, abuse, addiction, overdose and death with opioid antitussives

Because the risks for misuse, abuse, addiction, overdose and death are well known for all opioid containing products, we cannot examine those issues using spontaneous report data (e.g. FAERS), whose strength lies in detecting new safety signals. Therefore, population-based studies are needed to examine these safety outcomes. Although we know that codeine and hydrocodone, as opioids, are abused, currently available data make it very challenging to quantify the rates of abuse associated with opioids in different formulations (e.g., specific cough/cold products vs. various formulations of analgesics). Despite these challenges, illicit, exploratory, or recreational use of dextromethorphan and codeine/promethazine cough syrups is widely described in the medical literature.[23]

There are also sparse data available to understand whether legitimate medical use of opioids in children can increase these patients' risk of subsequently experiencing addiction, or engaging in misuse or abuse behaviors. FDA's recent review on this topic revealed only one longitudinal study examining this question in relation to opioid analgesic use by high school students.[24] This study observed a 33% (95% CI, 4% -70%) increased risk of future opioid misuse by 12th grade students who had previous legitimate medical use of opioid analgesics. The limitations of this analysis, and other studies examining non-medical use of opioid analgesics in children, are

[22] Nguyen A. Hydrocodone-containing cough and cold products: Pediatric Postmarketing Safety Analysis. Review finalized March 3, 2016.
[23] Burns JM, Boyer EW. Antitussives and Substance Abuse. Subst Abuse Rehabil. 2013; 4: 75–82.
[24] Coyle TD. Opioid analgesics in the pediatric population: a review of the epidemiologic literature examining the outcomes of misuse, abuse, addiction, overdose and death. Review finalized September 12, 2016.

discussed fully in the review. It is not clear how well these results can be applied to opioid-containing antitussives, or whether additional studies will confirm these preliminary risk estimates.

This review also found that recent data from the National Survey on Drug Use and Health (NSDUH) indicate that prevalence rates of non-medical use of prescription opioids (NMUPO) in the pediatric population are declining. However, a particularly striking area of continuing concern is the potential importance of reducing available drug supply: a large proportion of adolescents engaging in NMUPO obtain the drugs for free from friends or family, and from leftover medications in a medicine cabinet. One of the recommendations of this review was that "reducing availability of opioid analgesic products to this age group is critical to prevent such temptation. Prescribers are the gatekeepers to prescription opioid analgesics, and should grant access to these drugs only to patients who truly need them and in as small a supply as necessary." The extent to which opioid-containing antitussives may also provide opportunities for misuse and abuse by this age group is not known.

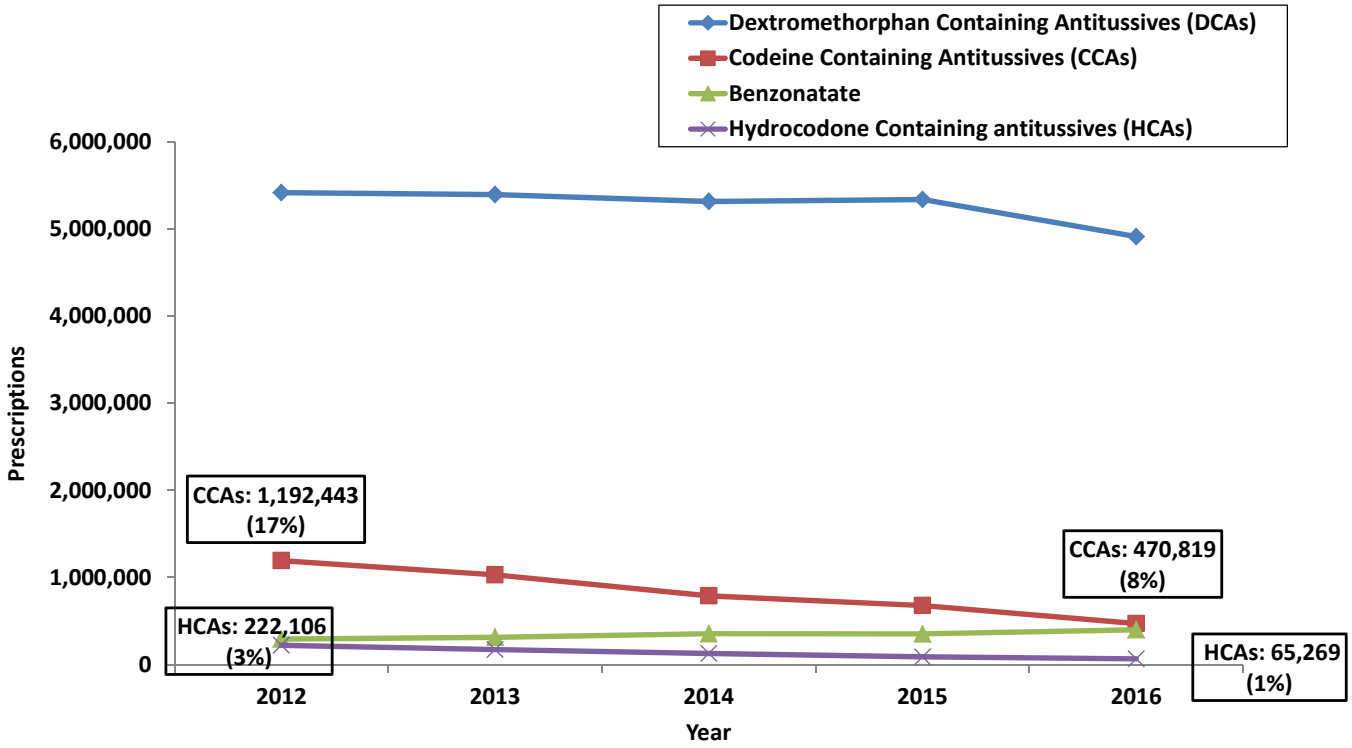
4. Utilization of Products to Treat Cough in Pediatric Patients

The Office of Surveillance and Epidemiology (OSE) has recently completed a review of national trends in the pediatric outpatient utilization of prescription opioid antitussives (prescription codeine and hydrocodone products), and non-opioid products (containing dextromethorphan and benzonatate) .[25] The purpose of this review is to provide the committee with a current context for the benefit/risk discussion of opioid antitussives in children.

The prescription dispensing data from U.S. outpatient retail pharmacies showed that an estimated 5.8 million antitussive prescriptions were dispensed to 4.3 million pediatric patients ages 17 years and younger in 2016 (Figure 1). The majority of prescriptions were dispensed for dextromethorphan containing antitussives at 84% (4.9 million prescriptions). Codeine and hydrocodone containing antitussives accounted for 8% (471,000 prescriptions) and 1% (65,000 prescriptions) of total prescriptions, respectively. The number of prescriptions dispensed for codeine and hydrocodone containing antitussives to pediatric patients decreased by 60.5% and 71%, respectively, from 2012 to 2016, although OTC sales of codeine containing products without a prescription were not included in this analysis. Primary care providers such as general pediatricians, family medicine/general practice/internal medicine, and nurse practitioners/physician assistants were the top prescriber specialties across all pediatric age groups for both prescription opioid and non-opioid antitussives.

[25] Pham T. Pediatric Outpatient Retail Utilization Patterns of Opioid and Non-Opioid Containing Antitussives. Review finalized July 31, 2017.

Figure 1. Nationally estimated number of antitussive prescriptions dispensed to pediatric patients (0-17 years) by active ingredient from U.S. outpatient retail pharmacies, 2012-2016



Source: QuintilesIMS, National Prescription Audit™. 2012-2016. Data extracted June 2017.

Based on surveys of office-based physicians, budesonide, albuterol, and dextromethorphan-containing antitussives were the top drugs mentioned during visits with cough diagnoses for pediatric patients ages 0-1 years in 2016. Among pediatric patients ages 2-17 years, dextromethorphan-containing antitussives followed by albuterol were the top drugs mentioned for cough relief. For the opioid antitussives, although combination codeine/guaifenesin was mentioned for cough relief in pediatric patients ages 2 years and older, there were no mentions of hydrocodone-containing antitussives in this data source, likely due to the low pediatric utilization of these products.

Overall, the outpatient retail utilization of prescription codeine and hydrocodone containing antitussives in pediatric patients was low and decreased from 2012 to 2016. Dextromethorphan containing antitussives accounted for the vast majority of pediatric prescription antitussive use throughout the study period. The overall utilization of dextromethorphan and codeine containing antitussives was underestimated in our analyses due to the availability of dextromethorphan and codeine products over-the-counter (OTC).

5. Treatment Alternatives for Cough

In considering the benefit risk assessment of prescription opioid antitussives, the availability of other products that are indicated for cough in children should be considered. The following table lists approved antitussive medications in children.

Active Ingredient (product name)	Class	Age	Relevant Labeling
Prescription Products			
Benzonatate (Tessalon and generics)	Peripheral Anesthetic	≥10 years	• Do not break, chew, crush • Temporary local anesthesia • Accidental ingestion resulting in death has been reported in children <10 years of age • Dosing information for children 10 years and older
Over-the-Counter Antitussive Products (FDA monograph 21 CFR341.14)			
Chlophedianol Hydrochloride	Centrally acting	≥6 years	• Non-narcotic for temporary relief of cough • Do not take for chronic cough • Children under 6 years of age: Consult a doctor • OTC Monograph also contains professional labeling for dosing in children 2 to <6 years of age
Dextromethorphan and Dextromethorphan hydrobromide	Centrally acting	≥2 years	• Non-narcotic for temporary relief of cough • Do not take for chronic cough • Children under 2 years of age: Consult a doctor
Diphenhydramine citrate and Diphenhydramine hydrochloride	Antihistamine /antitussive	≥6 years	• Non-narcotic for temporary relief of cough • May cause marked drowsiness • Alcohol, sedatives, and tranquilizers may increase sedative effect • Do not give to children less than 12 years of age who have a breathing problem • Children under 6 years of age: Consult a doctor • OTC Monograph also contains professional labeling for dosing in children 2 to <6 years of age
Camphor and Menthol	Topical (ointment, lozenge, steam inhalation)	≥2 years	• Topical: For external use only • Flammability: Safety concern about fire-related events when ointment vehicle or alcohol-based solutions are placed in hot water or heated in the microwave • Children under 2 years of age: Consult a doctor

Some of these products have known risks that may be important to consider as you discuss the benefit risk assessment of opioid cough products.

Dextromethorphan (DXM)
As seen in the drug utilization review (see section 4), DXM is the most commonly prescribed prescription cough suppressant in children, and it is likely that non-prescription products containing dextromethorphan are also used to treat children's cough.

The practice of ingesting high doses of DXM to experience euphoric effects is well documented, particularly among adolescents 14-17 years of age.[23,26] Multiple educational initiatives have been launched over the past 10 years to reduce abuse of DXM products among teens, and it has been the subject of previous FDA advisory committee discussions and a talk paper[27]. Although it remains non-scheduled under the Controlled Substances Act (CSA), at least 12 states have passed legislation prohibiting sales to minors (those aged 17 or younger), and several commercial pharmacy chains have imposed similar restrictions[28].

Benzonatate
Benzonatate is a prescription drug approved for relief of cough in patients over 10 years of age. The safety and effectiveness of benzonatate in children under 10 years of age have not been established. Benzonatate is sold under the brand-name Tessalon and is also sold in generic preparations. Although it is not prescribed as frequently as other products (see section 4), its use appears to be increasing in recent years. In 2010, FDA issued a Drug Safety Communication warning the public that accidental ingestion of benzonatate by children under the age of 10 years can result in death from overdose.[29] Benzonatate may be attractive to children because of the drug's appearance (it is a round-shaped liquid-filled gelatin capsule).

6. Perspectives on Use of Opioids for Treatment of Pediatric Cough by Other Organizations and Regulatory Authorities

In the past decade, the use of cough and cold medications, including opioid antitussive products, in pediatric patients has been reviewed. Cough in pediatric patients is commonly self-limiting and usually secondary to infection. For other patients, cough may be associated with more serious underlying conditions such as asthma, lower respiratory tract infection, allergy, or cystic fibrosis.[30] Symptomatic treatment of cough in certain conditions may be detrimental to patients either through masking underlying conditions or preventing the necessary clearance of abnormal

[26] Drug Enforcement Administration, Office of Diversion Control. Drug and Chemical Evaluation section. Dextromethorphan (Street Names: DXM, CCC, Triple C, Skittles, Robo, Poor Man's PCP). March, 2014. [http://www.deadiversion.usdoj.gov/drug_chem_info/dextro_m.pdf]
[27] Briefing Information for Dextromethorphan: [Weblink]
[28] CHPA. Dextromethorphan: Preventing Teen Cough Medicine Abuse. http://www.chpa.org/Dex.aspx
[29] Drug Safety Communication: Death resulting from overdose after accidental ingestion of Tessalon (benzonatate) by children under 10 years of age [https://www.fda.gov/Drugs/DrugSafety/ucm236651.htm]
[30] Brodlie M., Graham C., McKean MC. Childhood cough. *BMJ* 2012;344:e1177

airway secretions through the cough mechanism.[31] Thus, when a specific etiology of cough can be identified, therapy should be directed at treating the underlying condition and avoiding attempts at symptomatic treatment of cough.[32]

As outlined in the following sections, there have been changes in the recommendations for management of cough in children in the last decade, with respect to the use of opioid antitussives. Therefore, this section reviews public communications from organizations and regulatory authorities on the use of opioid-containing product for the treatment of cough in children.

American Academy of Pediatrics

The American Academy of Pediatrics has taken a formal opinion on the use of codeine (and dextromethorphan [DM]) for cough. In 1997, the AAP Committee on Drugs provided recommendations on the Use of Codeine and DM-Containing Cough Remedies in Children.[33] The AAP cautioned about the lack of studies to support the efficacy and safety of narcotics or dextromethorphan as antitussives in children. The Committee noted that because of adverse effects and overdosage associated with codeine and DM products for cough, patients and parents should be educated about the lack of proven antitussive effects and the potential risks of these products. The AAP also noted that cough due to URI is short-lived and suppression of cough may be hazardous. In 2007, AAP reaffirmed the statement.[34] More recently, the AAP published a Clinical Report[35] from the Section on Anesthesiology and Pain Medicine and the Committee on Drugs describing the concerns related to unanticipated respiratory depression and death due to codeine metabolism. The report noted the actions taken by the World Health Organization, FDA, Health Canada, and EMA to warn against the adverse effects and in the case of the EMA, to contraindicate the use of codeine in children less than 12 years.

American College of Chest Physicians

In 2006, the American College of Chest Physicians (ACCP) issued Guidelines for Evaluating Chronic Cough in Pediatrics. In these guidelines, one of the recommendations was the following: "In children with cough, cough suppressants and other OTC cough medications should not be used as patients, especially young children, may experience significant morbidity and mortality."

European Medicines Agency

In 2015, upon completion of a comprehensive review by the PRAC, EMA issued guidelines regarding the use of codeine for treatment of cough or cold in pediatric patients (contraindicated

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[31] American Academy of Pediatrics Committee on Drugs. Use of Codeine- and Dextromethorphan-Containing Cough Remedies in Children. *Pediatrics* 1997; 99(6):918-920.

[32] Chang AB, Glomb WB Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. *Chest* 2006 Jan;129(1 Suppl):260S-283S

[33] American Academy of Pediatrics Committee on Drugs. Use of Codeine- and Dextromethorphan-Containing Cough Remedies in Children. *Pediatrics* 1997; 99(6):918-920.

[34] American Academy of Pediatrics Policy Statement. AAP Publications Retired or Reaffirmed, October 2006. *Pediatrics* 2007; 119(2):405.

[35] Tobias JD, Green TP, Coté CJ, AAP Section on Anesthesiology and Pain Medicine, AAP Committee on Drugs. Codeine: Time To Say "No". *Pediatrics* 2016;138(4):e20162396

in patients younger than 12 years, and not recommended in patients between 12 and 18 years who have breathing problems.[36] These guidelines are consistent with 2013 guidelines recommending against the use of codeine for pain after obstructive sleep apnea surgery including adenotonsillectomy.

Health Canada

In 2008[37] and 2016[38], Health Canada cautioned against the use of over-the-counter (OTC) cough and cold medicines in pediatric patients younger than 6 years. Additionally, in 2013 Health Canada issued guidelines on the use of codeine in pediatric patients upon completion of a review of serious side effects (e.g., respiratory depression) and death in pediatric patients exposed by breast milk (original warning issued in 2008) or upon direct exposure.[39] In 2016, Health Canada issued an update to guidelines on the use of opioids, including codeine and hydrocodone, in pediatric patients.[40] While the 2016 Health Canada advisory did not focus on use of opioids for treatment of cough, the advisory stated:

- Cases of respiratory depression in children treated with hydrocodone were identified by Health Canada
- Hydrocodone is no longer recommended in children under age 6 years
- Neither prescription nor non-prescription codeine products should be used in children younger than 12 years
- Neither codeine nor hydrocodone should be used by patients with breathing problems

World Health Organization

The Department of Child and Adolescent Health and Development of the World Health Organization published a document in 2001 that discussed cough and cold remedies for the treatment of acute respiratory infections in young children. The document reviewed the efficacy and safety of cough and cold medicines in young children (under 5 years of age) including codeine and other opiate derivatives such as hydrocodone for cough. The document concludes the section on opioids stating that codeine preparations should not be recommended for the treatment of cough in young children.[41]

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[36] EMA/249413/2015. European Medicines Agency. Codeine not to be used in children below 12 years for cough and cold. April 24, 2015. [Weblink]

[37] Health Alert: RA-1100025511. Health Canada Releases Decision on the Labelling of Cough and Cold Products for Children. [Weblink]

[38] Health Alert #: RA-57622. Health Canada reminds parents not to give cough and cold medication to children under 6 years old. [http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/57622a-eng.php]

[39] Health Alert #: RA-33915. Health Canada's review recommends codeine only be used in patients aged 12 and over. June 6, 2013. [http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/33915a-eng.php]

[40] Health Alert #: RA-59584. New safety measures for prescription codeine and hydrocodone to further restrict use in children and adolescents. July 28, 2016. [Weblink]

[41] World Health Organization. (2001). Cough and Cold Remedies for the Treatment of Acute Respiratory Infections in Young Children. Retrieved from [http://www.who.int/maternal_child_adolescent/documents/fch_cah_01_02/en/]

7. Expert Roundtable Meeting on the Use of Cough Suppressants in Children

On April 27, 2017, FDA held a roundtable meeting of invited experts to discuss the experience of health care professionals with the use of cough suppressants in children (less than 18 years of age), particularly opioid antitussive products. The participants were representatives of professional organizations involved in the treatment of pediatric patients with cough, including the American Academy of Pediatrics, the American College of Chest Physicians, the American Osteopathic Association, the American Academy of Family Physicians, and the National Association of Pediatric Nurse Practitioners.

Participants recommended certain distinctions such as acute versus chronic cough, and productive versus non-productive coughs. The expert discussants emphasized the importance of identifying the underlying cause of cough in order to determine the most appropriate treatment, rather than focusing on cough suppression. Participants noted that the use of cough suppressants depends on the clinical situation, but that cough should not be suppressed unless it is causing clinical consequences, including, for example:

1. Cough leading to consecutive nights of poor sleep and/or vomiting
2. Cough leading to rib fractures
3. Cough severe enough to lead to hypoxia

Overall, the participants did not see a clear role for the use hydrocodone or codeine in the treatment of acute cough in pediatric patients. They stated that the benefits for cough suppression are questionable and there are concerns about harm from opioid use. Some participants stated that under no circumstance would they treat an acute cough with an opioid. Some participants stated that there are few situations in adolescents when codeine might be used (e.g., end of life situations for pain mainly with reduction of cough as an added benefit). The participants stated that they are concerned about safety and efficacy of opioids as cough suppressants.

The participants were asked to provide some alternative treatments for cough. Depending on the underlying cause, these included:

- Bronchodilators
- Inhaled and oral corticosteroids
- Lansoprazole if the cough is due to a gastrointestinal issue like GERD
- Anti-histamines
- Warm saline
- Honey
- Camphor
- Vapor rub (except in asthmatics as it may exacerbate their condition)
- Nasal suctioning and clearing

The following are the general comments from the meeting participants:

- Participants agreed about the need for outreach to inform and educate practitioners that prescribing opioids for cough in children is not recommended.
- Some participants suggested that removing the cough treatment indication for opioid products in labeling might help reduce pressure to treat patients, as described above.

Participants noted that removal of the indication might shift the treatment to other cough suppressants like dextromethorphan. There was concern, however, about resistance from some practitioners to removing the cough treatment indication for opioids, even though there are other treatment options.

- Some participants suggested investigating the characteristics of those physicians who prescribe these drugs more often than others.
- Participants supported educating the public and families about the concerns related to using opioids to treat pediatric patients.
- Participants agreed that the availability of non-opioid, cough controlling products approved for children would be of benefit.
- The suggestion was made to review the adverse event profile of alternative agents for chronic cough for comparison to codeine-containing cough products.

Participants encouraged FDA to include patient and family representatives, urgent care physicians, rural health prescribers, osteopathic practitioners, and representation from other practices in any future public meetings.

8. Considerations for Benefit/Risk Assessment

We are asking you to discuss the benefit/risk of the use of the prescription opioid antitussive products in children and adolescents. Some of the factors that the committee should consider in the benefit/risk assessment are provided below.

The benefit/risk profile of prescription opioid antitussives is not straightforward.

- Regarding benefit, prescription opioid cough products in combination with other antihistamines, decongestants and/or expectorants are indicated for "relief of cough and symptoms associated with upper respiratory allergies or the common cold." The FDA has determined that these products are effective for relief of cough.

- Regarding risk, opioid antitussives are associated with respiratory depression as outlined earlier in this memo, and these products are labeled with warnings regarding this risk and the safety concerns in children. Additionally, these products also have the risks of misuse, abuse, addiction, overdose, and death that are inherent to all opioid products.

- FDA has provided a summary of the expert roundtable meeting held to discuss the treatment of cough in pediatric patients, and the public communications regarding use of opioids from various organizations as background for the committee's understanding of current approaches to the treatment of cough in pediatric patients.

FDA is committed to fundamentally re-evaluating the benefit-risk paradigm of opioid-containing products to consider the wider public health effects, since deaths and hospitalizations due to opioid overdose have greatly increased in recent years. FDA is also committed to enhancing safety labeling of opioid-containing products. In an effort to address these issues, FDA is asking the advisory committee to provide their perspective on the benefits and risks of the use of prescription opioid antitussives in pediatric patients.

9. Issues for Discussion

The main issues for discussion will be the benefit/risk of opioid antitussives for pediatric patients for whom the products are not otherwise restricted (e.g., patients less than 12 years of age for codeine).

10. Appendices

The FDA Briefing Document includes the following additional resources:

- Summary of the April 27, 2017 Expert Meeting on Use of Cough Suppressants in Children
- FDA Summary Memorandum from December 10, 2015, FDA Advisory Committee Meeting.
- FDA Drug Safety Communication: FDA restrict use of prescription codeine pain and cough medicines in children April 20, 2017
- Pham T. Pediatric Outpatient Retail Utilization Patterns of Opioid and Non-Opioid Containing Antitussives. Review finalized July 28, 2017
- Nguyen A. Hydrocodone-containing cough and cold products: Pediatric Postmarketing Safety Analysis. Review finalized March 3, 2016
- Coyle TD. Opioid analgesics in the pediatric population: a review of the epidemiologic literature examining the outcomes of misuse, abuse, addiction, overdose and death. Review finalized September 12, 2016

Use of Cough Suppressants in Children

Expert Roundtable Meeting

April 27, 2017, 10 – 1 PM

FDA White Oak Campus, Silver Spring, MD

Meeting Purpose

Discuss the experience of health care professionals with the use of cough suppressants in children (<18 years of age), particularly opioid-containing antitussive (OCA) products.

Participants

FDA

John Alexander	Center for Drug Evaluation and Research (CDER)
Jason Bunting	CDER
Grace Chai	CDER
Susan McCune	Office of the Commissioner (OC)
Sally Seymour	CDER
Judy Staffa	CDER
Peter Starke	CDER
Shannon Thor	OC
Theresa Toigo	CDER
Scott Winiecki	CDER
Lynne Yao	CDER
Rosemary Addy	CDER
George Greeley	CDER
Meshaun Payne	CDER
Denise Pica-Branco	CDER
Jacquline Yancy	CDER

Health Professional Organizations

Jahn Avarello	American College of Emergency Physicians
Kathleen Brown	American College of Emergency Physicians

Tate Heuer	American Academy of PAs
Brian R. Wingrove	American Academy of PAs
Nick Schilligo	American Osteopathic Association
Scott Cyrus	American Osteopathic Association
Shawna Mudd	National Association Of Pediatric Nurse Practitioners
Millicent Collins	National Association Of Pediatric Nurse Practitioners
Hsiang (Shonna) Yin	NYU School of Medicine
Debra M Boyer	American Thoracic Society
Bridgette Jones (remote)	American Academy of Pediatrics
James Baumberger	American Academy of Pediatrics
Kathleen Neville	American Academy of Pediatrics
Kenneth Lin (remote)	American Academy of Family Physicians
Jan Towers	American Association of Nurse Practitioners
Sheila Heitzig	American Academy of Allergy Asthma and Immunology
Mandel Sher (remote)	American Academy of Allergy Asthma and Immunology
John Oppenheimer (remote)	American College of Chest Physicians (ACCP)

Summary of Discussion

FDA welcomed the representatives of health professional societies and briefly provided an overview of the purpose of the meeting: To obtain information on the use of cough suppressants, particularly opioid cough suppressants in children. FDA clarified that this meeting would not be used to make regulatory decisions, but to help inform a future advisory committee meeting.

> *FDA Question: What is your experience with the use of cough suppressants in children (<18 years of age), particularly opioid-containing antitussive (OCA) products, and do your organizations have any existing guidelines or recommendations on their use?*

Participants distinguished among categories of cough, stating that it is important to distinguish between cough that is productive or non-productive (irritant-causing) and cough that is acute or chronic. Participants emphasized the importance of identifying the underlying cause of cough in determining the appropriate treatment, rather than focusing on cough suppression.

Participants noted that the use of cough suppressants depends on the clinical situation, but that cough should not be suppressed unless it is causing clinical consequences, including, for example:

1. Cough leading to consecutive nights of poor sleep and/or vomiting
2. Cough leading to rib fractures
3. Cough severe enough to lead to hypoxia

Acute and Chronic Cough Treatments

Participants first focused on treatment of acute cough. Overall, participants felt that in the acute setting, if the cough is productive, identification of the cause and treatment of the underlying condition is important. Cough suppressants should not be used, in general, for acute productive cough.

> *FDA Question: What might be a determining factor that would lead to treating an acute cough and how might they treat it?*

Although the discussion at that point was focused on acute cough, the discussion also included treatments used in the setting of chronic cough. Participants included the following therapies for treatment of acute "irritant" cough:

1. Nasal saline
2. Increased humidification
3. Honey
4. Treatment of post-nasal drip (e.g., antihistamines and physical maneuvers)
5. Bronchodilators and both oral and/or inhaled corticosteroids
6. Dextromethorphan, guaifenesin, or benzonatate
7. Treatment of GERD when associated with cough

One expert noted that official guidelines from the American Academy of Chest Physicians recommend that acute cough not be suppressed and also noted that there are no interventions that have been evaluated in controlled studies that have demonstrated effectiveness.

Participants noted that treatment with bronchodilators and corticosteroids may be therapeutic and diagnostic. Participants acknowledged use of bronchodilators for cough, conveying the perception that the bronchodilators and other options listed were viewed as less likely to be harmful.

In addition, although not proven to be effective, some of the participants reported having used benzonatate and dextromethorphan and may treat with albuterol for bronchospasm or with another agent to minimize, but not suppress, the cough as some co-morbidities may be present.

One expert from the American Osteopathic Association described the use of osteopathic manipulative techniques for cough in pediatric patients.

Some of the participants stated that they might also treat acute cough with honey. Participants reiterated that the data indicate that there are no really good medications for treating acute cough with, perhaps, the exception of honey.

Overall, participants stated that for acute cough, the situations when a suppressant might be warranted would be in a setting of pretty significant consequences to the child (i.e. fractured ribs, consecutive nights of no sleep). Under no circumstance would participants treat with an opioid for acute cough.

> *FDA Request for Clarification: What would be the age cut-off for using codeine or hydrocodone? Specifically, do concerns about using these products apply mainly to younger children, or include adolescents?*

Participants indicated that the concerns applied to the entire pediatric age range, and some participants who treat adults suggested that their views on the use of opioid drugs to treat cough extended to adults.

Some participants stated that with respect to adult patients, long-acting hydrocodone may be useful for suppression of chronic cough in some cases, but a new approach (still investigational) would be to use neuromodulators (off label) as they have been observed to work for chronic cough.

Other participants stated that there are few situations in adolescents when codeine might be used (e.g., end of life situations for pain mainly with reduction of cough as an added benefit).

Overall, the participants did not see a role for the use hydrocodone or codeine for the use of cough in pediatric patients.

> *FDA Request for Clarification: Could you expand on the types of agents that could be used for suppression of cough in children, particularly for chronic cough?*

Depending on the patient status (in-patient/out-patient) and the underlying cause, different treatments could be given. Some of those treatments include:

- Inhaled and oral corticosteroids
- Lansoprazole if the cough is due to a gastrointestinal issue like GERD
- Anti-histamines
- Warm saline
- Honey
- Camphor
- Vapor rub (except in asthmatics as it may exacerbate their condition)
- Nasal suctioning and clearing

For cases of behavioral or habit cough, participants suggested speech or behavioral therapy.

Participants stated that distinguishing between a wet or dry cough with respect to a chronic cough should be considered. Several participants stated that there are no standard definitions of *chronic cough*, but some have used cough duration of less than or greater than 4 weeks. This is partly based on expected resolution of a viral condition by week 2, or a bacterial condition, like bacterial bronchitis or sinusitis, that may take 3 to 4 weeks to clear.

FDA Request: Could you describe the types of neuromodulators or other products you might use to treat adults with chronic irritant cough?

Examples given included (off-label) use of gabapentin, amitriptyline, pregabalin, and slow-release morphine (available in Europe). One participant stated that the paradigm is switching from chronic coughers to cough hypersensitivities. Thus, the focus has changed to products used for treatment of post-nasal drip, allergic rhinitis, etc.

Overall, participants emphasized that in chronic cough situations, it is extremely important to differentiate between a cough that is productive and an irritant cough. The participants agreed that when the cough is productive, it is important to identify the underlying condition.

Participants discussed how treatment for chronic and acute cough changes based on the age of the patient. Children between 4 and 5 years of age can usually do a lung function test that will allow the physician to determine if asthma is contributing to cough. However, for the younger patient, a trial of albuterol may be given. For older kids (older than 2 years), participants said the treatment for acute or chronic cough includes steroids and albuterol, unless the underlying cause is bacterial, then the treatment would be antibiotics and rest.

The Role of Opioid Cough Suppressants in Children

Participants stated that in general pediatrician office visits, if an opioid is needed for treatment, it should be prescribed by a specialist. However, participants repeated that there is no role for the use of an opioid in treating or suppressing acute cough. Many participants stated that they had never prescribed an opioid for children under 18, except for the extreme conditions mentioned earlier.

FDA Request for Clarification: Are the reasons for not prescribing opioid treatment based on safety or efficacy?

Participants stated that they are concerned about both: the benefits for cough suppression are questionable, and there are concerns about harm from opioid use. Overall, participants agreed that treatment of cough with opioid-containing products was ***not*** appropriate and that alternative treatments for cough would differ depending on the age of the child.

Participants also expressed the concern that, although they do not prescribe opioids to pediatric patients, there are some practitioners who do prescribe them. Some participants described pressures from caregivers to treat cough as well as indirect pressure from consumer reviews and ratings published on line.

General Comments

- Participants agreed about the need for outreach to inform and educate practitioners that prescribing opioids for cough in children is not recommended.
- Some commented that removing the cough treatment indication for opioid products in labeling might help reduce pressure to treat, as described above. Participants noted that removal of the indication might shift the treatment to other cough suppressants

like dextromethorphan. There was concern, however, about resistance from some practitioners to removing the cough treatment indication for opioids, even though there are other treatment options.

- Some participants suggested investigating the characteristics of those physicians who prescribe these drugs more often than others.
- Participants supported educating the public and families about the concerns related to using opioids to treat pediatric patients.
- Participants agreed that the availability of non-opioid, cough controlling products approved for children would be of benefit.
- The suggestion was made to review the adverse event profile of alternative agents for chronic cough for comparison to codeine-containing cough products.
- Participants encouraged FDA to include patient and family representatives, urgent care physicians, rural health prescribers, osteopathic practitioners, and representation from other practices in any future public meetings. One AAP representative suggested that the AAP could contact others about future public meetings.

Society/Organizational Recommendations/Guidelines on Treatment of Cough in Children

Participants provided a number of references and policy statements that specifically discuss (and typically discourage) opioid use for treating cough in pediatric patients. Although not exhaustive, the following list contains some of the references discussed during the meeting.

American Academy of Pediatrics. 1997 (Reaffirmed 2006). "Use of codeine- and dextromethorphan-containing cough remedies in children," in AAP Committee on Drugs Policy Statement., *Pediatr*., 1997, 99:6, pp 918-920. Available at http://pediatrics.aappublications.org/content/99/6/918.long. Accessed June 2017.

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Green JL, Wang GS, Reynolds KM, Reynolds KM, Banner W. Bond GR et al. 2017. Safety profile of cough and cold medication use in pediatrics. *Pediatrics*. 2017. 139:e20163070. Available at http://pediatrics.aappublications.org/content/early/2017/05/02/peds.2016-3070. Accessed June 2017.

Paul IM, Reynolds KM, Kauffman RE, Banner W, et al. Adverse events associated with pediatric exposures to dextromethorphan. *Clin Toxicol* (Phila). 2017 Jan; 55(1):25-32. doi: 10.1080/15563650.2016.1240803. Epub 2016 Oct 13.

Smith SM, Schroeder K, and Fahey T. 2014. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. Cochrane Database of Systematic Reviews 2014, Issue 11.

Available at http://www.cochrane.org/CD001831/ARI_over-the-counter-otc-medications-for-acute-cough-in-children-and-adults-in-community-settings. Accessed June 2017.

Tobias J, Green TP, and Coté CJ. 2016., "Codeine: Time to Say '"No,' AAP Clinical Report.," in AAP Section on Anesthesiology and Pain Medicine, AAP Committee on Drugs, *Pediatr*. 2016;138(4): e20162396. Available At http://pediatrics.aappublications.org/content/early/2016/09/15/peds.2016-2396.full. Accessed June 2017.

Vertigan AE, Murad MH, Pringsheim T, Feinstein A, Chang AB, Newcombe PA, et al. 2015. "Somatic Cough Syndrome (Previously Referred to as Psychogenic Cough) and Tic Cough (Previously Referred to as Habit Cough) in Adults and Children," in CHEST Guideline and Expert Panel Report. *Chest,* 2015; 148 (1): 24 - 31Jul;148(1):24-31. doi. Available at https://www.ncbi.nlm.nih.gov/pubmed/25856777. Accessed June 2017.

World Health Organization. Department of Child and Adolescent Health and Development. 2001. Cough and cold remedies for the treatment of acute respiratory infections in young children. Available at http://apps.who.int/iris/bitstream/10665/66856/1/WHO_FCH_CAH_01.02.pdf?ua=1&ua=1. Accessed June 2017.

Yancy WS, McCrory DC, Coeytaux RR, Schmit KM, Kemper AR, Goode A, et al. 2013. Efficacy and tolerability of treatments for chronic cough: a systematic review and meta-analysis. *Chest*, 2013; 144(6):1827–1838. Available at https://www.ncbi.nlm.nih.gov/pubmed/23928798. Accessed June 2017.

FDA Summary Memorandum

Date: November 12, 2015

From: Sally Seymour, MD
Deputy Director for Safety, Division of Pulmonary, Allergy, and Rheumatology Products

Judy Racoosin, MD, MPH
Deputy Director for Safety, Division of Anesthesia, Analgesia, and Addiction Products

David Moeny, R.Ph., MPH
Deputy Director, Division of Epidemiology II
Office of Surveillance and Epidemiology

Valerie Pratt, MD
Deputy Director for Safety, Division of Nonprescription Drug Products

To: Members, Pulmonary Allergy Drugs and Drug Safety and Risk Management Advisory Committees

Subject: The safety of codeine in children 18 years of age and younger

1. Introduction

Thank you for your participation in the Joint Pulmonary Allergy Drugs and Drug Safety and Risk Management Advisory Committee (PADAC/DSaRM) meeting to be held on December 10, 2015. As participants in this Advisory Committee (AC) meeting, you provide important expert scientific advice and recommendations to the US Food and Drug Administration (FDA) on the regulatory decision making process related to drugs marketed in the United States. The upcoming meeting is to discuss the safety of codeine in children 18 years of age and younger.

Codeine sulfate is an opioid indicated for the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate. Codeine for analgesia is marketed as single ingredient codeine or most often in combination with acetaminophen. Codeine is also indicated for the relief of cough and is available in combination with other medications in prescription products for cough and symptoms associated with upper respiratory allergies or common cold. Codeine is also available through the over the counter (OTC) Drug Monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products

(21 CFR 341.14, 21 CFR 341.74, 21 CFR341.90) in combination with other medications for cough and cold symptoms.

Codeine is partially metabolized to morphine, its most potent analgesic metabolite, through the CYP2D6 pathway. A high degree of variability exists for CYP2D6 metabolism of codeine because of underlying genetic differences in CYP2D6 activity. Because of this variability, depending on CYP2D6 activity, patients may be at risk for therapeutic failure or at risk for toxicity.

Given the variability in the metabolism of codeine, the safety of codeine use in children has been a concern for years, particularly the risk of respiratory depression and death. Over the past decade, FDA has updated the label for codeine-containing products regarding the risk of respiratory depression. In 2007, prescription codeine labels were updated with information regarding variable metabolism and the risk of respiratory depression, specifically in infants of nursing mothers who used codeine. In 2012, FDA issued a Drug Safety Communication about reports of death and respiratory depression in pediatric patients, primarily with use of codeine following tonsillectomy and/or adenoidectomy. In February 2013, after completing a review of the available safety data, FDA required a Boxed Warning and Contraindication for the use of codeine in this setting.[1] In June 2013, following a review of the relevant data, the European Medicines Agency (EMA) made the determination that "codeine-containing products indicated in the management of pain should only be indicated in children above 12 years of age and contraindicated in paediatric patients below 18 years of age undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea syndrome as well as in women during breast-feeding and in patients known to be CYP2D6 ultra-rapid metabolisers."

In April 2015, the (EMA) completed a review of the use of codeine for cough and cold indications. The EMA contraindicated the use of codeine in children below 12 years of age for cough and cold and recommended that codeine not be used in children and adolescents 12-18 years who have breathing problems.[2]

Given the continued concern with use of codeine in children, the Agency convened this AC meeting to discuss the available safety data with codeine use in children for cough or analgesia and to obtain input on whether the use of codeine in children should be restricted further beyond the current Contraindication and whether codeine should be available as an antitussive through the OTC Drug Monograph. Given that the FDA has made a determination about the efficacy of these products, the efficacy of codeine for analgesia and cough will not be addressed in the FDA Briefing Document or presentation. The focus of the meeting is safety.

The FDA Briefing Document includes the following:

1. Summary Memorandum that provides background and regulatory history for this safety issue as well as a summary of FDA's reviews;
2. Draft Points to Consider or topics for discussion at the upcoming meeting;
3. FDA Summary Memo for the 2012-2013 Codeine Safety Review
4. FDA 2013 Drug Safety Communication for Codeine

5. Racoosin JA, Roberson DW, Pacanowski MA, and Nielsen DR. New Evidence about an Old Drug – Risk with Codeine after Adenotonsillectomy. *N Engl J Medicine 2013;* 368:2155-2157.
6. Office of Clinical Pharmacology (OCP) 2012 review on the clinical pharmacology and pharmacogenomics of codeine and a 2015 addendum;
7. Office of Surveillance and Epidemiology (OSE) review of post-marketing safety reports, data on emergency room visits for codeine events, relevant literature, and data on codeine utilization in the US;
8. EMA Pharmacovigilance Assessment Committee (PRAC) June 2013 Assessment Report for codeine-containing medicinal products indicated in the management of pain in children
9. EMA Pharmacovigilance Assessment Committee (PRAC) March 2015 Report on codeine use in children for cough and cold
10. EMA April 2015 Recommendations for codeine use in children for cough and cold
11. Overview of FDA Monograph for Codeine

At the meeting, you will be asked to discuss the safety of codeine for use in the treatment of pain or cough in pediatric patients. Again, we are grateful for your participation in this meeting and thank you for providing your expertise and insight. We are hopeful that the discussion at this meeting will assist us in determining possible regulatory options, including, but not limited to, changes to the product labeling.

2. Clinical Pharmacology

Codeine is a prodrug that is metabolized by the CYP2D6 pathway. Approximately 5-10% of codeine is converted to morphine by CYP2D6, which is in turn metabolized to the glucuronide metabolites via UGT2B7, as shown in the figure below.

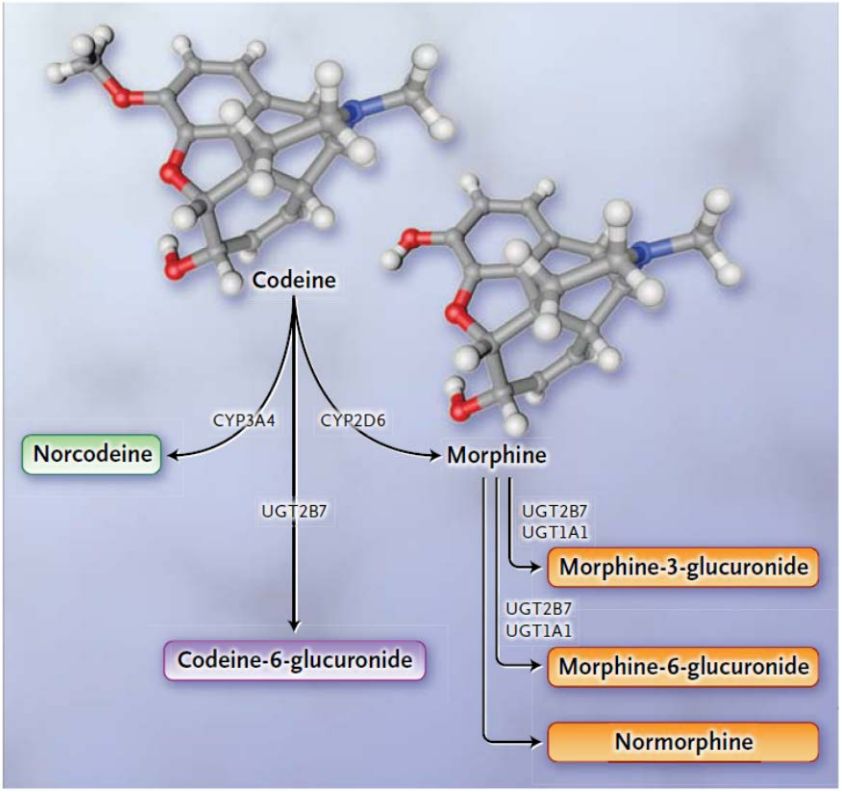

Figure 1. Codeine Metabolism

Source: *N Engl J Med* 2013: 368 (23): 2155-2157. Adapted from Crews KR, Gaedigk A, Dunnenberger HM, et al. *Clinical Pharmacology & Therapeutics* 2012; 91:321-6.

A high degree of variability exists for CYP2D6-mediated activation of codeine because of underlying genetic differences in CYP2D6 activity. Patients may be classified as having one of four metabolic phenotypes depending on the number of active genes the patient has, as shown in the table below.

Table 1. Pharmacogenomic Variations for CYP2D6

Predicted phenotype	Prevalence*	Genotypes	Examples of diplotypes
Ultrarapid metabolizer (UM)	~1–2%†	An individual carrying more than two copies of functional alleles	**1/*1xN, *1/*2xN*
Extensive metabolizer (EM)	~77–92%	An individual carrying two alleles encoding full or reduced function or one full function allele together with either one nonfunctional or one reduced-function allele	**1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10*
Intermediate metabolizer (IM)	~2–11%	An individual carrying one reduced and one nonfunctional allele	**4/*10, *5/*41*
Poor metabolizer (PM)	~5–10%	An individual carrying no functional alleles	**4/*4, *4/*5, *5/*5, *4/*6*
* Frequency data are for Caucasians. Frequencies may differ substantially by race/ethnicity † Ultrarapid metabolizer frequencies are as follows: African Americans, 3%; Arab, 16-28%; Caucasian, 1-10%; Chinese, 0.5-1%; Ethiopian, 16-28%; Hispanic, 0.5-1%; Japanese, 0.5-1%; North African, 16-28%			

Source: Adapted from Crews KR, Gaedigk A, Dunnenberger HM, et al. *Clinical Pharmacology & Therapeutics* 2012; 91:321-6.

Patients with CYP2D6 dysfunction may have therapeutic failure secondary to reduced biotransformation of codeine to morphine. Conversely, UMs may be at risk of toxicity because of more rapid and complete conversion to morphine. For example, Sindrup, et al. evaluated oral codeine (75 mg) in 12 EMs and 12 PMs identified using urinary sparteine metabolic ratios to study plasma concentrations and therapeutic response.[3] The authors found that morphine was undetectable in PMs (< 4 nM) and peak morphine concentrations were between 4.9–37.6 nM in EMs. In the EM group, codeine significantly decreased the pain threshold caused by laser stimuli, whereas no significant analgesic effects were observed in the PM group.

In a separate study, a single 50-mg dose of oral codeine led to a 20-fold higher AUC of morphine and M6-glucuronide in 8 EMs as compared to 6 PMs.[4] Individuals with the UM phenotype are at the highest risk for morphine exposure and toxicity, including respiratory depression. The codeine AUC and the Cmax were not significantly different in UMs compared to EMs, although the morphine AUC was 45.5% higher in UMs ($p<0.05$).[5] When examining outcomes, significantly more adverse effects were reported in the UM group compared with the EMs, suggesting that risk for codeine toxicity is dependent on morphine exposure. The clinical and pharmacokinetic literature has been extensively reviewed by the Clinical Pharmacogenetics Implementation Consortium.[6]

For a more detailed discussion of the clinical pharmacology and pharmacogenomics of codeine, refer to the review by the Office of Clinical Pharmacology.

3. Background

Codeine is an opioid that is a derivative of opium and a selective mu receptor agonist that has been available in the US since the 1950s. Codeine is currently approved as both an analgesic agent and as an antitussive. Dihydrocodeine is an ingredient in some headache treatments, but those products are not approved in children, and they will not be a topic of discussion at the advisory committee meeting.

A. Codeine for analgesia

Codeine is available as a single ingredient product and in combination with other medications (primarily acetaminophen) for the relief of mild to moderately severe pain. Single ingredient codeine products are not approved for use in children less than 18 years of age; however, codeine/acetaminophen combination products are labeled for pediatric use with dosing instructions down to three years of age. Table 2 shows the available prescription codeine products for analgesia indications and the relevant pediatric labeling.

Table 2. Available Prescription Codeine Products for Analgesia Indications

Application	Product	Dosage Form	Pediatric Labeling
NDA 22402 202245 (Roxane)	Codeine sulfate	Tablet Solution	Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine Contraindication for postoperative pain management in children post tonsillectomy and/or adenoidectomy (T&A) Safety and effectiveness and PK in children < 18 years of age have not been established.
ANDAs (multiple)	Codeine phosphate and acetaminophen*	Tablet Solution	Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine Contraindication for postoperative pain management in children post T&A Safe dosage of acetaminophen and codeine phosphate oral solution has not been established in pediatric patients below the age of 3 years.
NDA 11483	Synalgos DC (Dihydrocodeine, aspirin, caffeine)	Capsule	Preparations containing aspirin should be kept out of the reach of children. Synalgos-DC is not recommended for patients 12 years of age and under. Since there is no experience in children who have received this drug, safety and efficacy in children have not been established. Modifications to the Pediatric Use section to highlight the risk of respiratory depression and death in children who are undergoing tonsillectomy and/or adenoidectomy
ANDA 204785	Dihydrocodeine, acetaminophen, caffeine*	Capsule	Safety and effectiveness of acetaminophen, caffeine, and dihydrocodeine bitartrate capsules in pediatric patients have not been established. The Usage in Children section includes the class-wide statement about the risk of respiratory depression and death in children who are undergoing tonsillectomy and/or adenoidectomy
Source: FDA Orange Book search on September 30, 2015 * Product labels also contain a Boxed Warning for hepatotoxicity related to acetaminophen.			

B. Codeine for cough (prescription)

Codeine sulfate is indicated for the relief of cough and is available with a prescription in combination with other medications for cough and symptoms associated with upper respiratory allergies or the common cold. Table 3 shows the available prescription codeine products for cough/cold indications and the relevant pediatric labeling.

Table 3. Available Prescription Codeine Products for Cough/Cold Indications

Application	Product	Dosage Form	Relevant Pediatric Labeling
NDA 206323 (Spriaso)	Chlorpheniramine maleate; codeine phosphate	Extended Release Oral Tablet	Not indicated for patients <18 years; Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine Contraindication for postoperative pain management in children post T&A
NDA 207768 (Tris Pharma)	Chlorpheniramine polistirex; codeine polistirex (Tuzistra XR)	Extended Release Oral Suspension	
NDA 8306 ANDA (multiple)	Codeine phosphate; phenylephrine hydrochloride; promethazine hydrochloride	Oral Syrup	Contraindication in children < 6 yrs; Boxed Warning regarding respiratory depression in children (promethazine/codeine combo) Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine Contraindication for postoperative pain management in children post T&A Dosing information for children: • 12 years and older: 10 mg every 4 to 6 hours; NTE 60 mg in 24 hours • 6 to <12 years: 5 to 10 mg every 4 to 6 hours; NTE 60 mg in 24 hours
NDA 8306 ANDA (multiple)	Codeine phosphate; promethazine hydrochloride	Oral Syrup	
ANDA 88704 (Sti Pharma)	Codeine phosphate; pseudoephedrine hydrochloride; triprolidine hydrochloride (Triacin C)	Oral Syrup	Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine Contraindication for postoperative pain management in children post T&A Dosing information for children: • 12 years and older: 20 mg every 4 to 6 hours; NTE 80 mg in 24 hours • 6 to <12 years: 10 mg every 4 to 6 hours; NTE 40 mg in 24 hours • 2 to <6 years: 5 mg every 4 to 6 hours, NTE 10 mg
Source: FDA Orange Book search on June 4, 2015			

Combinations of codeine with promethazine were first approved in 1952 (NDA 8306), and were later the subject of a Drug Efficacy Study Implementation (DESI) review (DESI 6514). After reformulation in 1984, they were found effective as an antihistamine antitussive combination, with or without a decongestant. Promethazine is a phenothiazine derivative that acts as an H_1 receptor antagonist, sedative, antiemetic, and antitussive. Because of the potential for respiratory depression, promethazine product labels have a Boxed Warning for use in pediatric patients less than 2 years of age, along with a caution for use in pediatric patients 2 years of age and older. Combination promethazine and

codeine product labels currently contain a Boxed Warning for respiratory depression and a Contraindication in patients less than 6 years of age.

In addition to the Boxed Warning on promethazine and codeine combination products, all the approved codeine-containing products have a Boxed Warning regarding deaths related to ultra-rapid metabolism of codeine to morphine and a Contraindication for postoperative pain management in children post tonsillectomy and/or adenoidectomy.

As shown above in Table 3, some older codeine cough/cold combination products have dosing information for children as young as 2 years of age and other products for children as young as 6 years of age (e.g., promethazine and codeine products), whereas the newer approved codeine combination products do not currently have dosing information for children.

C. Codeine for cough (OTC)

Codeine is also available through the OTC Drug Monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (21 CFR 341.14, 21 CFR 341.74, 21 CFR 341.90) in combination with other medications for cough and cold symptoms. An OTC drug monograph describes the conditions for marketing for certain OTC drugs that are generally recognized as safe and effective (GRASE) if they meet the conditions of 21 CFR 330.1 and each of the conditions contained in the specific monograph. The conditions in 21 CFR 330.1 include, among other things, requirements that the product be unadulterated, be in compliance with current good manufacturing practices, and that it not be misbranded. If manufacturers comply with the conditions in the monograph, they may market an OTC product under the monograph without going through the FDA New Drug Application (NDA) review process.

21 CFR Part 341 is the monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use. The majority of the OTC medications for cold, cough, and allergy symptoms are brought to market under this monograph. Codeine, codeine phosphate, and codeine sulfate are listed as antitussive active ingredients in 21 CFR 341.14(a)(2). It is important to note that these codeine ingredients may be used only in combination with at least one nonnarcotic active ingredient (e.g. antihistamine and/or decongestant and/or analgesic/antipyretic) as stated in 21 CFR 290.2 and 21 CFR 1308.15, which also limits the concentration of codeine in such combinations and requires that the nonnarcotic ingredient confer "valuable medicinal qualities other than those possessed by codeine alone." The limits for codeine are:

- Not more than 200 milligrams of codeine per 100 milliliters or per 100 grams.
- Not more than 100 milligrams of dihydrocodeine per 100 milliliters or per 100 grams.

Also, FDA issued a final rule on February 1, 2002 (67 FR 4904) to amend regulations regarding certain label statements on prescription drugs. 21 CFR 290.1 was added to make clear the agency's determination that a controlled substance in Schedules II-V of the

Controlled Substance Act must be dispensed by prescription only unless otherwise determined by the Agency. 21 CFR 290.2 was added to allow the exemption for small amounts defined as not more than 200 milligrams of codeine per 100 milliliters or per 100 grams.

The OTC monograph for codeine includes labeling for children down to 6 years of age (21 CFR 341.74(d)(1)(ii)) and includes professional labeling for children down to 2 years of age (21 CFR3 41.90). Relevant labeling for codeine is highlighted below:

OTC monograph requirements for the "Directions" section of the Drug Facts Label:

For products containing codeine ingredients identified in 21 CFR 341.14(a)(2), labeling is outlined in 21 CFR 341.74

- Adults and children 12 years of age and over: 10 to 20 milligrams every 4 to 6 hours, not to exceed 120 milligrams in 24 hours, or as directed by a doctor.
- Children 6 to under 12 years of age: Oral dosage is 5 to 10 milligrams every 4 to 6 hours, not to exceed 60 milligrams in 24 hours, or as directed by a doctor.
- Children under 6 years of age: Consult a doctor. A special measuring device should be used to give an accurate dose of this product to children under 6 years of age.
- Giving a higher dose than recommended by a doctor could result in serious side effects for your child.

OTC monograph requirements for the "Warnings" section of the Drug Facts Label:

For oral and topical antitussives

- "A persistent cough may be a sign of a serious condition. If cough persists for more than 1 week, tends to recur, or is accompanied by fever, rash, or persistent headache, consult a doctor."

For oral and topical antitussives labeled for adults or for adults and children under 12 years of age

- "Do not take this product for persistent or chronic cough such as occurs with smoking, asthma, or emphysema, or if cough is accompanied by excessive phlegm (mucus) unless directed by a doctor."

For products containing codeine ingredients identified in 21 CFR 341.14(a)(2)

- "May cause or aggravate constipation."

For products containing codeine ingredients identified in 21 CFR 341.14(a)(2) when labeled for use in adults and children under 12 years of age

- "Adults and children who have a chronic pulmonary disease or shortness of breath, or children who are taking other drugs, should not take this product unless directed by a doctor."

OTC monograph requirements for professional labeling (provided to health professionals but not the general public)

- Children 2 to under 6 years of age: 1 milligram per kilogram body weight per day administered in four equal divided doses. The average body weight for each age may also be used to determine dosage as follows:
    - children 2 years of age (average body weight, 12 kilograms), the dosage is 3 milligrams every 4 to 6 hours, not to exceed 12 milligrams in 24 hours;
    - children 3 years of age (average body weight, 14 kilograms), the dosage is 3.5 milligrams every 4 to 6 hours, not to exceed 14 milligrams in 24 hours;
    - children 4 years of age (average body weight, 16 kilograms), the dosage is 4 milligrams every 4 to 6 hours, not to exceed 16 milligrams in 24 hours:
    - children 5 years of age (average body weight, 18 kilograms), the dosage is 4.5 milligrams every 4 to 6 hours, not to exceed 18 milligrams in 24 hours.
- The manufacturer must relate these dosages for its specific product dosages for its specific product to the use of the calibrated measuring device discussed in paragraph (c)(3) of this section. If age is used to determine the dose, the directions must include instructions to reduce the dose for low-weight children.
- Parents should be instructed to obtain and use a calibrated measuring device for administering the drug to the child, to use extreme care in measuring the dosage, and not exceed the recommended daily dosage.
- A dispensing device (such as a dropper calibrated for age or weight) should be dispensed along with the product when it is intended for use in children 2 to under 6 years of age to prevent possible overdose due to improper measuring of the dose.
- Codeine is not recommended for use in children under 2 years of age. Children under 2 years may be more susceptible to the respiratory depressant effects of codeine, including respiratory arrest, coma, and death

A 2015 review by FDA found 45 products currently registered with FDA to be marketed under the OTC monograph. Two unapproved new drug products were also found, and additional products may have been marketed previously and subsequently withdrawn, or not registered. The registered products comprise 13 distinct combinations of codeine with various other active ingredients, and were registered by 18 different companies.

Twenty-eight states and the District of Columbia permit the sale of codeine without a prescription, while 22 states and Puerto Rico prohibit the sale of codeine without a prescription.[7] Most if not all of the state laws allowing the OTC sale of codeine require the pharmacist to oversee or personally complete the transaction, and allow the pharmacist to choose not to sell the product OTC. For codeine that is sold OTC, all states require that the purchaser's identifying information and details of the sale be recorded. States differ on the maximum allowable quantity which can be purchased at one time (60 mL to 240 mL), the amount of time required before additional purchases are permitted (48 hours to 96 hours), and the minimum age of a purchaser (18 years to 21 years). The variations between states involve regulations and laws which are more restrictive than the federal requirements in 21 CFR 1306.26.

Keep in mind that while the input from this AC panel will be considered in determination of whether further labeling revisions are warranted for codeine products, the regulatory pathway for changing the labeling for the NDA/ANDA products and the monograph products is quite different. Changing labeling for the NDA/ANDA products can be

accomplished by working with the manufacturers. However, implementing labeling changes for the FDA monograph products is accomplished through a two-phase rulemaking process and would be expected to be quite lengthy in duration.

4. Recent Developments in Codeine Safety

The following is a brief summary of recent developments in codeine safety that are relevant to the discussion at the upcoming AC meeting.

- Neonatal toxicity related to exposure to high levels of morphine through the breast milk of an ultra-rapid metabolizer mother taking codeine
    - A 2006 publication in the Lancet described the death of a nursing infant who was exposed to high levels of morphine in breast milk because the mother, who was taking codeine, was an ultra-rapid metabolizer of codeine, a CYP2D6 substrate.[8]
    - In 2007, FDA revised codeine labeling to warn of this risk and also issued communications to healthcare providers and the public regarding use of codeine in nursing mothers and the risk to infants exposed to morphine in breast milk from mothers who were ultra-rapid metabolizers of codeine.[9]
- Fatal and life-threatening respiratory depression in children following codeine treatment for pain post-adenotonsillectomy who were CYP2D6 ultra-rapid metabolizers
    - Following identification of a case series published in *Pediatrics* in April 2012,[10] FDA embarked on an evaluation of the issue.
    - In August 2012, FDA issued a Drug Safety Communication acknowledging the case series about the risk of death or life-threatening respiratory depression following adenotonsillectomy in some children who received codeine for pain control following surgery, and describing that an evaluation was under way.[11]
    - In February 2013, FDA issued a Safety Labeling Change notification letter to codeine- and dihydrocodeine-containing products to require a contraindication for use in children following tonsillectomy and/or adenoidectomy and a boxed warning describing the risks of being an ultra-rapid metabolizer of codeine.[1]
    - The FDA's assessment of this safety issue was published online in April 2013 as a Perspective in the *New England Journal of Medicine* - "New Evidence about an Old Drug — Risk with Codeine after Adenotonsillectomy".[12]
    - The required labeling changes were approved in May 2013. The relevant labeling is shown below.

WARNING: DEATH RELATED TO ULTRA-RAPID METABOLISM OF CODEINE TO MORPHINE

Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism.

CONTRAINDICATION

Codeine sulfate is contraindicated for postoperative pain management in children who have undergone tonsillectomy and/or adenoidectomy.

WARNING

Death Related to Ultra-Rapid Metabolism of Codeine to Morphine

Respiratory depression and death have occurred in children who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 [CYP2D6] or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine.

Some individuals may be ultra-rapid metabolizers because of a specific CYP2D6 genotype (gene duplications denoted as *1/*1xN or *1/*2xN). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing).

Children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy.

When prescribing codeine, healthcare providers should choose the lowest effective dose for the shortest period of time and inform patients and caregivers about these risks and the signs of morphine overdose.

PEDIATRIC USE

Respiratory depression and death have occurred in children with obstructive sleep apnea who received codeine in the postoperative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 or high morphine concentrations). These children may be particularly sensitive to the respiratory depressant effects of codeine that has been rapidly metabolized to morphine. Codeine is contraindicated for post-operative pain management in all pediatric patients undergoing tonsillectomy and/or adenoidectomy [see Contraindications (4)].

A summary memo of the Agency's review of this safety issue from 2012-13 is included in the FDA Briefing Package.

- In October 2012, the EMA initiated a review of codeine focusing on codeine use in children for pain relief. In June 2013, the EMA Pharmacovigilance Risk Assessment Committee (PRAC) recommended the following, which was endorsed by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh).[13]
    - Codeine-containing medicines should only be used to treat acute (short-lived) moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers such as paracetamol [acetaminophen] or ibuprofen, because of the risk of respiratory depression associated with codeine use.
    - Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory problems.
    - The product information of these medicines should carry a warning that children with conditions associated with breathing problems should not use codeine.
    - The risk of side effects with codeine may also apply to adults. Codeine should therefore not be used in people of any age who are known to be ultra-rapid metabolisers nor in breastfeeding mothers (because codeine can pass to the baby through breast milk). The product information for codeine should also include general information for healthcare professionals, patients and carers on the risk of morphine side effects with codeine, and how to recognise their symptoms.

- In June 2013, Health Canada announced that it reviewed the safety of prescription pain and cough medications containing codeine and is no longer recommending their use in children less than 12 years of age. This recommendation was based on very rare cases of serious side effects and deaths in children that have been attributed to codeine, when given directly to a child, or to babies from breast milk.[14]

- In April 2014, the EMA initiated a review of codeine use in children for cough and cold. In March 2015, the PRAC recommended the following which was endorsed by CMDh.[15]

- Codeine should be contraindicated in children below 12 years. This means it must not be used in this patient group.
- Use of codeine for cough and cold is not recommended in children and adolescents between 12 and 18 years who have problems with breathing.

The EMA recommendations for restrictions regarding codeine use in children for cough and cold indications is the primary reason that the Agency decided to re-open this safety issue and convene this Advisory Committee meeting.

5. Clinical Considerations – Analgesia

Few analgesics have been studied sufficiently to support pediatric-specific labeling for efficacy or safety, but work is ongoing to attempt to fill this important clinical gap.[16] As safety concerns arose with codeine, some professional societies and scientific organizations have provided assessments or recommendations specifically about the use of codeine. These are summarized below.

American Academy of Pediatrics
The American Academy of Pediatrics (AAP) has not taken a formal position on codeine for analgesia in children.

American Academy of Otolaryngology-Head and Neck Surgery
The clinical practice guideline on tonsillectomy in children published by the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) in 2011 includes a discussion of post-operative pain control.[17] The guideline did not recommend prescribing specific drugs because they consider that pain "can often be managed with over-the-counter analgesics and hydration." The guideline goes on to say that "acetaminophen with codeine does not provide superior control of pain compared with acetaminophen only following tonsillectomy either at rest or with swallowing." But it also notes that in some cases acetaminophen will not provide adequate pain control. Regarding other pain management options, the guideline states that use of non-steroidal anti-inflammatory drugs (NSAIDs) has been controversial because of the known adverse effect on platelet function associated with NSAID use. They cite a Cochrane Collaboration review of 13 randomized controlled trials (including about 1000 children) that found that "NSAIDs did not significantly alter postoperative bleeding compared with placebo or other analgesics.,.", and go on to conclude that NSAIDs (except for ketorolac) "can be used safely for the postoperative treatment of pain following tonsillectomy."

Subsequently, in an editorial coauthored by the FDA and AAO-HNS about the risk associated with codeine after adentonsillectomy[11], the AAO-HNS notes that they "…supported the labeling changes [restricting codeine use in children following adenotonsilectomy] because of the increasing evidence that these extremely rare but catastrophic events can be related to codeine use, because codeine is ineffective in some patients (poor metabolizers), and because of emerging clarity that a variety of other drugs

(e.g., some nonsteroidal antiinflammatory drugs) are safe to use and do not increase the risk of bleeding."

World Health Organization
In March 2011, the World Health Organization removed codeine from the list of essential medicines for children[18] using the rationale below (excerpted from the report):

> The Committee therefore recommended the deletion of codeine from Section 2.2 of the Model List of Essential Medicines for children due to evidence indicating that the analgesic effect is low or absent in neonates and young children; evidence of considerable pharmacogenetic variability among populations, making its efficacy and safety questionable in an unpredictable proportion of the paediatric population and low quality evidence indicating that it is not safer or more efficacious than paracetamol or ibuprofen for the treatment of musculoskeletal trauma in children. The Committee also noted the need to improve access to appropriate analgesia, especially morphine, in all settings.

6. Clinical Considerations - Cough

In the past decade, the use of cough and cold medications, including codeine, has been of interest and various groups have raised concern about the treatment of cough/cold in pediatric patients as outlined below.

American Academy of Pediatrics
The American Academy of Pediatrics has taken a formal opinion on the use of codeine (and dextromethorphan [DM]) for cough. In 1997, the AAP Committee on Drugs provided recommendations on the Use of Codeine and DM-Containing Cough Remedies in Children.[19] The AAP cautioned about the lack of studies to support the efficacy and safety of narcotics or dextromethorphan as antitussives in children. The Committee noted that because of adverse effects and overdosage associated with codeine and DM products for cough, patients and parents should be educated about the lack of proven antitussive effects and the potential risks of these products. The AAP also noted that cough due to URI is short-lived and suppression of cough may be hazardous. In 2007, AAP reaffirmed the statement. [20]

American College of Chest Physicians
In 2006, the American College of Chest Physicians (ACCP) issued Guidelines for Evaluating Chronic Cough in Pediatrics.[21] In these guidelines, one of the recommendations was the following: "In children with cough, cough suppressants and other OTC cough medications should not be used as patients, especially young children, may experience significant morbidity and mortality."

EMA and Health Canada
As noted in the section above, both Health Canada and EMA have made recommendations to not use codeine pain and cough medications in children less than 12 years of age.

Food and Drug Administration

The following FDA activities are included for completeness, although the focus of these activities was on OTC cough and cold products rather than on codeine.

In March 2007, FDA received a Citizen's Petition regarding OTC cough/cold medications regarding concerns that the products have not been shown to be safe and effective for the treatment of cough and cold in children under 6 years of age.

In response to the Citizen's Petition, FDA convened a Joint Nonprescription Drugs Advisory Committee and Pediatric Advisory Committee in October 2007 to discuss the safety and efficacy of OTC cough and cold products for pediatric use. The available efficacy and safety data for OTC cough and cold medications and extrapolation were topics for discussion; however, codeine products were not a focus of the discussion. At that time the committee voted that antihistamines, nasal decongestants, and antitussives should not be used for the common cold in the following age groups:

- Less than 2 years of age – Yes: 21, No 1, Abstain: 0
- 2 to 6 years of age – Yes: 13, No 9, Abstain: 0
- 6 to 12 years of age – Yes: 7, No 15, Abstain: 0

Based upon the Advisory Committee recommendations and the Agency's review, FDA issued a press release in January 2008, recommending that OTC cough/cold medicines not be used in children younger than 2 years of age.[22] The Agency did not make any formal recommendation about the use of these products in children older than 2 years. In October 2008, the Consumer Healthcare Products Association (CHPA) announced voluntary actions by its members to modify product labels of OTC cough/cold medicines to state "do not use" in children under 4 years of age.[23]

Approved Non-Codeine Containing Antitussive Medications

Because the committee is being tasked with providing recommendations on the use of codeine for cough in pediatric patients, information about alternative products available for the treatment of cough in pediatric patients is summarized briefly. Antitussive non-codeine containing medications that are approved for the treatment of cough, including both prescription and OTC products, are shown in Table 4 on the following page.

With regard to prescription antitussive agents, there are two approved active ingredients, benzonatate and hydrocodone. Benzonatate (Tessalon, NDA 11210, and generics) is a local anesthetic that acts peripherally by anesthetizing and dampening the activity of the stretch receptors located in the respiratory passages, lungs, and pleura. It is available as an oral capsule, and has labeling regarding the risk of severe hypersensitivity reactions, including bronchospasm, laryngospasm and cardiovascular collapse, if the capsule is sucked or chewed. Therefore, benzonatate use is limited to children 10 years of age and older who can swallow the capsule without holding it in their mouths or chewing on it. Hydrocodone (Hycodan, NDA 05213) was first approved in 1942. While Hycodan, an immediate-release product, is now discontinued, generics to it are available. Like codeine, hydrocodone is a centrally acting opioid antitussive that is available in as a single ingredient (with homatropine) or combination with other cough/cold medications. Unlike

codeine, hydrocodone is not metabolized by the CYP2D6 pathway to morphine. Nevertheless, hydrocodone can cause respiratory depression, which can be fatal in younger children. As a result, the hydrocodone antitussive products have information in the product labeling about respiratory depression in children less than 6 years of age.

With regard to non-prescription antitussive agents, there are several non-narcotic alternative agents listed in the OTC Monograph, including chlophedianol, dextromethorphan, diphenhydramine, and topical agents. Many dextromethorphan-containing products are available OTC. Dextromethorphan does not carry the same risk of respiratory depression as either codeine or hydrocodone. Diphenhydramine-containing products are also available; however, diphenhydramine does carry the risk of sedation as well as paradoxical excitatory activity, particularly in younger children. Finally, topical agents (menthol and camphor) are available in several formulations; however, topical agents are most often used in lozenge form, which is not appropriate for younger children. Further, camphor is absorbed through the skin and is toxic if taken internally, so its use as an antitussive is limited.

Table 4. Approved Non-Codeine Containing Antitussive Medications

Active Ingredient (product name)	Class	Age	Relevant Labeling
Prescription Products			
Benzonatate (Tessalon and generics)	Peripheral Anesthetic	≥10 years	• Do not break, chew, crush • Temporary local anesthesia • Accidental ingestion resulting in death has been reported in children <10 years of age • Dosing information for children 10 years and older
Hydrocodone + homatropine (Hycodan and generics) + chlorpheniramine (Tussionex)	Centrally acting opioid	≥6 years	• Tussionex: Contraindicated for use in patients less than 6 years of age because use is associated with cases of fatal respiratory depression • Hycodan: Warning about respiratory depression in patients less than 6 years of age • Use with caution in children 6 years of age and older
Hydrocodone + chlorpheniramine (Vituz) + pseudoephedrine (Rezira) + chlorpheniramine and pseudoephedrine (Zutripro) + guaifenesin (Obredon, Flowtuss) + guaifenesin, pseudoephedrine (Hycofenix)	Centrally acting opioid	≥18 years	• Not indicated for pediatric patients under 18 years of age • Warning regarding respiratory depression, including fatalities in children less than 6 years of age
Over-the-Counter Antitussive Products (FDA monograph 21 CFR341.14)			
Chlophedianol Hydrochloride	Centrally acting	≥6 years	• Non-narcotic for temporary relief of cough • Do not take for chronic cough • Children under 6 years of age: Consult

Active Ingredient (product name)	Class	Age	Relevant Labeling
			a doctor • OTC Monograph also contains professional labeling for dosing in children 2 to <6 years of age
Dextromethorphan and Dextromethorphan hydrobromide	Centrally acting	≥2 years	• Non-narcotic for temporary relief of cough • Do not take for chronic cough • Children under 2 years of age: Consult a doctor
Diphenhydramine citrate and Diphenhydramine hydrochloride	Antihistamine /antitussive	≥6 years	• Non-narcotic for temporary relief of cough • May cause marked drowsiness • Alcohol, sedatives, and tranquilizers may increase sedative effect • Do not give to children less than 12 years of age who have a breathing problem • Children under 6 years of age: Consult a doctor • OTC Monograph also contains professional labeling for dosing in children 2to <6 years of age
Camphor and Menthol	Topical (ointment, lozenge, steam inhalation)	≥2 years	• Topical: For external use only • Flammability: Safety concern about fire-related events when ointment vehicle or alcohol-based solutions are placed in hot water or heated in the microwave • Children under 2 years of age: Consult a doctor

7. Safety Review (FAERS and Literature)

The Division of Pharmacovigilance I (DPV-I) in the Office of Surveillance and Epidemiology (OSE) completed a review of codeine and respiratory depression in pediatric patients. OSE also completed a review in 2012 that focused on cases with codeine in children with fatal outcomes. The most recent review for this AC meeting is a cumulative review of all serious cases of respiratory depression for all codeine-containing products, and there is overlap of identified death cases that were previously discussed in the 2012 FDA Drug Safety Communication (and in the 2012-13 Summary Review) in which the FDA warns of the risk that codeine use in certain children after tonsillectomy and/or adenoidectomy may lead to rare, but life-threatening adverse events or death.

DPV-I searched the FDA Adverse Event Reporting System (FAERS) database for reports of cases of respiratory depression with codeine-containing products with a serious outcome in children 18 years and younger. Details of the search strategy are described in the OSE Review (Table 1 in OSE Review). The FAERS search identified 64 serious respiratory

depression cases, from 1965 to 2015, in pediatric patients who had used a codeine-containing product. Descriptive characteristics of the FAERS cases are shown in Table 5.

The majority (n=50) of the 64 cases were in patients under 12 years old. There were 24 deaths, 21 hospitalizations, and 16 life threatening cases in the series. Twenty-one of the death cases involved children less than 12 years old. Twelve of the 21 deaths in patients under 12 years old occurred when a codeine-containing product was used unrelated to tonsillectomy or adenoidectomy. The indications for codeine in these 12 cases were the following:

- cough and cold (n=7),
- general pain (n=2),
- postoperative pain not associated with tonsillectomy and/or adenoidectomy (n=2), and
- sore/strep throat pain (n=1).

Since the FDA issued the Drug Safety Communication regarding the risk in patients post tonsillectomy and/or adenoidectomy in August 2012, only one case was reported in this setting. Refer to the OSE Review for details of this case.

Among the 48 cases that reported reason for use, 34 reported pain management and 14 reported cough and cold management. The most frequently reported codeine-containing product was acetaminophen with codeine (n= 26). Promethazine with codeine (with [n=5] and without phenylephrine [n=5]) was the most frequently reported codeine-containing product in the cough and cold setting.

A temporal relationship was observed with the events occurring as early as after one dose of a codeine-containing product. Only 10 cases noted CYP2D6 genotype, so the information is limited. The OSE review includes details, including narratives for some cases.

Table 5. Descriptive characteristics of serious pediatric FAERS cases of respiratory depression reported with codeine-containing products, received by FDA as of May 26, 2015

Characteristics (N = 64)		
Sex	Male Female Unknown	35 24 5
Age (years)	Mean Median Range 0-1 year 2-5 years 6-11 years 12-18 years	6 2.9 0.03 – 17.21 16 23 11 14
Country	United States Foreign	41 23
Initial FDA Received	1969-2012	42

Characteristics (N = 64)		
Year[*]	2013	9
	2014	11
	2015	2
Event Year[*]	1969-2012	33
	2013	4
	2014	1
	Unknown	26
Report Type	Expedited	44
	Direct	16
	Periodic	4
Time to event onset from start of therapy	Median	5 doses
	Range	1-18 doses
	1 dose	10
	2 doses	5
	3 doses	4
	4 doses	3
	6 doses	3
	10 doses	1
	12 doses	3
	18 doses	2
	Unknown	33
Codeine-Containing Products[†]	Acetaminophen with codeine	26
	Codeine unspecified	23
	Promethazine, phenylephrine with codeine	5
	Promethazine with codeine	5
	Guaifenesin with codeine	2
	Chlorpheniramine, phenylephrine with dihydrocodeine	1
	Triprolidine, pseudoephedrine with codeine	1
	Aspirin with codeine	1
	Dihydrocodeine unspecified	1
Serious Outcomes[‡]	Death	24
	Cough and cold use	7
	Post tonsillectomy and/or adenoidectomy	7
	General pain	2
	Other postoperative pain	2
	Sore throat/tonsillitis pain	2
	Dental pain	1
	Unknown use	3
	Hospitalization	21
	Life-threatening	16
	Disability	2
	Other Serious	30
Preferred Terms (Top 10)	Respiratory Depression	13
	Apnoea	9
	Dyspnoea	9
	Unresponsive to Stimuli	8
	Death	7
	Pyrexia	7

Characteristics (N = 64)		
	Toxicity to Various Agents	7
	Loss of Consciousness	6
	Vomiting	6
	Cyanosis	5
	Overdose	5
Reasons for Use	Pain	34
	Post tonsillectomy and/or adenoidectomy	17
	Other surgery	5
	General pain	7
	Sore throat/Tonsillitis	3
	Dental pain	2
	Unknown	16
	Cough and Cold	14
Mention of CYP2D6 Genotype	Without mention	54
	With mention	10
	Ultra-rapid metabolizer (UM)	7
	Extensive metabolizer (EM)	3
Codeine or morphine levels (n=15) §	Above therapeutic range	13
	Blood levels	2
	Postmortem	11
	Therapeutic range	2
	Blood levels	1
	Postmortem	1

* Reports received prior to the DSC issued by the FDA in 2012 were grouped together.
† Cases may contain more than one codeine-containing product.
‡ Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may include multiple outcomes.
§ There was one FAERS literature case that did not contain levels within the report; however, levels were obtained from the literature article.

OSE also conducted a literature search which identified 3 additional case reports of death in children 4-10 years of age associated with codeine-containing products in different clinical settings. These cases are briefly summarized here with more details in Section 3.3.1.1 and 3.3.2.1 of the OSE Review:

- 10-year-old overweight Guatemalan female 5 days status post orthopedic surgery found un-responsive following treatment with acetaminophen with codeine (2 doses) and diazepam (1 dose). Postmortem codeine and morphine blood concentrations were in the toxic range.

- 4-year-old obese female status post tonsillectomy/adenoidectomy discharged home with acetaminophen with codeine every 4 hours for pain. She received a total of 4 doses at 4-hour intervals, went to bed, and was found unresponsive the following morning. Resuscitative measures were unsuccessful. CYP2D6 testing found the patient to have an extensive metabolizer (normal) phenotype.

- 6-year-old overweight female was prescribed guaifenesin with codeine for severe cough and respiratory infection. She received a total of 3 doses throughout the day and was noted by her mother to be a "little bit blue" after her last dose. The patient was found dead the next morning by her mother. Postmortem codeine and morphine blood concentrations were in the toxic range.

Overall, the OSE review concludes that there is some case report evidence of respiratory depression, sometimes resulting in death, following codeine-containing product use for both pain and cold/cough treatment, particularly in the pediatric population less than 12 years of age. The FAERS data cannot be used to generate reliable estimates of the incidence of life-threatening or fatal respiratory depression with the pediatric use of codeine-containing products.

8. Drug Utilization

Given that the Agency is asking the AC panel whether it recommends additional restriction of use of codeine in pediatric patients, it is important to understand how codeine is currently being used in pediatric patients in the US. The Agency's Division of Epidemiology II (DEPI-II) assessed the utilization data for codeine, and a brief overview is summarized here. The detailed utilization data is located in the OSE Review.

Figure 2 below and Table 2.3.2 in the OSE review provide the pediatric utilization of prescription codeine-containing products over time. While Figure 2 shows the data for the 0-11 and 12-18 year age group, Table 2.3.2 in the OSE review includes details on age subgroups: 0-1, 2-5, 6-11, and 12-18. Over 2010-2014, the number of pediatric patients (0-18 years old) who received dispensed prescriptions for codeine decreased 40% to about 1.9 million patients in 2014 (Figure 2), in 2014, pediatric patients accounted for 14% of all patients (13.2 million patients) who received dispensed prescriptions of codeine-containing (analgesic or cough/cold) products from U.S. retail pharmacies. Of the 1.9 million pediatric patients in 2014, 56% were under age 12 years and 45% were ages 12-18 years.[i] By drug class, 76% of pediatric patients received prescriptions for analgesic codeine-containing products and 26% of pediatric patients received prescriptions for cold/cough products in 2014 (Table 2.3.2 OSE Review).

Of the pediatric patients who received analgesic codeine-containing products, 99.6% of pediatric patients received prescriptions for analgesic codeine-acetaminophen combination products in 2014. In 2014, 52% and 42% of pediatric patients received cough/cold codeine-guaifenesin and codeine-promethazine combination products, respectively, (Table 2.3.2 OSE Review) in 2014. Primary care practitioners were the top prescriber specialties for both cough/cold and analgesic codeine-containing products (Table 2.3.3 OSE Review).

[i] Summing patients across patient age bands and time periods will result in double counting and overestimates of patient counts. Moreover, the sum of the percentages will be greater than 100% because patients are double counted across age bands.

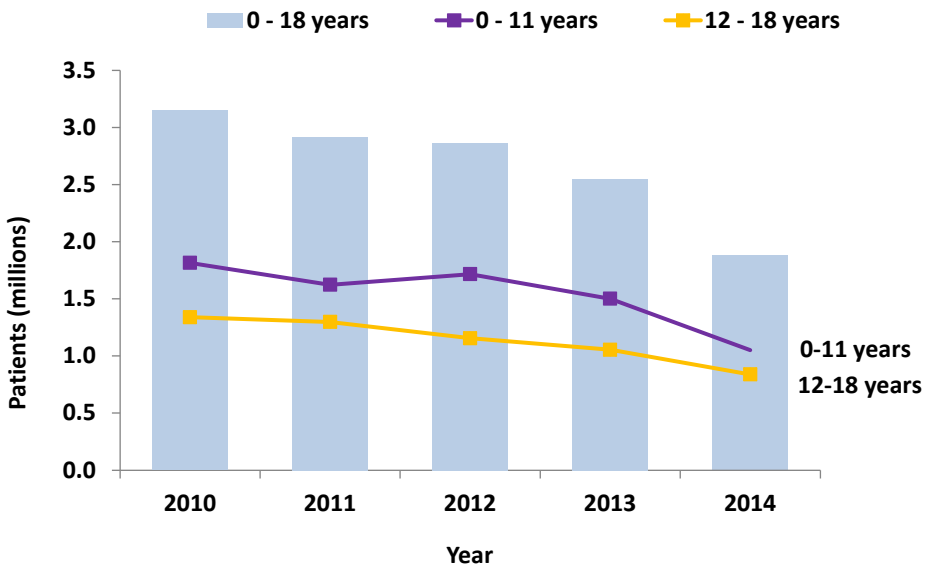

Figure 2. National estimates of <u>pediatric patients (0-18 years)</u> who received dispensed prescriptions for codeine-containing products by patient age from U.S. outpatient retail pharmacies, years 2010-2014

Source: IMS Health, Vector One®: Total Patient Tracker. Years 2010-2014. Data extracted June and August 2015.

Because codeine is available OTC, DEPI assessed the utilization of codeine-containing cough/cold products sold OTC. Compared to 2010, the U.S. retail OTC sales of codeine-containing cough/cold products decreased 85% to 169,000 bottles/packages sold in 2014 (Table 2.3.1 OSE review). Since 2012, combination codeine-guaifenesin accounted for the majority of total retail OTC sales of codeine-containing cough/cold products at 61%-100%. There is no demographic information provided for patients using OTC codeine cough/cold products because such information is not collected in the data resources available to the FDA.

9. Epidemiology Data

DEPI examined other epidemiological data sources for adverse effects from use of codeine-containing products in children. The National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project collects data (from 63 hospitals) on emergency department (ED) visits for adverse drug events (ADEs). All the cases in NEISS-CADES are ED visits for a condition that the treating clinician explicitly attributed to the use of a drug or a drug-specific effect, but exclude intentional self-harm, drug therapeutic failures, drug withdrawal, and drug abuse. Only visits by patients alive at the time of discharge from the ED are included in these data.

The NEISS-CADES data for patients age 18 years and under during the years 2004-2013 , included 73 ED visits for codeine **cough and cold** products and 261 ED visits for codeine **analgesic** products as shown in Table 6. (Note: These are counts, not national projections,

of visits from a sample of hospitals over the whole 2004-2013 period.) Accidental/unintentional ingestion and allergic reaction accounted for the majority of these codeine-related pediatric ED visits. The specific ADEs are listed in Table 4.2.3.3 in the OSE Review; although GI complaints were the most common, there were cases of dyspnea, somnolence, and altered/ depressed level of consciousness.[ii]

Table 6. NEISS-CADES 2004 – 2013: Summary of codeine-containing product-related ED visits by adverse drug event category and age group

Codeine-containing Cough and Cold Products				
Age Group	**Adverse Drug Event**			
	Accidental/ Unintentional	**Allergic Reaction**	**Adverse Effect**	**Total**
<2 years	13	1	0	14
2-5 years	19	4	3	26
6-11 years	4	6	1	11
12-18 years	4	13	5	22
Total	**40**	**24**	**9**	**73**
Codeine-containing Analgesic Products				
Age Group	**Adverse Drug Event**			
	Accidental/ Unintentional	**Allergic Reaction**	**Adverse Effect**	**Total**
<2 years	27	5	0	32
2-5 years	29	17	10	56
6-11 years	4	34	19	57
12-18 years	14	61	41	116
Total	**74**	**117**	**70**	**261**

Data from SAMHSA's Drug Abuse Warning Network (DAWN) for 2004-2011 are used to publish national annual estimates of ED visits resulting from an adverse drug reaction (ADR). This category includes ED visits in which an adverse health consequence (e.g., side effect or an allergic reaction) resulted when taking prescription drugs, OTC medications, or dietary supplements. For methodological details of DAWN, see the OSE Review.

National annual estimates of ED visits for ADRs for codeine-containing **cough and cold** products in the pediatric population were not published due to estimate imprecision from small case counts. The DAWN national estimate of ADR ED visits related to codeine/combination **analgesic** products for 2011 was 1073 for children 12-17 years (Table 7). There were not enough data for the younger age groups to estimate ED visits for 2011. The DAWN data do not provide details on the types of ADRs leading to the ED visits.

[ii] In a previous DEPI review focused on adverse reactions involving codeine use for tonsillectomy pain, 14 pediatric ED cases (in children aged 12-18 years) were identified in the 2004-2010 NEISS-CADES data.

Table 7. DAWN 2004-2011: National Estimates of Adverse Drug Reaction ED Visits associated with Codeine-containing Analgesic products, by year and pediatric age group

DAWN: 2004-2011								
Codeine/combination Analgesics	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
0-5 years	*	*	*	*	542	853	*	*
95% Confidence Intervals					106, 979	233, 1,474		
6-11 years	*	846	822	1,207	1,060	1,342	*	*
95% Confidence Intervals		328, 1,364	120, 1,524	202, 2,213	524, 1,597	460, 2,223		
12-17 years	841	653	1,520	984	609	1,707	1,043	1,073
95% Confidence Intervals	184, 1498	145, 1,161	781, 2,259	439, 1,530	220, 998	734, 2,679	398, 1,688	123, 2,023

* indicates figure does not meet standards of precision. Estimates with a relative standard error greater than 50% or an unweighted count or estimate less than 30 are suppressed.
Source: Center for Behavioral Health Statistics and Quality, SAMHSA, Drug Abuse Warning Network, 2011.

To summarize, both NEISS-CADES (2004-2013) and DAWN (2004-2011) data show that there were ED visits associated with the use of codeine-containing products in pediatric patients.

10. Codeine as a Controlled Substance

Finally, it is important to note that codeine is a controlled substance under the Controlled Substances Act (CSA); thus, we have included information regarding the CSA and codeine. Depending on the dose of codeine and whether it is in combination with another drug, codeine products are controlled in Schedules II, III, or V of the CSA, as described below:

- Schedule II – high potential for abuse which may lead to severe psychological or physical dependence
    - codeine single ingredient products
- Schedule III – potential for abuse less than Schedules I or II and abuse may lead to moderate or low physical dependence or high psychological dependence
    - codeine ≤ 90mg per dosage unit (e.g. acetaminophen with codeine)
- Schedule V – low potential for abuse relative to substances listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics.
    - codeine ≤ 200mg codeine per 100 mL or per 100 grams (e.g. promethazine with codeine)

The codeine cough/cold combination preparations for discussion at this AC meeting would fall under Schedule III or V.

Under 21 CFR1306.26, a "controlled substance listed in Schedules II, III, IV, or V which is not a prescription drug as determined under the Federal Food, Drug, and Cosmetic Act, may be dispensed by a pharmacist without a prescription to a purchaser at retail, provided that:"

"(a) Such **dispensing is made only by a pharmacist** (as defined in part 1300 of this chapter), and not by a nonpharmacist employee even if under the supervision of a pharmacist (although after the pharmacist has fulfilled his professional and legal responsibilities set forth in this section, the actual cash, credit transaction, or delivery, may be completed by a nonpharmacist);

(b) **Not more than 240 cc. (8 ounces)** of any such controlled substance containing opium, nor more than 120 cc. (4 ounces) of any other such controlled substance nor more than 48 dosage units of any such controlled substance containing opium, nor more than 24 dosage units of any other such controlled substance may be dispensed at retail to the same purchaser in any given 48-hour period;

(c) The **purchaser is at least 18 years of age**;

(d) The pharmacist requires every purchaser of a controlled substance under this section not known to him to furnish suitable **identification** (including proof of age where appropriate);

(e) A **bound record book** for dispensing of controlled substances under this section is maintained by the pharmacist, which book shall contain the name and address of the purchaser, the name and quantity of controlled substance purchased, the date of each purchase, and the name or initials of the pharmacist who dispensed the substance to the purchaser (the book shall be maintained in accordance with the recordkeeping requirement of Sec. 1304.04 of this chapter); and

(f) A **prescription is not required** for distribution or dispensing of the substance pursuant to any other Federal, State or local law.

(g) Central fill pharmacies may not dispense controlled substances to a purchaser at retail pursuant to this section" *[bold emphasis added]*

11. Concluding Remarks

Codeine has been approved for use for pain or cough in pediatric patients for decades. Over time, new information about the pharmacogenomics and variability in metabolism of codeine has become available. A review of the safety data shows reports of respiratory depression and death in pediatric patients following treatment with codeine. Some reports suggest the variability in metabolism of codeine could play a role. Because of these reports, various professional societies have raised concern about the use of codeine in pediatric patient populations. Some regulatory agencies, including FDA, have taken regulatory actions to limit the use of codeine in children in certain settings. Given the continued concern with use of codeine in children, you will be asked to discuss the safety of codeine for use in the treatment of pain or cough in pediatric patients. We seek your input on whether the use of codeine in children should be restricted further beyond the current Contraindication for pain management in children post-adenotonsillectomy and whether codeine should be available as an antitussive through the OTC Drug Monograph. Thank you again for your participation in this advisory committee meeting. We look forward to the discussion.

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The Drug Safety Communication (DSC) below was issued by FDA on April 20, 2017, and is posted on the FDA website at: https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women

This is an update to the FDA Drug Safety Communications:

- FDA evaluating the potential risks of using codeine cough-and-cold medicines in children issued on July 1, 2015, and
- FDA evaluating the risks of using the pain medicine tramadol in children aged 17 and younger issued on September 21, 2015.

Safety Announcement

[4-20-2017] The Food and Drug Administration (FDA) is restricting the use of codeine and tramadol medicines in children. Codeine is approved to treat pain and cough, and tramadol is approved to treat pain. These medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children. These medicines should also be limited in some older children. Single-ingredient codeine and all tramadol-containing products are FDA-approved only for use in adults. We are also recommending against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants.

As a result, we are requiring several changes to the labels of all prescription medicines containing these drugs. These new actions further limit the use of these medicines beyond our 2013 restriction of codeine use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids. We are now adding:

- FDA's strongest warning, called a *Contraindication*, to the drug labels of codeine and tramadol alerting that codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years.
- A new *Contraindication* to the tramadol label warning against its use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- A new *Warning* to the drug labels of codeine and tramadol to recommend against their use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.
- A strengthened *Warning* to mothers that breastfeeding is not recommended when

taking codeine or tramadol medicines due to the risk of serious adverse reactions

in breastfed infants. These can include excess sleepiness, difficulty breastfeeding, or serious breathing problems that could result in death.

Caregivers and patients should always read the label on prescription bottles to find out if a medicine contains codeine or tramadol. You can also ask your child's health care provider or a pharmacist. Watch closely for signs of breathing problems in a child of any age who is taking these medicines or in infants exposed to codeine or tramadol through breastmilk. These signs include slow or shallow breathing, difficulty or noisy breathing, confusion, more than usual sleepiness, trouble breastfeeding, or limpness. If you notice any of these signs, stop giving the medicine and seek medical attention immediately by going to an emergency room or calling 911.

Health care professionals should be aware that tramadol and single-ingredient codeine medicines are FDA-approved only for use in adults. Consider recommending over-the-counter (OTC) or other FDA-approved prescription medicines for cough and pain management in children younger than 12 years and in adolescents younger than 18 years, especially those with certain genetic factors, obesity, or obstructive sleep apnea and other breathing problems. Cough is often secondary to infection, not serious, and usually will get better on its own so treatment may not be necessary.

Codeine and tramadol are a type of narcotic medicine called an opioid. Codeine is used to treat mild to moderate pain and also to reduce coughing. It is usually combined with other medicines, such as acetaminophen, in prescription pain medicines. It is frequently combined with other drugs in prescription and over-the-counter (OTC) cough and cold medicines. Tramadol is a prescription medicine approved only for use in adults to treat moderate to moderately severe pain. However, data show it is being used in children and adolescents despite the fact that it is not approved for use in these patients.

In early 2013, FDA added a *Boxed Warning* to the codeine drug label cautioning against prescribing codeine to children of any age to treat pain after surgery to remove tonsils or adenoids. We also issued Drug Safety Communications in July 2015 and September 2015 warning about the risk of serious breathing problems in some children who metabolized codeine and tramadol much faster to their active form than usual (called ultra-rapid metabolism), causing potentially dangerously high levels in their bodies too quickly. At that time, we said we would continue to evaluate this safety issue. As part of that safety review, the codeine-related safety issues were discussed at an FDA Advisory Committee meeting in December 2015.

Our review of several decades of adverse event reports submitted to FDA* from January 1969 to May 2015 identified 64 cases of serious breathing problems, including 24 deaths, with codeine-containing medicines in children younger than 18 years. This includes only reports submitted to FDA, so there may be additional cases about which we are unaware. We also identified nine cases of serious breathing problems, including three deaths, with the use of tramadol in children younger than 18 years from January 1969 to March 2016 (see Data Summary). The majority of serious side effects with both codeine and tramadol

occurred in children younger than 12 years, and some cases occurred after a single dose of the medicine.

In our review of the medical literature[1-19] for data regarding codeine use during breastfeeding, we found numerous cases of excess sleepiness and serious breathing problems in breastfed infants, including one death. A review of the available medical literature[4,5,23,24] for data regarding tramadol use during breastfeeding did not reveal any cases of adverse events. However, tramadol and its active form are also present in breast milk, and tramadol has the same risks associated with ultra-rapid metabolism as codeine.

We will continue to monitor this safety issue. We are considering additional regulatory action for the OTC codeine products that are available in some states. OTC codeine products are available in combination with other medicines for cough and cold symptoms. We are also considering an FDA Advisory Committee meeting to discuss the role of prescription opioid cough-and-cold medicines, including codeine, to treat cough in children.

We urge patients and health care professionals to report side effects involving codeine- and tramadol- containing medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS).

List of Prescription Codeine and Tramadol Pain and Cough Medicines

Medicines Containing Codeine	Medicines Containing Tramadol
Codeine Sulfate	Conzip
Butalbital, Acetaminopen, Caffeine, and Codeine phosphate	Ultracet
Fiorinal with codeine	Ultram
Soma Compound with codeine	Ultram ER
Tylenol with codeine	Generic products containing tramadol
Promethazine with codeine (cough)	
Prometh VC with codeine (cough)	
Triacin-C (cough)	
Tuxarin ER (cough)	
Tuzistra-XR (cough)	
Generic products containing codeine	
Medicines Containing Dihydrocodeine	
Synalgos-DC	

Facts about Codeine and Tramadol

- Codeine

- An opioid pain reliever used to treat mild to moderate pain. It is usually combined with other medicines, such as acetaminophen, in prescription pain medicines.
- Single-ingredient codeine is approved for pain management in adults only.
- Also used to reduce coughing. It is frequently combined with promethazine in prescription cough-and-cold medicines and with other cold remedies in over-the-counter (OTC) preparations.
- Common side effects include drowsiness, lightheadedness, dizziness, feeling tired, shortness of breath, nausea, vomiting, stomach pain, constipation, itching, or rash.
- In 2014, nearly 1.9 million patients 18 years of age and younger received a dispensed prescription for codeine-containing products from U.S. outpatient retail pharmacies. Of the total pediatric patients, nearly 1.4 million patients received codeine-containing analgesic products, and 483,000 patients received codeine-containing cough-and-cold products.[20]

- Tramadol
  - An opioid pain reliever FDA-approved only in adults to treat moderate to moderately severe pain.
  - Available as a single ingredient under the brand names Ultram, Ultram ER, Conzip and also as generics.
  - Also available in combination with acetaminophen under the brand name Ultracet and as generics.
  - Common side effects include headache, dizziness, drowsiness, feeling tired, constipation, diarrhea, nausea, vomiting, stomach pain, itching, or flushing.
  - In 2014, nearly 167,000 patients younger than 18 years of age received a dispensed prescription for tramadol-containing products from U.S. outpatient retail pharmacies. [21]

Additional Information for Caregivers and Patients

- FDA is warning about several safety issues with prescription medicines containing codeine used for pain or cough and tramadol used for pain:
  - Codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years due to the risk of serious side effects, including slowed or difficult breathing and death.
  - Codeine is not recommended to treat cough or pain and tramadol is not recommended to treat pain in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease that may increase the risk of breathing problems.
  - Tramadol should not be used to treat pain in children up to 18 years of age after surgery to remove their tonsils and/or adenoids. The drug label for codeine already warns against use in children up to 18 years of age after surgery to remove their tonsils and/or adenoids.

    - Breastfeeding is not recommended during treatment with codeine or tramadol because the medicine passes through breast milk and can harm the baby.
- Talk to your health care provider or a pharmacist to find out if a medicine your child is taking contains codeine or tramadol.
- Always read the label on prescription bottles to find out if a medicine contains codeine or tramadol, or ask your child's health care provider or a pharmacist.
- If patients of any age are known to be CYP2D6 ultra-rapid metabolizers, which means their bodies convert codeine or tramadol into their active forms faster and more completely than usual, they should not use codeine or tramadol.
- If a child has taken codeine or tramadol and you notice any signs of slow or shallow breathing, difficult or noisy breathing, confusion, or unusual sleepiness in a child of any age, seek medical attention immediately by taking the child to an emergency room or calling 911.
- Report any side effects from codeine- or tramadol- containing medicines to your health care professional and the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA is warning about several safety issues with prescription medicines containing codeine used for pain or cough and tramadol used for pain and requiring the following changes to the drug labels:
    - FDA's strongest warning, called a *Contraindication*, alerting that codeine and tramadol should not be used to treat pain in children younger than 12 years, and codeine should not be used to relieve cough in these children.
    - A new *Contraindication* to the tramadol label to restrict its use in children younger than 18 years to treat pain after a tonsillectomy and/or adenoidectomy. The label of codeine-containing products already carry this Contraindication.
    - A new *Warning* to the drug labels of codeine and tramadol to recommend against their use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or compromised respiratory function, that may increase the risk of serious breathing problems.
    - Strengthening the *Warning* to patients that breastfeeding is not recommended during treatment with codeine or tramadol due to the potential for serious adverse reactions in a breastfed infant, such as excess sedation, respiratory depression, and death.
- All tramadol-containing products and single-ingredient codeine drugs are FDA-approved for use only in adults.
- If you have determined that a codeine-or tramadol-containing product is appropriate for an adolescent patient, counsel parents and caregivers on how to recognize the signs of opioid toxicity, and advise them to stop giving the adolescent codeine or tramadol and seek medical attention immediately if their adolescent is exhibiting these signs.

- Report adverse events involving codeine- or tramadol- containing medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

Codeine

A search of the FDA Adverse Event Reporting System (FAERS) database from January 1969 to May 2015 identified 64 worldwide cases of respiratory depression, including 24 deaths, with codeine-containing medicines in children younger than 18 years. Fifty cases were reported in children younger than 12 years. Respiratory depression occurred after the children received a range of one to 18 doses, with a median of five doses. The most frequently reported codeine-containing medicines in the cases were acetaminophen with codeine used for pain, and promethazine with codeine (with or without phenylephrine) used for cough and cold.

Of the 24 cases reporting death, 21 occurred in children younger than 12 years. The reasons for codeine-containing medicine use in these cases included post-tonsillectomy and/or adenoidectomy pain management, other post-operative pain, general pain, sore or strep throat pain, and cough and cold.

Ten of the 64 cases mentioned the status of cytochrome P450 isoenzyme 2D6 (CYP2D6) genotype. Seven of these patients were ultra-rapid metabolizers, five of whom died. Ultra-rapid metabolizers of substrates of CYP2D6 convert codeine in their bodies too quickly into potentially dangerously high levels of morphine, the active form of codeine, contributing to life-threatening or fatal respiratory depression. The three other patients were extensive metabolizers, with one death.

Fifteen of the 64 cases reported codeine or morphine blood levels; the remaining 49 cases did not. In 13 cases, the blood levels were above the therapeutic range, and in two cases the blood levels were within the therapeutic range. One patient who had blood levels in the therapeutic range died following pain management post-tonsillectomy and adenoidectomy.

Tramadol

A search of the FAERS database from January 1969 to March 2016 identified nine cases worldwide of respiratory depression in children younger than 18 years of age, including three deaths. With the exception of a 15-year-old treated for multiple days with tramadol, respiratory depression occurred within the first 24 hours of drug administration.

The three fatalities occurred outside the U.S. in children younger than 6 years. Elevated serum tramadol concentrations were noted in all three. The reasons for tramadol treatment in these children were to treat pain after tonsillectomy, pain after clubfoot surgery, and to manage fever. All three cases involved tramadol oral drops, a formulation not available in the U.S.

The one case in which CYP2D6 ultra-rapid metabolizer status was reported occurred in a 5-year-old child from France who was prescribed a single tramadol dose in the evening post-adenotonsillectomy and returned to the healthcare facility the next morning with opioid intoxication; he was resuscitated.[22] A urine sample showed increased metabolite concentrations. Genotyping of CYP2D6 was conducted, and three functional alleles were found that were consistent with ultra-rapid metabolism.

One non-fatal U.S. case involved a 6-year-old who was prescribed tramadol for neuropathy of the hands and feet. After the third dose, the patient experienced respiratory depression and was unresponsive. The patient fully recovered after receiving two doses of naloxone.

Four other non-fatal cases reported in teenagers using tramadol for musculoskeletal pain or sciatica described unresponsiveness or somnolence after one or a few doses of tramadol; all required medical intervention. Two of these were U.S. cases.

Breastfeeding Mothers

Codeine and its active metabolite, morphine, are present in breast milk. A search of the medical literature[1-19] for relevant data regarding codeine use during lactation revealed numerous reports of respiratory depression and sedation, including one infant death, especially in mothers who have the CYP2D6 ultra-rapid metabolizer genotype.

In the case of the infant death, the mother was found to be a CYP2D6 ultra-rapid metabolizer, which potentially led to higher levels of morphine secreted into the breast milk leading to the infant's death. In other studies comparing drowsiness in breastfed babies whose mothers took codeine/acetaminophen compared to acetaminophen alone, the frequency of somnolence was higher in the codeine/acetaminophen-exposed group. Some of the mothers of those babies were CYP2D6 ultra-rapid metabolizers.[15,16]

Mothers who are ultra-rapid metabolizers of codeine achieve higher-than-expected serum levels of morphine, potentially leading to higher levels of morphine in breast milk that can be dangerous to their breastfed infants. In women with normal codeine metabolism, the amount of codeine secreted into breast milk is low and dose-dependent.

According to *Drugs in Pregnancy and Lactation*[5], both tramadol and its pharmacologic active metabolite (O-desmethyltramadol) are excreted into human milk. The mean absolute bioavailability of a 100-mg dose is 75%. Thus, ingestion of the recommended dose may produce drug amounts in breast milk that could exceed those reported above. The effect of this exposure on a nursing infant is unknown.

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Related Information

FDA statement from Douglas Throckmorton, M.D., Deputy Center Director for Regulatory Programs, Center for Drug Evaluation and Research, on new warnings about the use of codeine and tramadol in children & nursing mothers

Consumer Update: Codeine and Tramadol Can Cause Breathing Problems for Children

Use of Codeine and Tramadol Products in Breastfeeding Women – Questions and Answers

Codeine Information

Tramadol Information

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pediatric Drug Utilization Review

Date:	August 1, 2017
Reviewer:	Tracy Pham, Pharm.D. Division of Epidemiology II
Team Leader:	Rajdeep Gill, Pharm.D. Division of Epidemiology II
Deputy Director for Drug Utilization:	LCDR Grace Chai, Pharm.D. Division of Epidemiology II
Associate Office Director for Public Health Initiatives:	Judy Staffa, Ph.D., R.Ph Office of Surveillance and Epidemiology
Subject:	Pediatric Outpatient Retail Utilization Patterns of Opioid and Non-Opioid Containing Antitussives
Drug Names:	Codeine Containing Antitussives Hydrocodone Containing Antitussives Dextromethorphan Containing Antitussives Benzonatate
Application Type/Number:	Multiple
Applicant/Sponsor:	Multiple
OSE RCM #:	2017-342

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EXECUTIVE SUMMARY

A meeting of the Pediatric Advisory Committee (PAC) will be held on September 11, 2017, to discuss the risks and benefits, and the pediatric labeling of opioid containing antitussives (OCAs). In preparation for this meeting, we examined national trends in the pediatric outpatient prescription utilization of OCAs (codeine and hydrocodone containing antitussives) and non-OCAs (benzonatate and dextromethorphan containing antitussives) from 2012 through 2016. The pediatric utilization of codeine and dextromethorphan containing antitussives over-the-counter (OTC) was not analyzed due to the Agency's lack of access to OTC utilization data. The drug utilization analyses in this review will be used to provide context for the AC discussion.

The prescription dispensing data from U.S. outpatient retail pharmacies showed that an estimated 5.8 million antitussive prescriptions were dispensed to 4.3 million pediatric patients ages 17 years and younger in 2016. The majority of prescriptions were dispensed for dextromethorphan containing antitussives at 84% (4.9 million prescriptions). Codeine and hydrocodone containing antitussives accounted for 8% (471,000 prescriptions) and 1% (65,000 prescriptions), respectively. The number of prescriptions dispensed for codeine and hydrocodone containing antitussives to pediatric patients decreased by 60.5% and 71%, respectively, from 2012 to 2016. Primary care providers such as general pediatricians, family medicine/general practice/internal medicine, and nurse practitioners/physician assistants were the top prescriber specialties across all pediatric age groups for both OCAs and non-OCAs.

Based on surveys of office-based physicians, budesonide, albuterol, and dextromethorphan containing antitussives were the top drugs mentioned for cough relief for pediatric patients ages 0-1 years in 2016. Among pediatric patients ages 2-17 years, dextromethorphan containing antitussives followed by albuterol were the top drugs mentioned for cough relief. For the OCAs, although combination codeine/guaifenesin was mentioned for cough relief in pediatric patients ages 2 years and older, there were no mentions of hydrocodone containing antitussives in this datasource, likely due to the low pediatric utilization of these products.

Overall, the outpatient retail utilization of codeine and hydrocodone containing antitussives in pediatric patients was low and decreased from 2012 to 2016. Dextromethorphan containing antitussives accounted for the vast majority of pediatric prescription antitussive use throughout the study period. The overall utilization of dextromethorphan and codeine containing antitussives was underestimated in our analyses due to the availability of dextromethorphan and codeine products over-the-counter (OTC) and the Agency's lack of access to such OTC utilization data.

1 INTRODUCTION

1.1 BACKGROUND

As part of the Agency's effort towards reducing opioid abuse, dependence, and overdose in the U.S., the Agency seeks expert advice from the Pediatric Advisory Committee on recommendations regarding a framework for pediatric opioid labeling before any new labeling is approved. Currently, the Agency is re-assessing the need for removing or restricting the use of opioid containing antitussives (OCAs) in children. The agency will convene the Pediatric Advisory Committee (PAC) on September 11, 2017, to discuss the risks and benefits of the use of these products in children, and obtain recommendations on the pediatric labeling of OCAs for cough relief. In preparation for this upcoming AC meeting, the Division of Pediatric and Maternal Health (DPMH) and the Division of Pulmonary, Allergy, and Rheumatology

Products (DPARP) requested the Division of Epidemiology II (DEPI II) to provide pediatric outpatient retail utilization of codeine and hydrocodone containing antitussives, as well as benzonatate and dextromethorphan containing antitussives, to provide context for the AC meeting discussion.

1.2 REGULATORY HISTORY

1.2.1 Codeine Containing Products

Codeine is an opioid analgesic indicated for the relief of mild to moderately severe pain where the use of an opioid analgesic is appropriate. Codeine is also an active ingredient in cough and cold preparations due to its antitussive effects.[1] It is available by prescription and over-the-counter (OTC) through the OTC Drug Monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products. Twenty-eight states and the District of Columbia permit the sale of codeine without a prescription, while 22 states and Puerto Rico prohibit the sale of codeine without a prescription.[2] Most if not all of the state laws allowing the OTC sale of codeine require the pharmacist to oversee or personally complete the transaction, and allow the pharmacist to choose not to sell the product OTC. For codeine that is sold OTC, all states require that the purchaser's identifying information and details of the sale be recorded. States differ on the maximum allowable quantity which can be purchased at one time (60 mL to 240 mL), the amount of time required before additional purchases are permitted (48 hours to 96 hours), and the minimum age of a purchaser (18 years to 21 years). The variations between states involve regulations and laws which are more restrictive than the federal requirements in 21 CFR 1306.26.[3]

The use of codeine in children has been a concern because of the risk of respiratory depression and death in patients who are ultra-rapid metabolizers of codeine and in turn at risk for high exposure to morphine, which is converted from codeine. Over the past decade, the Agency has taken multiple efforts to update the codeine label and to communicate the risks associated with codeine use to healthcare professionals and the public.

In August 2012, the Agency issued a Drug Safety Communication (DSC) about reports of death and respiratory depression in pediatric patients, primarily with the use of codeine following tonsillectomy and/or adenoidectomy.[4]

In February 2013, the Agency asked the sponsors of codeine or dihydrocodeine containing products to update the Boxed Warning, Contraindication, Warnings/Precautions, Pediatric Use, and Patient Counseling Information labeling sections of their respective products to provide new safety information on the risk of serious adverse events or death associated with the use of codeine or dihydrocodeine containing products for pain relief after tonsillectomy and/or adenoidectomy.[5]

In April 2015, the European Medicines Agency (EMA) contraindicated the use of codeine-containing products for cough and cold indications in children less than 12 years of age, and limited the use in children and adolescents ages 12-18 years with a history of breathing problems.[6]

In July 2015, the Agency issued another DSC regarding the risk of respiratory depression associated with the use of codeine to treat cough and cold in children less than 18 years of age.[7]

In December 2015, the Agency convened the Pulmonary-Allergy Drugs Advisory Committee (PADAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee to discuss the safety data associated with codeine use in children and to obtain advice on whether the use of codeine in children should be restricted beyond the current agency's contraindication and whether codeine should be available through the OTC Drug Monograph. The AC panel recommended to contraindicate the use of codeine for analgesia or cough in children younger than 18 years of age, and to remove codeine from the

OTC monograph for both adults and children. As of June 8, 2015, 26 states had placed further restrictions on the sale of codeine containing antitussives.

On April 20th, 2017, the Agency issued another DSC contraindicating the use of codeine-containing products for the treatment of pain or cough in children younger than 12 years of age. The DSC also warned against the use of codeine in children between 12 and 18 years of age who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems. The DSC also warned against the use of codeine in breastfeeding mothers.[8]

1.2.2 Hydrocodone Containing Products

Hydrocodone is an opioid with both analgesic and antitussive effects. It is used in combination with various active ingredients, such as acetaminophen for the relief of moderate to severe pain, and guaifenesin for the symptomatic relief of cough. Most hydrocodone containing antitussives are indicated for the relief of cough in patients 18 years and older. However, hydrocodone in combination with homatropine or chlorpheniramine is indicated for the relief of cough in patients 6 years of age and older.

Multiple adverse event cases including cases of medication errors associated with the use of Tussionex® Pennkinetic® (hydrocodone-chlorpheniramine) reported respiratory depression and death in children and adults. Based on these adverse events cases, the Agency issued a Public Health Advisory (PHA) in March 2008 to alert healthcare professionals about the risk of life-threatening and fatal respiratory depression and death with the use of Tussionex® Pennkinetic® in adults and children.[9] The PHA highlighted recommendations and considerations for healthcare professionals, including a contraindication for use in patients less than 6 years old.

In August 2014, the Drug Enforcement Administration (DEA) issued a final rule to reschedule hydrocodone combination products from schedule III to schedule II of the Controlled Substances Act. This rule became effective on October 6, 2014.[10]

Soon after the December 2015 PADAC and DSaRM AC meeting to discuss the safety of codeine, the Agency assessed the safety of hydrocodone containing antitussives in children and considered updating the pediatric label for these products because these products might be used as an alternative to codeine containing antitussives. In March 2016, the Division of Pharmacovigilance (DPV) completed a safety review of hydrocodone containing antitussives in children under 18 years of age. DPV identified reports of respiratory depression associated with the use of hydrocodone containing antitussives in children, and a drug interaction safety issue between hydrocodone-containing cough products and CYP3A4 inhibitors. DPV recommended adding a drug interaction with CYP3A4 inhibitors under the Warnings and Precautions of the label of all hydrocodone containing antitussives.[11]

1.2.3 Dextromethorphan Containing Antitussives

Dextromethorphan is a cough suppressant which is often used in combination with various active ingredients in many cough/cold products. When consumed at high doses exceeding the maximum recommended dosages on the label, dextromethorphan causes euphoria, hallucination, distorted visual perception, loss of motor coordination, and dissociative sedation.[12] Deaths have also been reported among teenagers who ingested high doses of dextromethorphan powder.[13]

In 2005, the Agency issued a Talk Paper to warn the public about the risks of abuse of dextromethorphan.[14] Since 2007, the Consumer Healthcare Products Association (CHPA) introduced a variety of voluntary education initiatives to reduce dextromethorphan abuse among teenagers.[15] On September 14, 2010, the Agency convened the Drug Safety and Risk Management Advisory Committee (DSaRM) to discuss the abuse and the risks and benefits of dextromethorphan, and the Drug Enforcement

Administration (DEA) request for dextromethorphan scheduling recommendation. The committee voted 15 to 9 against the scheduling of dextromethorphan. Dextromethorphan remains an uncontrolled substance under the Controlled Substances Act; however, several states have restricted the over-the-counter (OTC) sales of dextromethorphan to minors 17 years of age and younger.[15]

1.2.4 Benzonatate

Benzonatate is an antitussive agent approved under the brand name Tessalon® as a prescription drug product for the symptomatic relief of cough.[16] The safety and effectiveness of benzonatate in children under 10 years of age have not been established. Potential side effects of benzonatate include hypersensitivity reactions, psychiatric effects such as hallucinations, and numbness of the mouth which could result in choking. Overdose of benzonatate has been reported in adults and adolescents. Accidental ingestions of benzonatate in children under 10 years of age have also been reported. In December 2010, the Agency issued a DSC and a podcast to warn the public and healthcare professionals that accidental ingestion of benzonatate by children under the age of 10 years can result in death from overdose.[17,18]

2 METHODS AND MATERIALS

2.1 PRODUCTS INCLUDED

This review focused on the following antitussives dispensed by prescription in the outpatient retail setting. See Appendix C for a comprehensive list of products[a].

- Opioid containing antitussives
  - Hydrocodone containing antitussives
  - Codeine containing antitussives (prescription only, although available OTC)
- Non-opioid containing antitussives
  - Dextromethorphan containing antitussives (prescription only, although available OTC)
  - Benzonatate

2.2 DATA SOURCES USED

Proprietary databases available to the Agency were used to conduct the drug utilization analyses in this review (see Appendix A for full database descriptions).

2.2.1 Prescription Data

The QuintilesIMS, National Prescriptions Audit™ database was used to provide the nationally estimated number of prescriptions dispensed for opioid or non-opioid containing antitussives, stratified by patient age (0-1, 2-5, 6-11, 12-17, and 18+ years), from U.S. outpatient retail pharmacies from 2012 through 2016. The prescriber specialty data were also obtained from this database for 2016. Of note, prescription claims for dextromethorphan containing antitussives, including over-the-counter (OTC) products, were captured in this database when the prescriptions written for these products were filled and dispensed at the

[a] Source: QuintilesIMS, National Prescription Audit™. 2012-2016. Data extracted July 2017. File: NPA 2017-342 cough products molecule 7-10-2017.xlsx

pharmacy. This database does not capture OTC sales of dextromethorphan or codeine containing antitussives purchased by consumers without a prescription.

2.2.2 Patient Data

The QuintilesIMS, Total Patient Tracker™ database was used to provide the nationally estimated number of unique patients who received prescriptions dispensed for opioid or non-opioid containing antitussives, stratified by patient age (0-1, 2-5, 6-11, 12-17, and 18+ years), from U.S. outpatient retail pharmacies from 2012 through 2016. The unique number of patients who filled a prescription for dextromethorphan containing antitussives, including OTC products, at the pharmacy was also captured in this database. This database does not capture OTC sales of dextromethorphan or codeine containing antitussives purchased by consumers without a prescription.

2.2.3 Office-Based Physician Survey Data

The inVentiv Health Research and Insights LLC., TreatmentAnswers™ with Pain Panel database was used to obtain the nationally estimated number of drug use mentions associated with the use of drug products (prescription or OTC) for the diagnosis for cough (ICD-10 code R05) in pediatric patients (0-17 years), stratified by patient age (0-1, 2-5, 6-11, and 12-17 years), as reported by U.S. office-based physician surveys in 2016. The purpose of this analysis was to better understand the products that physicians in office-based practice mention during office visits related to pediatric diagnoses of cough.

3 RESULTS

3.1 DETERMINING SETTINGS OF CARE[b]

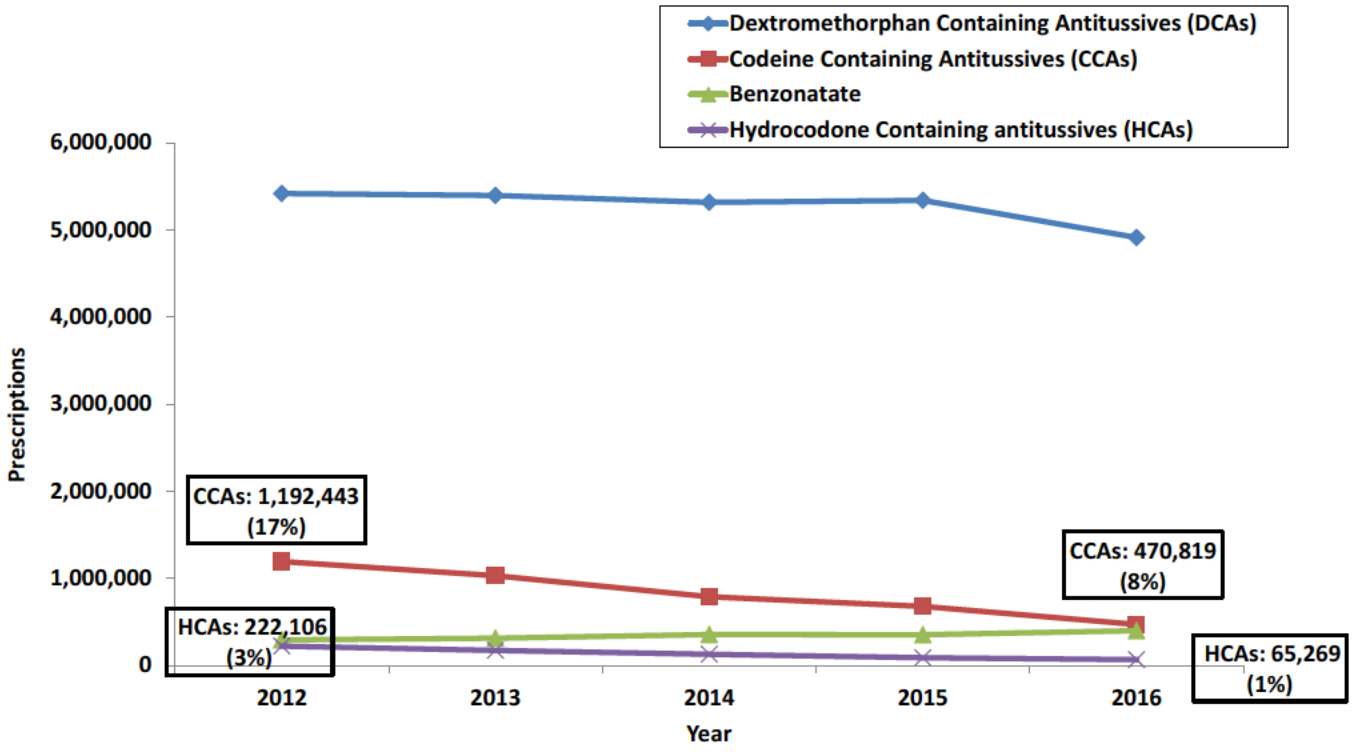
Based on the QuintilesIMS, National Sales Perspectives™ data in 2016, approximately 90.5% of bottles/packages of opioid and non-opioid containing antitussives (prescription and OTC) were distributed to outpatient retail pharmacies. As a result, the outpatient retail pharmacy utilization of opioid and non-opioid containing antitussives was examined. Data from non-retail and mail-order/specialty pharmacy settings, which accounted for 9% and <1% of sales, respectively, were not included in this review.

3.2 PRESCRIPTION DATA

Figure 1 below and Table 1 in Appendix B provide the nationally estimated number of antitussive prescriptions dispensed to pediatric patients ages 17 years and younger from U.S. outpatient retail pharmacies. In 2016, approximately 5.8 million antitussive prescriptions were dispensed to pediatric patients, an 18% decrease from 7.1 million prescriptions dispensed in 2012. Dextromethorphan containing antitussives accounted for 84% (4.9 million prescriptions) of total antitussive prescriptions dispensed to pediatric patients in 2016. Codeine and hydrocodone containing antitussives accounted for approximately 8% (471,000 prescriptions) and 1% (65,000 prescriptions), respectively, of total antitussive prescriptions dispensed to pediatric patients.

[b] Source: QuintilesIMS, National Sales Perspectives™. 2016. Data extracted April 2017. File: NSP 2017-342 total Rx OTC cough channel 4-28-2017.xlsx

Figure 1. Nationally estimated number of antitussive prescriptions dispensed to pediatric patients (0-17 years) by active ingredient from U.S. outpatient retail pharmacies, 2012-2016



Source: QuintilesIMS, National Prescription Audit™. 2012-2016. Data extracted June 2017.

From 2012 to 2016, the number of prescriptions dispensed to pediatric patients for codeine or hydrocodone containing antitussives decreased by approximately 60.5% and 71%, respectively. The number of prescriptions dispensed for dextromethorphan containing antitussives to pediatric patients decreased by 9% during the same time period. In contrast, the number of benzonatate prescriptions dispensed to pediatric patients increased by 36%.

3.3 Patient Data

Table 2 in Appendix B provides the nationally estimated number of pediatric patients ages 17 years and younger who received antitussive dispensed prescriptions from U.S. outpatient retail pharmacies. In 2016, approximately 4.3 million pediatric patients ages 17 years and younger received antitussive dispensed prescriptions. Overall, the patient utilization trends across time were similar to the dispensed prescription data.

The utilization of codeine and hydrocodone containing antitussives among pediatric patients ages 17 years and younger decreased over the study period. For the non-OCAs, the prescription utilization of dextromethorphan containing antitussives decreased among patients ages 0-1 years and 2-5 years from 2012 to 2016 while the benzonatate utilization was negligible. In contrast, the utilization of benzonatate and dextromethorphan containing antitussives increased among patients ages 6-11 years and 12-17 years.

3.4 Prescriber Specialties

Table 3 in Appendix B provides the top prescriber specialties by patient age based on antitussive prescription dispensing data from U.S. outpatient retail pharmacies in 2016. Among pediatric patients ages 0-11 years, general pediatrician was the top prescriber specialty, followed by nurse practitioner/physician assistant and family medicine/general practice/internal medicine practitioners for both OCAs and non-OCAs. Among pediatric patients ages 12-17 years, nurse practitioner/physician assistant was the top prescriber specialty, followed by general pediatrician and family medicine/general practice/internal medicine practitioners.

3.5 OFFICE-BASED PHYSICIAN SURVEY DATA

Table 4 in Appendix B provides the drug use mentions[c] associated with the use of drug products for the diagnosis for cough (ICD-10 R05) in pediatric patients (0-17 years), stratified by patient age, as reported by U.S. office-based physician survey database in 2016.

Among pediatric patients ages 0-1 years, budesonide, albuterol, and dextromethorphan containing antitussives were the top drugs mentioned for cough relief at 27.5%, 24%, and 10% of drug use mentions, respectively, in 2016. Dextromethorphan containing antitussives followed by albuterol were the top drugs mentioned for cough relief in pediatric patients ages 2-17 years.

For the OCAs, combination codeine/guaifenesin was mentioned for cough relief at 1% among patients ages 2-5 years, 4% among patients ages 6-11 years, and 9% among patients ages 12-17 years. There was no mention of hydrocodone containing antitussives - most likely due to the low pediatric utilization of these products. Benzonatate was mentioned for cough relief at less than 1% among patients ages 6-11 years and 9% among patients ages 12-17 years. Other drug products such as antibiotics and agents with demulcent properties, such as glycerin and honey, were also mentioned for cough relief in some pediatric patients. The number of drug use mentions for drug products, including OCAs and benzonatate, which were below 100,000 in each pediatric age group, were too low to provide reliable national estimates and should be interpreted with caution.

4 DISCUSSION

Analysis of outpatient prescription utilization of opioid and non-opioid containing antitussives showed that although still widely utilized by pediatric patients, antitussive utilization decreased from 2012 to 2016. In 2016, an estimated 5.8 million antitussive prescriptions were dispensed to pediatric patients ages 17 years and younger. Dextromethorphan containing antitussives, which are also available over-the-counter, accounted for the majority of antitussive prescriptions dispensed to pediatric patients throughout the study period. OCAs accounted for less than 10% of total pediatric antitussive use in 2016, a decrease from 20% of prescription antitussive use in 2012. Overall, the number of prescriptions dispensed to pediatric patients for codeine or hydrocodone containing antitussives decreased by approximately 60.5% and 71%, respectively, although OTC sales of codeine containing products were not included in this analysis.

[c] inVentiv Health Research and Insights, LLC uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Findings from this review should be interpreted in the context of the known limitations of the databases used. The QuintilesIMS dispensed prescription and patient data capture retail prescription activity; the OTC drug utilization data are captured in these databases only when prescriptions written for these products are filled and dispensed at the pharmacy. A reliable estimate of all OTC product usage is not possible to obtain, given FDA's lack of access to such data. Therefore, the true extent of pediatric use of dextromethorphan and codeine antitussives (both available OTC) is likely to be substantially underestimated in this analysis.

In addition, the dispensed prescription and patient estimates should be interpreted with caution due to the following limitations: 1) certain estimates may be a result of errors such as wrong date of birth on prescriptions; however, medical charts were not available for validation; 2) the estimates should be interpreted with caution for the low patient or prescription numbers which are based on small sample sizes; and 3) the estimates provided in this review are national estimates, but no statistical tests were performed to determine statistically significant changes over time or between products.

According to U.S. office-based physician survey data in 2016, various drug products such as antiasthmatics, antibiotics, antitussives, and agents with demulcent properties such as glycerin and honey were mentioned for cough relief in pediatric patients. This is consistent with clinical treatment guidelines recommending treatment of the underlying cause of cough.[19] A study done by Oduwole O, et al., also showed evidence supporting the use of honey for the relief of acute cough.[20] Although combination codeine/guaifenesin was mentioned for cough relief among patients ages 2-17 years, hydrocodone containing antitussives were not mentioned most likely due to the low pediatric utilization of these products. The office-based physician survey data were obtained from surveys of a sample of 3,200 office-based physicians with 115 pain specialists reporting on patient activity during one day per month; therefore, survey data provide an insight into the prescriber intent, but are not directly linked to dispensed prescriptions. Due to the small sample sizes captured with correspondingly large confidence intervals, these data should be interpreted with caution and may not be representive of national trends.

5 CONCLUSIONS

We analyzed the extent of pediatric prescription antitussive utilization in the outpatient retail setting to provide context for the AC meeting discussion in September 2017. In 2016, approximately 5.8 million antitussive prescriptions were dispensed to pediatric patients ages 17 years and younger in the outpatient retail setting. Although the overall utilization of dextromethorphan containing antitussives was clearly underestimated in our analyses, these products accounted for the vast majority of pediatric prescription antitussive use. The pediatric utilization of prescription codeine and hydrocodone containing antitussives were low and decreased over the study period, although OTC sales of codeine containing products were not included in this analysis.

6 APPENDIX A: DATABASE DESCRIPTIONS

QuintilesIMS, National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

QuintilesIMS, National Prescription Audit™

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 - 75% (varies by class and geography) of mail service pharmacies and approximately 70-85% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

QuintilesIMS, Total Patient Tracker™ (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

inVentiv Health Research and Insights LLC., TreatmentAnswers™ with Pain Panel

inVentiv Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

7 APPENDIX B: TABLES

Table 1. Nationally estimated number of antitussive dispensed prescriptions by patient age and active ingredient from U.S. outpatient retail pharmacies, 2012-2016

	Year									
	2012		2013		2014		2015		2016	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total Dispensed Prescriptions	**33,703,942**	***100.0%***	**35,122,271**	***100.0%***	**34,677,573**	***100.0%***	**35,790,258**	***100.0%***	**35,773,850**	***100.0%***
0-17 years	**7,125,481**	***21.1%***	**6,913,832**	***19.7%***	**6,586,415**	***19.0%***	**6,455,837**	***18.0%***	**5,848,343**	***16.3%***
Dextromethorphan Containing Antitussives	**5,418,436**	***76.0%***	**5,397,861**	***78.1%***	**5,316,819**	***80.7%***	**5,339,240**	***82.7%***	**4,913,394**	***84.0%***
Codeine Containing Antitussives	**1,192,443**	***16.7%***	**1,031,301**	***14.9%***	**788,024**	***12.0%***	**676,798**	***10.5%***	**470,819**	***8.1%***
Benzonatate	**292,496**	***4.1%***	**312,322**	***4.5%***	**354,278**	***5.4%***	**352,187**	***5.5%***	**398,861**	***6.8%***
Hydrocodone Containing Antitussives	**222,106**	***3.1%***	**172,348**	***2.5%***	**127,294**	***1.9%***	**87,612**	***1.4%***	**65,269**	***1.1%***
18+ years	**26,116,800**	***77.5%***	**27,727,190**	***78.9%***	**27,644,242**	***79.7%***	**29,123,848**	***81.4%***	**29,888,506**	***83.5%***
Unknown	**461,661**	***1.4%***	**481,249**	***1.4%***	**446,916**	***1.3%***	**210,573**	***0.6%***	**37,001**	***0.1%***
Prescriptions Dispensed to Pediatric Patients	**7,125,481**	***21.1%***	**6,913,832**	***19.7%***	**6,586,415**	***19.0%***	**6,455,837**	***18.0%***	**5,848,343**	***16.3%***
0-1 years	**474,699**	***6.7%***	**400,018**	***5.8%***	**339,482**	***5.2%***	**268,211**	***4.2%***	**211,041**	***3.6%***
Dextromethorphan Containing Antitussives	**458,034**	***96.5%***	**388,241**	***97.1%***	**330,907**	***97.5%***	**261,574**	***97.5%***	**206,611**	***97.9%***
Codeine Containing Antitussives	**14,510**	***3.1%***	**10,416**	***2.6%***	**7,435**	***2.2%***	**5,418**	***2.0%***	**3,406**	***1.6%***
Hydrocodone Containing Antitussives	**2,009**	***0.4%***	**1,196**	***0.3%***	**974**	***0.3%***	**1,010**	***0.4%***	**851**	***0.4%***
Benzonatate	**146**	***0.0%***	**165**	***0.0%***	**166**	***0.0%***	**209**	***0.1%***	**173**	***0.1%***
2-5 years	**2,446,905**	***34.3%***	**2,285,761**	***33.1%***	**2,143,568**	***32.5%***	**2,053,886**	***31.8%***	**1,668,969**	***28.5%***
Dextromethorphan Containing Antitussives	**2,183,636**	***89.2%***	**2,083,897**	***91.2%***	**2,006,000**	***93.6%***	**1,949,912**	***94.9%***	**1,603,069**	***96.1%***
Codeine Containing Antitussives	**245,096**	***10.0%***	**188,985**	***8.3%***	**128,118**	***6.0%***	**97,660**	***4.8%***	**61,651**	***3.7%***
Hydrocodone Containing Antitussives	**17,467**	***0.7%***	**12,126**	***0.5%***	**8,594**	***0.4%***	**5,527**	***0.3%***	**3,606**	***0.2%***
Benzonatate	**706**	***0.0%***	**753**	***0.0%***	**856**	***0.0%***	**787**	***0.0%***	**643**	***0.0%***
6-11 years	**2,464,581**	***34.6%***	**2,454,463**	***35.5%***	**2,370,520**	***36.0%***	**2,361,081**	***36.6%***	**2,230,461**	***38.1%***
Dextromethorphan Containing Antitussives	**1,891,690**	***76.8%***	**1,968,639**	***80.2%***	**1,994,368**	***84.1%***	**2,050,302**	***86.8%***	**1,999,069**	***89.6%***
Codeine Containing Antitussives	**453,962**	***18.4%***	**388,782**	***15.8%***	**288,415**	***12.2%***	**237,710**	***10.1%***	**161,388**	***7.2%***
Benzonatate	**44,459**	***1.8%***	**44,190**	***1.8%***	**49,887**	***2.1%***	**47,492**	***2.0%***	**50,928**	***2.3%***
Hydrocodone Containing Antitussives	**74,470**	***3.0%***	**52,852**	***2.2%***	**37,850**	***1.6%***	**25,577**	***1.1%***	**19,076**	***0.9%***
12-17 years	**1,739,296**	***24.4%***	**1,773,590**	***25.7%***	**1,732,845**	***26.3%***	**1,772,659**	***27.5%***	**1,737,872**	***29.7%***
Dextromethorphan Containing Antitussives	**885,076**	***50.9%***	**957,084**	***54.0%***	**985,544**	***56.9%***	**1,077,452**	***60.8%***	**1,104,645**	***63.6%***
Benzonatate	**247,185**	***14.2%***	**267,214**	***15.1%***	**303,369**	***17.5%***	**303,699**	***17.1%***	**347,117**	***20.0%***
Codeine Containing Antitussives	**478,875**	***27.5%***	**443,118**	***25.0%***	**364,056**	***21.0%***	**336,010**	***19.0%***	**244,374**	***14.1%***
Hydrocodone Containing Antitussives	**128,160**	***7.4%***	**106,174**	***6.0%***	**79,876**	***4.6%***	**55,498**	***3.1%***	**41,736**	***2.4%***

Source: QuintilesIMS, National Prescription Audit™. 2012-2016. Data extracted June 2017. File: NPA 2017-342 total cough products age MD ad hoc 6-23-17.xlsx

Table 2. Nationally estimated number of patients* who received antitussive dispensed prescriptions by patient age and active ingredient from U.S. outpatient retail pharmacies, 2012-2016**

	Year									
	2012		2013		2014		2015		2016	
	N	%	N	%	N	%	N	%	N	%
Total Patients	22,885,513	100.0%	23,861,812	100.0%	23,730,185	100.0%	24,671,309	100.0%	24,804,145	100.0%
0 - 17 years	5,044,391	22.0%	4,881,152	20.5%	4,711,555	19.9%	4,670,039	18.9%	4,287,990	17.3%
Dextromethorphan Containing Antitussives	3,789,816	75.1%	3,782,169	77.5%	3,777,292	80.2%	3,844,415	82.3%	3,599,179	83.9%
Codeine Containing Antitussives	966,123	19.2%	825,570	16.9%	638,486	13.6%	557,663	11.9%	387,767	9.0%
Benzonatate	266,034	5.3%	282,754	5.8%	324,883	6.9%	320,136	6.9%	365,510	8.5%
Hydrocodone Containing Antitussives	183,553	3.6%	143,102	2.9%	106,186	2.3%	72,847	1.6%	53,911	1.3%
18+ years	17,555,503	76.7%	18,602,940	78.0%	18,682,547	78.7%	19,878,485	80.6%	20,472,803	82.5%
Unknown Age	282,723	1.2%	427,806	1.8%	388,271	1.6%	188,303	0.8%	33,129	0.1%
Pediatric Patients Receiving Antitussive Prescriptions	5,044,391	22.0%	4,881,152	20.5%	4,711,555	19.9%	4,670,039	18.9%	4,287,990	17.3%
0 - 1 years	300,362	6.0%	253,063	5.2%	233,793	5.0%	184,648	4.0%	143,947	3.4%
Dextromethorphan Containing Antitussives	288,978	96.2%	245,066	96.8%	225,015	96.2%	178,422	96.6%	140,427	97.6%
Codeine Containing Antitussives	11,759	3.9%	8,183	3.2%	6,209	2.7%	4,381	2.4%	2,807	2.0%
Hydrocodone Containing Antitussives	1,528	0.5%	1,056	0.4%	878	0.4%	788	0.4%	683	0.5%
Benzonatate	120	<0.1%	132	0.1%	156	0.1%	181	0.1%	155	0.1%
2 - 5 years	1,589,276	31.5%	1,476,857	30.3%	1,402,080	29.8%	1,369,119	29.3%	1,132,537	26.4%
Dextromethorphan Containing Antitussives	1,416,414	89.1%	1,348,146	91.3%	1,312,309	93.6%	1,299,423	94.9%	1,091,124	96.3%
Codeine Containing Antitussives	189,689	11.9%	143,147	9.7%	98,149	7.0%	75,575	5.5%	46,999	4.1%
Hydrocodone Containing Antitussives	14,054	0.9%	9,928	0.7%	7,109	0.5%	4,449	0.3%	2,984	0.3%
Benzonatate	581	<0.1%	623	<0.1%	801	0.1%	697	0.1%	579	0.1%
6 - 11 years	1,801,564	35.7%	1,779,847	36.5%	1,726,113	36.6%	1,731,074	37.1%	1,646,039	38.4%
Dextromethorphan Containing Antitussives	1,389,217	77.1%	1,437,374	80.8%	1,459,833	84.6%	1,510,504	87.3%	1,484,234	90.2%
Codeine Containing Antitussives	366,116	20.3%	308,406	17.3%	229,927	13.3%	192,704	11.1%	130,533	7.9%
Benzonatate	39,789	2.2%	39,288	2.2%	45,471	2.6%	42,633	2.5%	46,465	2.8%
Hydrocodone Containing Antitussives	60,832	3.4%	43,817	2.5%	31,525	1.8%	21,110	1.2%	15,378	0.9%
12 - 17 years	1,363,042	27.0%	1,382,075	28.3%	1,360,827	28.9%	1,396,395	29.9%	1,376,450	32.1%
Dextromethorphan Containing Antitussives	718,666	52.7%	772,781	55.9%	799,762	58.8%	873,905	62.6%	898,944	65.3%
Benzonatate	225,959	16.6%	243,251	17.6%	278,590	20.5%	277,779	19.9%	318,701	23.2%
Codeine Containing Antitussives	399,492	29.3%	366,666	26.5%	305,042	22.4%	285,995	20.5%	207,798	15.1%
Hydrocodone Containing Antitussives	107,422	7.9%	88,564	6.4%	66,841	4.9%	46,844	3.4%	34,961	2.5%
18+ years	17,555,503	76.7%	18,602,940	78.0%	18,682,547	78.7%	19,878,485	80.6%	20,472,803	82.5%
Unknown Age	282,723	1.2%	427,806	1.8%	388,271	1.6%	188,303	0.8%	33,129	0.1%

Source: QuintilesIMS, Total Patient Tracker. 2012-2016. Data extracted June 2017. File: TPT stability 2017-342 total Rx & OTC cough age no vet 6-23-2017.xls

*Patient subtotals may not sum exactly because patients may received multiple products and aged over the examined time. For these reasons, summing patients across age groups, products, or time periods is not advisable and will result in overestimates of patient counts. Moreover, the sum of the percentages will be greater than 100% because patients are double counted across age groups, products, and time periods.

**Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0-16 years include patients less than 17 years old (16 years and 11 months).

Table 3. Nationally estimated number of antitussive prescriptions dispensed to pediatric patients ages 0-17 years by patient age and top five prescriber specialties from U.S. outpatient retail pharmacies in 2016

	Year 2016	
	TRxs	%
Total Prescriptions Dispensed to Pediatric Patients Ages 0-17 Years	**5,848,343**	***100.0%***
0-1 years	**211,041**	***3.6%***
Pediatrician	**126,528**	***60.0%***
Nurse Practitioner/Physician Assistant	**44,535**	***21.1%***
Family Medicine/General Practice/Internal Medicine	**22,729**	***10.8%***
Hospitalist	**4,546**	***2.2%***
Emergency Medicine	**3,679**	***1.7%***
All Others	**9,024**	***4.3%***
2-5 years	**1,668,969**	***28.5%***
Pediatrician	**867,333**	***52.0%***
Nurse Practitioner/Physician Assistant	**462,674**	***27.7%***
Family Medicine/General Practice/Internal Medicine	**206,130**	***12.4%***
Hospitalist	**33,329**	***2.0%***
Emergency Medicine	**32,579**	***2.0%***
All Others	**66,924**	***4.0%***
6-11 years	**2,230,461**	***38.1%***
Pediatrician	**984,596**	***44.1%***
Nurse Practitioner/Physician Assistant	**683,746**	***30.7%***
Family Medicine/General Practice/Internal Medicine	**366,402**	***16.4%***
Hospitalist	**52,598**	***2.4%***
Emergency Medicine	**50,824**	***2.3%***
All Others	**92,295**	***4.1%***
12-17 years	**1,737,872**	***29.7%***
Nurse Practitioner/Physician Assistant	**628,281**	***36.2%***
Pediatrician	**492,956**	***28.4%***
Family Medicine/General Practice/Internal Medicine	**422,511**	***24.3%***
Emergency Medicine	**71,242**	***4.1%***
Hospitalist	**48,455**	***2.8%***
All Others	**74,427**	***4.3%***

Source: QuintilesIMS, National Prescription Audit™. 2016. Data extracted June 2017. File: NPA 2017-342 total cough products age MD ad hoc 6-23-17.xlsx

Table 4. Drug use mentions associated with the use of drug products for the diagnosis for cough (ICD-10 R05) in pediatric patients (0-17 years) by patient age as reported by U.S. office-based physician surveys in 2016

	Year 2016		
	Uses (000)	95% CI (000)	%
Drug Products Intended for Cough Relief (R05) in Children	**2,609**	**2,325 - 2,893**	***100.0%***
0-1 years	**429**	**314 - 545**	***16.5%***
budesonide	118	58 - 179	*27.5%*
albuterol	105	48 - 161	*24.3%*
dextromethorphan containing antitussives	44	7 - 81	*10.3%*
loratadine	34	1 - 66	*7.9%*
diphenhydramine	18	<0.5 - 42	*4.3%*
prednisolone	18	<0.5 - 41	*4.1%*
decongestant	14	<0.5 - 35	*3.3%*
cetirizine hydrochloride	14	<0.5 - 34	*3.2%*
amoxicillin	9	<0.5 - 26	*2.2%*
thimerosal/boric acid	9	<0.5 - 26	*2.1%*
triprolidine hydrochloride	9	<0.5 - 26	*2.1%*
fluticasone	9	<0.5 - 25	*2.0%*
honey/h20/asa/cit acd/zinc g1	9	<0.5 - 25	*2.0%*
ceftriaxone sodium	9	<0.5 - 25	*2.0%*
melatonin	8	<0.5 - 24	*1.9%*
montelukast sodium	4	<0.5 - 14	*0.8%*
2-5 years	**770**	**616 - 925**	***29.5%***
dextromethorphan containing antitussives	260	170 - 350	*33.7%*
albuterol	162	91 - 233	*21.0%*
budesonide	87	35 - 139	*11.3%*
prednisolone	76	27 - 124	*9.8%*
hyaluronan/glycerin	23	<0.5 - 50	*3.0%*
cetirizine hydrochloride	22	<0.5 - 48	*2.8%*
diphenhydramine	21	<0.5 - 46	*2.7%*
prednisolone sodium phosphate	14	<0.5 - 35	*1.8%*
azithromycin	13	<0.5 - 34	*1.8%*
dexamethasone sod phosphate	12	<0.5 - 31	*1.5%*
amoxicillin trihydrate	11	<0.5 - 29	*1.4%*
homeopathic products	10	<0.5 - 28	*1.4%*
amoxicillin	10	<0.5 - 27	*1.3%*
thimerosal/boric acid	9	<0.5 - 26	*1.2%*
prednisone	8	<0.5 - 25	*1.1%*
guaifenesin	8	<0.5 - 25	*1.1%*
loratadine	8	<0.5 - 24	*1.1%*
codeine/guaifenesin	8	<0.5 - 24	*1.1%*
amoxicillin/clavulanate	8	<0.5 - 23	*1.0%*

	Year 2016		
	Uses (000)	95% CI (000)	%
Drug Products Intended for Cough Relief (R05) in Children	**2,609**	**2,325 - 2,893**	***100.0%***
6-11 years	**791**	**634 - 947**	***30.3%***
dextromethorphan containing antitussives	349	245 - 452	*44.1%*
albuterol	168	96 - 240	*21.3%*
montelukast sodium	37	3 - 71	*4.7%*
codeine/guaifenesin	35	2 - 68	*4.4%*
amoxicillin trihydrate	29	<0.5 - 59	*3.7%*
prednisone	25	<0.5 - 53	*3.1%*
honey/h20/asa/cit acd/zinc g1	23	<0.5 - 50	*2.9%*
loratadine	20	<0.5 - 45	*2.5%*
diphenhydramine	17	<0.5 - 40	*2.2%*
budesonide	15	<0.5 - 37	*1.9%*
mometasone furoate	13	<0.5 - 34	*1.7%*
guaifenesin/phenylephrine	10	<0.5 - 28	*1.3%*
brompheniramine/phenylpropanolamine	10	<0.5 - 28	*1.3%*
beclomethasone dipropionate	9	<0.5 - 25	*1.1%*
cefdinir	9	<0.5 - 25	*1.1%*
guaifenesin	8	<0.5 - 24	*1.0%*
homeopathic products	6	<0.5 - 20	*0.8%*
omeprazole	4	<0.5 - 15	*0.5%*
benzonatate	3	<0.5 - 14	*0.4%*
fluticasone	<0.5	<0.5 - 3	*0.0%*
12-17 years	**619**	**480 - 757**	***23.7%***
dextromethorphan containing antitussives	178	104 - 252	*28.7%*
albuterol	157	87 - 227	*25.4%*
codeine/guaifenesin	54	13 - 96	*8.8%*
benzonatate	54	13 - 96	*8.8%*
azithromycin	51	11 - 90	*8.2%*
fluticasone	28	<0.5 - 58	*4.6%*
beclomethasone dipropionate	20	<0.5 - 45	*3.2%*
budesonide	15	<0.5 - 36	*2.4%*
amoxicillin	14	<0.5 - 35	*2.2%*
fluticasone/vilanterol	10	<0.5 - 27	*1.6%*
diphenhydramine	10	<0.5 - 27	*1.6%*
loratadine/pseudoephedrine	8	<0.5 - 25	*1.4%*
amoxicillin trihydrate	8	<0.5 - 24	*1.3%*
glycerin	6	<0.5 - 19	*0.9%*
montelukast sodium	6	<0.5 - 19	*0.9%*

Source: inVentiv Health Research and Insights, LLC., TreatmentAnswers™. 2016. Data extracted July 2017. File: GC2PDDA_2017-342_cough_ICD10_R05_age_molecule_6-22-2017.xls

*Diagnosis data are not directly linked to dispensed prescriptions, but are obtained from surveys of a sample of 3,200 office-based physicians reporting on patient activity during one day per month. Because of the small sample sizes with correspondingly large confidence intervals, the drug use mentions <100,000 are too low to provide reliable national estimates for the diagnoses and therefore, preclude meaningful interpretation of data trends.

8 APPENDIX C: LIST OF OPIOID AND NON-OPIOID CONTAINING ANTITUSSIVES

8.1 HYDROCODONE CONTAINING ANTITUSSIVES

AMMONIUM!CHLORPHENIRAMINE!HYDROCODONE!PHENINDAMINE!PHENYLEPHRINE!PYRILAMINE
BROMODIPHENHYDRAMINE!HYDROCODONE!PHENYLEPHRINE
BROMPHENIRAMINE!HYDROCODONE!PHENYLEPHRINE
BROMPHENIRAMINE!HYDROCODONE!PSEUDOEPHEDRINE
CHLORPHENIRAMINE!GUAIFENESIN!HYDROCODONE!PSEUDOEPHEDRINE
CHLORPHENIRAMINE!HYDROCODONE
CHLORPHENIRAMINE!HYDROCODONE!PHENYLEPHRINE
CHLORPHENIRAMINE!HYDROCODONE!PHENYLEPHRINE!PSEUDOEPHEDRINE!PYRILAMINE
CHLORPHENIRAMINE!HYDROCODONE!PSEUDOEPHEDRINE
DEXBROMPHENIRAMINE!HYDROCODONE!PHENYLEPHRINE
DEXCHLORPHENIRAMINE!HYDROCODONE!PHENYLEPHRINE
DIPHENHYDRAMINE!HYDROCODONE!PHENYLEPHRINE
GUAIACOLSULFONATE!HYDROCODONE
GUAIFENESIN!HYDROCODONE
GUAIFENESIN!HYDROCODONE!PHENYLEPHRINE
GUAIFENESIN!HYDROCODONE!PSEUDOEPHEDRINE
HOMATROPINE!HYDROCODONE
HYDROCODONE!PHENYLEPHRINE
HYDROCODONE!PHENYLEPHRINE!PYRILAMINE
HYDROCODONE!PSEUDOEPHEDRINE
HYDROCODONE!PSEUDOEPHEDRINE!TRIPROLIDINE

8.2 CODEINE CONTAINING ANTITUSSIVES

ACETAMINOPHEN!CHLORPHENIRAMINE!CODEINE
ACETAMINOPHEN!CODEINE!GUAIFENESIN!PSEUDOEPHEDRINE
BROMPHENIRAMINE!CODEINE
BROMPHENIRAMINE!CODEINE!PHENYLEPHRINE
BROMPHENIRAMINE!CODEINE!PHENYLPROPANOLAMINE
BROMPHENIRAMINE!CODEINE!PSEUDOEPHEDRINE
CHLORCYCLIZINE!CODEINE
CHLORCYCLIZINE!CODEINE!PHENYLEPHRINE
CHLORCYCLIZINE!CODEINE!PSEUDOEPHEDRINE
CHLORPHENIRAMINE!CODEINE
CHLORPHENIRAMINE!CODEINE!PHENYLEPHRINE
CHLORPHENIRAMINE!CODEINE!PSEUDOEPHEDRINE
CODEINE!DEXBROMPHENIRAMINE!PSEUDOEPHEDRINE
CODEINE!DEXCHLORPHENIRAMINE!PHENYLEPHRINE
CODEINE!DIPHENHYDRAMINE!PHENYLEPHRINE
CODEINE!GUAIFENESIN
CODEINE!GUAIFENESIN!PHENYLEPHRINE
CODEINE!GUAIFENESIN!PSEUDOEPHEDRINE
CODEINE!IODINATED GLYCEROL
CODEINE!PHENYLEPHRINE
CODEINE!PHENYLEPHRINE!PROMETHAZINE
CODEINE!PHENYLEPHRINE!PSEUDOEPHEDRINE
CODEINE!PHENYLEPHRINE!PYRILAMINE
CODEINE!PHENYLEPHRINE!TRIPROLIDINE
CODEINE!PROMETHAZINE
CODEINE!PSEUDOEPHEDRINE
CODEINE!PSEUDOEPHEDRINE!PYRILAMINE
CODEINE!PSEUDOEPHEDRINE!TRIPROLIDINE
CODEINE!PYRILAMINE
CODEINE!TERPIN HYDRATE

8.3 DEXTROMETHORPHAN CONTAINING ANTITUSSIVES

ACETAMINOPHEN!CHLORPHENIRAMINE!DEXTROMETHORPHAN
ACETAMINOPHEN!CHLORPHENIRAMINE!DEXTROMETHORPHAN!GUAIFENESIN
ACETAMINOPHEN!CHLORPHENIRAMINE!DEXTROMETHORPHAN!GUAIFENESIN!PHENYLEPHRINE
ACETAMINOPHEN!CHLORPHENIRAMINE!DEXTROMETHORPHAN!PHENYLEPHRINE
ACETAMINOPHEN!CHLORPHENIRAMINE!DEXTROMETHORPHAN!PSEUDOEPHEDRINE
ACETAMINOPHEN!DEXTROMETHORPHAN
ACETAMINOPHEN!DEXTROMETHORPHAN!DIPHENHYDRAMINE
ACETAMINOPHEN!DEXTROMETHORPHAN!DIPHENHYDRAMINE!GUAIFENESIN!PHENYLEPHRINE
ACETAMINOPHEN!DEXTROMETHORPHAN!DIPHENHYDRAMINE!PHENYLEPHRINE
ACETAMINOPHEN!DEXTROMETHORPHAN!DOXYLAMINE
ACETAMINOPHEN!DEXTROMETHORPHAN!DOXYLAMINE!GUAIFENESIN
ACETAMINOPHEN!DEXTROMETHORPHAN!DOXYLAMINE!GUAIFENESIN!PHENYLEPHRINE
ACETAMINOPHEN!DEXTROMETHORPHAN!DOXYLAMINE!PHENYLEPHRINE
ACETAMINOPHEN!DEXTROMETHORPHAN!DOXYLAMINE!PSEUDOEPHEDRINE
ACETAMINOPHEN!DEXTROMETHORPHAN!GUAIFENESIN!PHENYLEPHRINE
ACETAMINOPHEN!DEXTROMETHORPHAN!GUAIFENESIN!PSEUDOEPHEDRINE
ACETAMINOPHEN!DEXTROMETHORPHAN!PHENYLEPHRINE
ACETAMINOPHEN!DEXTROMETHORPHAN!PSEUDOEPHEDRINE
ACETYLSALICYLIC ACID!CHLORPHENIRAMINE!DEXTROMETHORPHAN
ACETYLSALICYLIC ACID!DEXTROMETHORPHAN!DOXYLAMINE!PHENYLEPHRINE
BENZOCAINE!DEXTROMETHORPHAN
BENZOCAINE!DEXTROMETHORPHAN!MENTHOL
BROMPHENIRAMINE!DEXTROMETHORPHAN!GUAIFENESIN
BROMPHENIRAMINE!DEXTROMETHORPHAN!GUAIFENESIN!PHENYLEPHRINE
BROMPHENIRAMINE!DEXTROMETHORPHAN!GUAIFENESIN!PSEUDOEPHEDRINE
BROMPHENIRAMINE!DEXTROMETHORPHAN!PHENYLEPHRINE
BROMPHENIRAMINE!DEXTROMETHORPHAN!PHENYLPROPANOLAMINE
BROMPHENIRAMINE!DEXTROMETHORPHAN!PSEUDOEPHEDRINE
CARBETAPENTANE!DEXTROMETHORPHAN
CARBINOXAMINE!DEXTROMETHORPHAN!PSEUDOEPHEDRINE
CHLORPHENIRAMINE!DEXTROMETHORPHAN
CHLORPHENIRAMINE!DEXTROMETHORPHAN!GUAIFENESIN!METHSCOPOLAMINE!PHENYLEPHRINE
CHLORPHENIRAMINE!DEXTROMETHORPHAN!GUAIFENESIN!PHENYLEPHRINE
CHLORPHENIRAMINE!DEXTROMETHORPHAN!GUAIFENESIN!PSEUDOEPHEDRINE
CHLORPHENIRAMINE!DEXTROMETHORPHAN!METHSCOPOLAMINE
CHLORPHENIRAMINE!DEXTROMETHORPHAN!PHENYLALANINE!PSEUDOEPHEDRINE
CHLORPHENIRAMINE!DEXTROMETHORPHAN!PHENYLEPHRINE
CHLORPHENIRAMINE!DEXTROMETHORPHAN!PSEUDOEPHEDRINE
CITRIC ACID!DEXTROMETHORPHAN!GUAIFENESIN!IPECAC
CITRIC ACID!DEXTROMETHORPHAN!GUAIFENESIN!POTASSIUM
DEXBROMPHENIRAMINE!DEXTROMETHORPHAN!GUAIFENESIN!PHENYLEPHRINE
DEXBROMPHENIRAMINE!DEXTROMETHORPHAN!PHENYLEPHRINE
DEXBROMPHENIRAMINE!DEXTROMETHORPHAN!PHENYLEPHRINE!PYRILAMINE
DEXBROMPHENIRAMINE!DEXTROMETHORPHAN!PSEUDOEPHEDRINE
DEXCHLORPHENIRAMINE!DEXTROMETHORPHAN!PHENYLEPHRINE
DEXCHLORPHENIRAMINE!DEXTROMETHORPHAN!PHENYLEPHRINE!PYRILAMINE
DEXCHLORPHENIRAMINE!DEXTROMETHORPHAN!PSEUDOEPHEDRINE
DEXTROMETHORPHAN
DEXTROMETHORPHAN!DIPHENHYDRAMINE!GUAIFENESIN!PSEUDOEPHEDRINE
DEXTROMETHORPHAN!DIPHENHYDRAMINE!PHENYLEPHRINE
DEXTROMETHORPHAN!DOXYLAMINE
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DEXTROMETHORPHAN!DOXYLAMINE!PSEUDOEPHEDRINE
DEXTROMETHORPHAN!GUAIACOLSULFONATE
DEXTROMETHORPHAN!GUAIACOLSULFONATE!GUAIFENESIN
DEXTROMETHORPHAN!GUAIACOLSULFONATE!PHENYLEPHRINE!PYRILAMINE
DEXTROMETHORPHAN!GUAIFENESIN
DEXTROMETHORPHAN!GUAIFENESIN!PARGEVERINE
DEXTROMETHORPHAN!GUAIFENESIN!PHENYLEPHRINE
DEXTROMETHORPHAN!GUAIFENESIN!PHENYLPROPANOLAMINE
DEXTROMETHORPHAN!GUAIFENESIN!PHENYLPROPANOLAMINE!PYRILAMINE
DEXTROMETHORPHAN!GUAIFENESIN!POTASSIUM
DEXTROMETHORPHAN!GUAIFENESIN!PSEUDOEPHEDRINE
DEXTROMETHORPHAN!IODINATED GLYCEROL
DEXTROMETHORPHAN!MENTHOL
DEXTROMETHORPHAN!PHENIRAMINE!PHENYLEPHRINE
DEXTROMETHORPHAN!PHENYLEPHRINE
DEXTROMETHORPHAN!PHENYLEPHRINE!PYRILAMINE
DEXTROMETHORPHAN!PHENYLEPHRINE!THONZYLAMINE
DEXTROMETHORPHAN!PHENYLEPHRINE!TRIPROLIDINE
DEXTROMETHORPHAN!PROMETHAZINE
DEXTROMETHORPHAN!PSEUDOEPHEDRINE
DEXTROMETHORPHAN!PSEUDOEPHEDRINE!PYRILAMINE
DEXTROMETHORPHAN!PSEUDOEPHEDRINE!TRIPROLIDINE
DEXTROMETHORPHAN!PYRILAMINE

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Pharmacovigilance Review

Date:	March 3, 2016
Reviewer:	Annie Nguyen, RPh, Safety Evaluator Division of Pharmacovigilance I
Team Leader:	Eileen Wu, PharmD, Safety Evaluator Team Leader Division of Pharmacovigilance I
Deputy Director:	Cindy Kortepeter, PharmD, Deputy Director (acting) Division of Pharmacovigilance I
Division Director:	Robert L. Levin, MD, Division Director Division of Pharmacovigilance I
Product Name:	Hydrocodone-containing cough and cold products
Subject:	Pediatric Postmarketing Safety Analysis
Application Type/Number:	NDA 204307 and other multiple NDAs and ANDAs
Applicant/Sponsor:	Cypress Pharmaceuticals and other multiple sponsors
OSE RCM #:	2015-2786

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The purpose of this review is for the Division of Pharmacovigilance I (DPV-I) in the Office of Surveillance and Epidemiology (OSE) to provide to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) a safety analysis of the postmarketing data in the FDA Adverse Event Reporting System (FAERS) database and the medical literature for all hydrocodone-containing cough and cold products in pediatric patients less than 18 years of age. DPARP requested the safety analysis as they consider potential pediatric labeling updates for both codeine- and hydrocodone-containing cough and cold products.

This review identified 38 serious pediatric cases of respiratory depression with hydrocodone-containing cough and cold products. The most frequently reported product was hydrocodone polistirex/chlorpheniramine polistirex suspension. A large majority of the cases (29/38 cases) were associated with inadvertent overdoses, especially in children less than 6 years of age. The inadvertent overdoses varied in nature and included cases of accidental ingestion, incorrect dose measurements, and prescription labeling errors.

There were two FAERS cases and one literature case involving co-administration of Cytochrome P450 3A4 (CYP3A4) inhibitors with hydrocodone-containing cough and cold products that may have increased hydrocodone plasma levels. Labeling for newly approved hydrocodone-containing analgesic products includes a boxed warning that states, "The concomitant use with all cytochrome P450 CYP3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression." The current labeling for hydrocodone-containing cough and cold products does not include such warning with CYP3A4 inhibitors.

Based on a review of serious FAERS pediatric cases and medical literature of respiratory depression and Designated Medical Events[a] with hydrocodone-containing cough and cold products, DPV identified a safety issue of drug interaction between hydrocodone-containing cough and cold products and CYP3A4 inhibitors.

DPV recommends the following for consideration:

- Include drug interaction with hydrocodone-containing cough and cold products and CYP3A4 inhibitors in the Warnings and Precautions section of all hydrocodone-containing cough and cold products for harmonization of labeling across all hydrocodone-containing products.

[a] Designated Medical Events (DMEs) are adverse events that are considered rare, serious, and associated with a high drug-attributable risk and which constitute an alarm with as few as one to three reports. OSE created the DME list for working purposes; it has no regulatory significance. See Appendix C, Section 8.3 for a list of OSE's DMEs.

1 INTRODUCTION

The purpose of this review is for the Division of Pharmacovigilance I (DPV-I) in the Office of Surveillance and Epidemiology (OSE) to provide to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) a safety analysis of the postmarketing data in the FDA Adverse Event Reporting System (FAERS) database and the medical literature for all hydrocodone-containing cough and cold products in pediatric patients less than 18 years of age. DPARP requested the safety analysis as they consider potential pediatric labeling updates for both codeine- and hydrocodone-containing cough and cold products.

1.1 BACKGROUND

Hydrocodone is a semisynthetic opioid with analgesic and antitussive properties. Hydrocodone is extensively metabolized via Cytochrome P450 2D6 (CYP2D6) and Cytochrome P450 3A4 (CYP3A4) to hydromorphone and norhydrocodone, respectively.[1] The primary metabolic pathway of hydrocodone is via CYP3A4 mediated N-demethylation to norhydrocodone with a lower contribution from CYP2D6 mediated O-demethylation to hydromorphone.[2] It has been suggested that hydrocodone is a prodrug and requires metabolism to hydromorphone. However, in a study that evaluated the inhibition of biotransformation of hydrocodone to hydromorphone in rats, the results suggested that hydrocodone has significant pharmacological activity and does not require conversion to hydromorphone.[3]

On December 10, 2015, a joint meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee was held to discuss the safety of codeine-containing products in children under the age of 18 because of specific concerns regarding CYP2D6 polymorphisms that led to ultra-rapid metabolism of codeine to morphine. The committee voted in favor of contraindicating the use of codeine-containing products for children under the age of 18 in all clinical settings. Before any labeling updates are made regarding the use of codeine-containing products in children, a safety analysis of hydrocodone-containing cough and cold products in children under the age of 18 is needed because these products may be used as an alternative to codeine-containing cough and cold products.

On December 28, 2015, DPARP consulted DPV-I to review available data for cases of death, respiratory depression, and Designated Medical Events (DME) with hydrocodone-containing cough and cold products in children under the age of 18.

1.2 REGULATORY HISTORY

On March 23, 1943, the first hydrocodone-containing cough and cold product, Hycodan (hydrocodone bitartrate and homatropine methylbromide), was approved in the US. For the treatment of cough and cold, hydrocodone is available as a prescription drug in combination with various ingredients such as guaifenesin or chlorpheniramine.

Table 1 provides a list of current FDA approved hydrocodone-containing cough and cold products and the recommended age indication by product.

Table 1. Current FDA approved hydrocodone-containing cough and cold products			
Active ingredient	**Application #**	**Approval date**	**Age indication**
Hydrocodone bitartrate/homatropine methylbromide (Hycodan)	NDA 005213 ANDA 040613 ANDA 088008 ANDA 088017 ANDA 091528* ANDA 088508*	March 23, 1943 February 8, 2008 March 3, 1983 July 5, 1983 April 20, 2011 July 30, 1985	6 years of age and above
Hydrocodone bitartrate/guaifenesin (Flowtuss)	NDA 022424	May 14, 2015	18 years old and above
Hydrocodone bitartrate/guaifenesin/ pseudoephedrine (Hycofenix)	NDA 022279	May 14, 2015	18 years old and above
Hydrocodone polistirex/chlorpheniramine polistirex (Tussionex)	NDA 019111 ANDA 091632 ANDA 091671 ANDA 077273*	December 31, 1987 October 1, 2010 June 29, 2012 September 24, 2007	Contraindicated in children less than 6 years of age
Hydrocodone bitartrate/guaifenesin (Obredon)	NDA 205474	November 14, 2014	18 years old and above
Hydrocodone bitartrate/pseudoephedrine (Rezira)	NDA 022442 ANDA 203839 ANDA 204658 ANDA 205658	June 8, 2011 October 28, 2014 April 24, 2014 November 17, 2015	18 years old and above
Hydrocodone bitartrate/chlorpheniramine maleate (Vituz)	NDA 204307 ANDA 206438	February 20, 2013 January 27, 2015	18 years old and above
Hydrocodone bitartrate/chlorpheniramine maleate/pseudoephedrine hydrochloride (Zutripro)	NDA 022439 ANDA 203838 ANDA 204627 ANDA 205657	June 8, 2011 November 26, 2014 April 14, 2014 August 3, 2015	18 years old and above
Hydrocodone bitartrate/phenylpropanolamine hydrochloride	ANDA 075103†	September 29, 2000	Label is not available

* Tablet formulation
† Product discontinued per Drugs@FDA

In March 2008, the FDA issued a Public Health Advisory (PHA) to alert patients, caregivers, and healthcare professionals regarding information on the safe and appropriate use of Tussionex Pennkinetic Extended-Release Suspension (hydrocodone polistirex/chlorpheniramine polistirex).[4] Important highlights from the PHA are reproduced below:

- Do not give to children less than 6 years old. The FDA has received reports of death due to respiratory depression with use of Tussionex in patients less than 6 years old.
- Healthcare professionals should not prescribe and patients should not take Tussionex more often than every 12 hours. Taking this cough medicine more often than every 12

hours may result in a narcotic overdose. Too much hydrocodone can cause life-threatening breathing problems and death.

- Healthcare professionals who prescribe and patients who use Tussionex should be aware of the signs of hydrocodone overdose including the following: trouble breathing, slow or shallow breathing; slow heartbeat; severe sleepiness; cold, clammy skin; trouble walking or talking; or feeling faint, dizzy or confused.
- Patient and parents should use a device designed to accurately measure Tussionex. Household teaspoons or tablespoons vary in size and can result in giving too much of the medicine.

1.3 SELECT HYDROCODONE PRODUCT LABELING

The following is the safety information in the Tussionex Prescribing Information[5] that is relevant to this review.

CONTRAINDICATIONS
Tussionex Pennkinetic Extended-Release Suspension is contraindicated in patients with a known allergy or sensitivity to hydrocodone or chlorpheniramine.

The use of Tussionex Pennkinetic Extended-Release Suspension is contraindicated in children less than 6 years of age due to the risk of fatal respiratory depression.

WARNINGS
Respiratory Depression: As with all narcotics, Tussionex Pennkinetic Extended-Release Suspension produces dose-related respiratory depression by directly acting on brain stem respiratory centers. Hydrocodone affects the center that controls respiratory rhythm and may produce irregular and periodic breathing. Caution should be exercised when Tussionex Pennkinetic Extended-Release Suspension is used postoperatively and in patients with pulmonary disease, or whenever ventilatory function is depressed. If respiratory depression occurs, it may be antagonized by the use of naloxone hydrochloride and other supportive measures when indicated.

PEDIATRIC USE
The use of Tussionex Pennkinetic Extended-Release Suspension is contraindicated in children less than 6 years of age (see CONTRAINDICATIONS).

In pediatric patients, as well as adults, the respiratory center is sensitive to the depressant action of narcotic cough suppressants in a dose-dependent manner. Caution should be exercised when administering Tussionex Pennkinetic Extended-Release Suspension to pediatric patients 6 years of age and older. Overdose or concomitant administration of Tussionex Pennkinetic Extended-Release Suspension with other respiratory depressants may increase the risk of respiratory depression in pediatric patients. Benefit to risk ration should be carefully considered, especially in pediatric patients with respiratory embarrassment (e.g., croup) (see PRECAUTIONS).

PRECAUTIONS
Cough Reflex: Hydrocodone suppresses the cough reflex; as with all narcotics, caution should be exercised when Tussionex Pennkinetic Extended-Release Suspension is used postoperatively, and in patients with pulmonary disease.

Pediatric Use: The use of Tussionex Pennkinetic Extended-Release Suspension is contraindicated in children less than 6 years of age. Tussionex Pennkinetic Extended-Release Suspension should be used with caution in pediatric patients 6 years of age and older.

Drug Interactions: Patients receiving narcotics, antihistaminics, antipsychotics, antianxiety agents, or other CNS depressants (including alcohol) concomitantly with Tussionex Pennkinetic Extended-Release Suspension may exhibit an additive CNS depression. When combined therapy is contemplated, the dose of one or both agents should be reduced.

The use of MAO inhibitors or tricyclic antidepressants with hydrocodone preparations may increase the effect of either the antidepressant or hydrocodone.

The concurrent use of other anticholinergics with hydrocodone may produce paralytic ileus.

ADVERSE REACTIONS

Nervous System Disorders: *Sedation, drowsiness, mental clouding, lethargy, impairment of mental and physical performance, anxiety, fear, dysphoria, euphoria, dizziness, psychic dependence, mood changes.*

Respiratory, Thoracic and Mediastinal Disorders: *Dryness of the pharynx, occasional tightness of the chest, and respiratory depression (see CONTRAINDICATIONS).*

Tussionex Pennkinetic Extended-Release Suspension may produce dose-related respiratory depression by acting directly on brain stem respiratory centers (see OVERDOSAGE).

OVERDOSAGE

Serious overdosage with hydrocodone is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. Although miosis is characteristic of narcotic overdose, mydriasis may occur in terminal narcosis or severe hypoxia. In severe overdosage apnea, circulatory collapse, cardiac arrest and death may occur. The manifestations of chlorpheniramine overdosage may vary from central nervous system depression to stimulation.

DOSAGE AND ADMINISTRATION

Adults and Children 12 Years and Older: 5 ml every 12 hours; do not exceed 10 ml in 24 hours.
Children 6-11 Years of Age: 2.5 ml every 12 hours; do not exceed 5 ml in 24 hours.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

For the purpose of this review, we used the following case definition for respiratory depression and Designated Medical Events (DME):

2.1.1 Respiratory Depression

Case Inclusion Criteria:

- Temporal association with ingestion of a hydrocodone-containing cough and cold product that results in a serious[b] outcome

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, confusion or unusual sleepiness
- Death outcome without a strong alternative explanation

We excluded reports that were related to suicide, substance abuse, and child abuse. We also excluded reports that had a strong alternative explanation for the development of respiratory depression and reports that lacked information for proper assessment.

2.1.2 Designated Medical Events (DME)

We evaluated reports describing DME to identify any new (unlabeled), clinically serious, or otherwise compelling safety signals.

Case Inclusion Criteria:

- All hydrocodone-containing cough and cold reports with Preferred Terms (PT) in the OSE DME list (see Appendix C, Section 8 for the list of events) and a serious[b] outcome

We excluded reports that had a strong alternative explanation for the development of the DME and reports that lacked information for proper assessment.

2.2 FAERS SEARCH STRATEGY

DPV-I searched the FDA Adverse Event Reporting System (FAERS) database with the strategies described in Tables 2 and 3.

2.2.1 Respiratory Depression

Table 2. FAERS Search Strategy for Pediatric Reports of Respiratory Depression with Hydrocodone-containing Cough and Cold Products with a Serious Outcome*	
Date of search	January 12, 2016
Time period of search	January 1, 1969[†] – January 12, 2016
Search type	FBIS quick query
Outcome	Serious[††]

[b] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

Table 2. FAERS Search Strategy for Pediatric Reports of Respiratory Depression with Hydrocodone-containing Cough and Cold Products with a Serious Outcome*	
Product Terms	Product Active ingredient: hydrocodone, hydrocodone bitartrate, hydrocodone hydrochloride, hydrocodone polistirex
MedDRA Search Terms (Version 18.0)	High Level Terms (HLTs): Breathing abnormalities, Respiratory failures, Death and sudden death, Tracheal therapeutics procedures, Disturbances in consciousness, Coma states, Conditions associated with abnormal gas exchange[§]
Age range	17 years of age and below
* See Appendix A for a description of the FAERS database. [†] Date that FDA started to receive adverse events in the AERS/FAERS database. [††] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may include multiple outcomes. [§] See Appendix B, Section 8.2 for PTs associated with HLT search terms.	

2.2.2 Designated Medical Events

Table 3. FAERS Search Strategy for Pediatric Reports of DME with Hydrocodone-containing Cough and Cold Products with a Serious Outcome*	
Date of search	January 14, 2016
Time period of search	January 1, 1969[†] – January 14, 2016
Search type	FBIS quick query
Outcome	Serious[††]
Product terms	Product Active ingredient: hydrocodone, hydrocodone bitartrate, hydrocodone hydrochloride, hydrocodone polistirex
MedDRA search terms (Version 18.0)	OSE DME list: Acute pancreatitis, Acute respiratory failure, Agranulocytosis, Anaphylaxis and anaphylactoid reactions, Aplastic anemia, Blind, Congenital anomalies, Deaf, Disseminated intravascular coagulation, Endotoxic shock, confirmed or suspected, Hemolytic anemia, Haemolysis, Liver failure, Liver necrosis, Liver transplant, Pancytopenia, Pulmonary fibrosis, Pulmonary hypertension, Renal failure, Rhabdomyolysis, Seizure, Stevens-Johnson syndrome, Sudden death, Torsade de Pointes, Toxic epidermal necrolysis, Thrombotic thrombocytic purpura, Ventricular fibrillation, Suicide, Neuroleptic malignant syndrome, Amyotropic lateral sclerosis, Serotonin syndrome, Colitis ischaemic, Progressive multifocal leukoencephalopathy, Product infectious disease transmission[§]
Age range	17 years of age and below
* See Appendix A for a description of the FAERS database.	

Table 3. FAERS Search Strategy for Pediatric Reports of DME with Hydrocodone-containing Cough and Cold Products with a Serious Outcome*
† Date that FDA started to receive adverse events in the AERS/FAERS database. †† Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may include multiple outcomes. § See Appendix C, Section 8.3 for a description of PTs listed under each DME.

3 LITERATURE CASE REPORTS

3.1 LITERATURE SEARCH STRATEGY

Table 4. Literature Search Strategy	
Date of search	January 20, 2016
Database	PubMed@FDA
Search terms	Hydrocodone AND [children OR pediatric]
Years included in search	cumulative through January 20, 2016

4 RESULTS

4.1 FAERS CASE SELECTION

4.1.1 Respiratory Depression

The FAERS search retrieved 264 reports based on the search strategy described in Table 2. After applying the case definition in Section 2.1.1 and accounting for duplicate reports, 38 cases were included in the case series for respiratory depression reported with hydrocodone-containing cough and cold products in pediatric patients (see Figure 1).

Figure 1. FAERS Case Selection

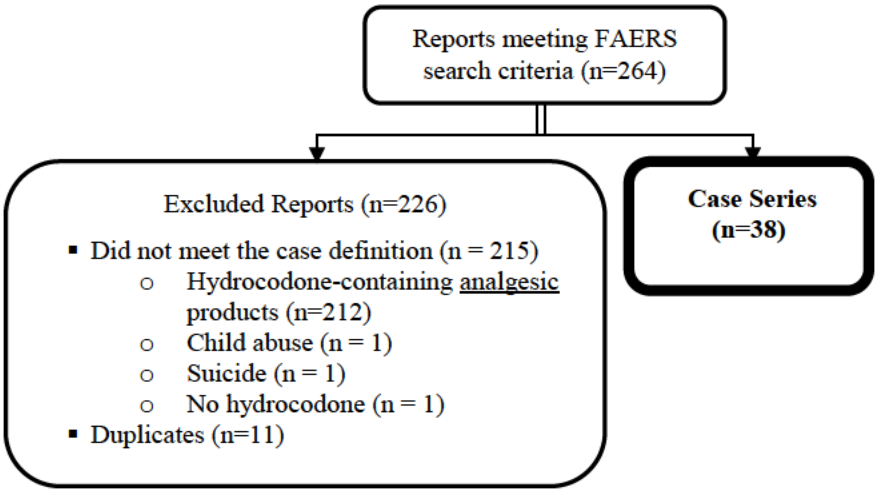


Table 5 summarizes the important information about the 38 serious FAERS cases of respiratory depression in pediatric patients reported with hydrocodone-containing cough and cold products for this case series.

Appendix D lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control numbers for the 38 cases in this case series.

Table 5. Descriptive characteristics of serious pediatric FAERS cases of respiratory depression reported with hydrocodone-containing cough and cold products, received by FDA as of January 12, 2016 (N = 38)		
Sex	Male	14
	Female	22
	Unknown	2
Age	Mean	4.1 years
	Median	2.96 years
	Range	2 months – 17 years
	0-1 year	12
	2-5 years	19
	6-11 years	3
	12-18 years	4
Country	United States	34
	Foreign	4
Initial FDA Received Year	1974	1
	1979	1
	1982	1
	1983	1
	1985	1
	1987	3
	1988	1
	1990	1
	1991	1
	1992	2
	1993	1
	1995	1
	1998	3
	1999	2
	2001	1
	2003	8
	2004	1
	2005	3
	2006	2
	2008	1
	2010	2
Report Type	Expedited	25
	Direct	4
	Periodic	9
Hydrocodone-Containing Cough and Cold Products	Hydrocodone polistirex/chlorpheniramine polistirex	25
	Hydrocodone/homatropine	3
	Hydrocodone/chlorpheniramine unspecified	3
	Hydrocodone unspecified	2
	Hydrocodone/guaifenesin/pseudoephedrine	1
	Hydrocodone/guaifenesin/chlorpheniramine	1

Table 5. Descriptive characteristics of serious pediatric FAERS cases of respiratory depression reported with hydrocodone-containing cough and cold products, received by FDA as of January 12, 2016 (N = 38)		
	Hydrocodone/chlorpheniramine/ phenylephrine	1
	Hydrocodone/phenylpropanolamine	1
	Hydrocodone/phenyltoloxamine	1
Serious Outcomes*	Death	23
	Hospitalization	10
	Life-threatening	5
	Disability	1
	Other Serious	4
Preferred Terms (Top 10)	Coma	11
	Accidental Overdose	8
	Death	7
	Medication error	7
	Cardio-respiratory arrest	5
	Apnoea	4
	Cyanosis	4
	Lethargy	4
	Overdose	4
	Respiratory depression	4
	Sedation	4

* Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events. Reports may include multiple outcomes.

Thirty-one of 38 cases in this case series involved children less than 6 years of age, and 25 of 38 cases involved hydrocodone polistirex/chlorpheniramine polistirex suspension.

Twenty-nine of 38 cases were associated with inadvertent overdoses – 19 cases resulted in death and seven resulted in hospitalization. The inadvertent overdoses varied in nature and included cases of accidental ingestion, incorrect dose measurements, and prescription labeling errors. Of the 29 inadvertent overdose cases, 25 involved children less than 6 years of age and 20 involved hydrocodone polistirex/chlorpheniramine polistirex suspension.

Four of the 23 death cases were not related to an inadvertent overdose. Three of the four cases involved children less than 6 years of age; all three cases had limited information and only reported the patient died following hydrocodone polistirex/chlorpheniramine polistirex suspension administration. The remaining death case involving a 7-year-old (FAERS Case # 3147696) is discussed below.

Reviewer comment: There are currently no hydrocodone-containing cough and cold products that are indicated for children less than 6 years of age. The cases involving hydrocodone polistirex/chlorpheniramine polistirex suspension were all reported prior to the public health advisory issued by the FDA in 2008.

Sample Respiratory Depression Cases

FAERS Case # 3244320, US, Life-threatening, 1999: A 15-year-old female received one dose of a multi-ingredient syrup containing hydrocodone 2.5mg, phenylephrine 5mg, and chlorpheniramine 2mg for suspected bronchitis. Within minutes of receiving the dose, the patient lurched up and threw herself on the floor. She experienced tremors, shaking, loss of bladder control, and difficulty breathing. Emergency services were called and the patient was treated with fluids intravenously. She did not respond to the paramedics when they attempted to talk to her. Naloxone was administered. Within 60 seconds of administration, the patient was able to state her name and the correct day. The patient was then transported to the emergency department and discharged home the same day. Other concomitant medication included clarithromycin. No other pertinent medical history was reported.

Reviewer comment: It should be noted that the reporter was the patient's father, who received the details of the event second-hand from the patient's friend who was present at the time of dose administration. Therefore, the time to onset of the initial events was relayed to the reporter from the friend. This case presents with possible alternative etiologies for the patient's clinical presentation. If the timing and the eyewitness account of the events following the naloxone administration were accurate, then it is possible that this patient's resolution of symptoms was a result of the naloxone counteracting the effects of the hydrocodone. Additionally, co-administration of clarithromycin, a potent CYP3A4 inhibitor, with the cough syrup may have resulted in increased hydrocodone plasma concentrations. Administration of CYP3A4 inhibitors can increase opioid concentrations, thereby prolonging and intensifying analgesic effects and adverse opioid effects, such as respiratory depression.[2,6]

FAERS Case # 3147696, US, Death, 1998: A 7-year-old female was prescribed amoxicillin and a multi-ingredient syrup containing hydrocodone, guaifenesin, and pseudoephedrine for an upper respiratory tract infection and pharyngitis. The patient was also prescribed desmopressin acetate for nocturnal enuresis. The mother was instructed to delay the administration of desmopressin until therapy with the hydrocodone, guaifenesin, and pseudoephedrine syrup was completed. The mother started desmopressin therapy concomitantly with the cough syrup. The patient returned to the prescriber's office with continued symptoms of the upper respiratory tract infection. Her antibiotic therapy was switched from amoxicillin to azithromycin. The following day, the patient was noted to be hypoxic and hypotensive. She was taken to the emergency room where she subsequently died.

Reviewer comment: The cause of death in this case was unclear and there were several factors that may have contributed to the patient's outcome. The concomitant administration of desmopressin and azithromycin were factors to consider. Desmopressin is labeled for hyponatremia. Some signs or symptoms associated with hyponatremia that are similar to those of respiratory depression are fatigue, lethargy, disorientation, coma, and respiratory arrest. The desmopressin label also describes a potential for a drug interaction with opioids because they are known to increase the risk of hyponatremia. The length of therapy for the desmopressin was not provided for this patient. Additionally, co-administration of azithromycin, a weak CYP3A4 inhibitor, may have some effect on increased hydrocodone levels.

FAERS Case # 6129939, US, Hospitalization, 2000: A 35-month-old female received ¼ teaspoon of hydrocodone polistirex/chlorpheniramine polistirex suspension. Fifteen hours later, she received a second dose and was noted to have labored breathing and lethargy. Her physician admitted her to the hospital for observation. During her hospitalization, two doses of naloxone were administered and her symptoms resolved within 24 hours.

Reviewer Comment: *The case lacked some clinical detail. However, the resolution of symptoms after naloxone administration was noteworthy. The current product label for hydrocodone polistirex/chlorpheniramine polistirex suspension contraindicates use in pediatric patients less than 6 years of age.*

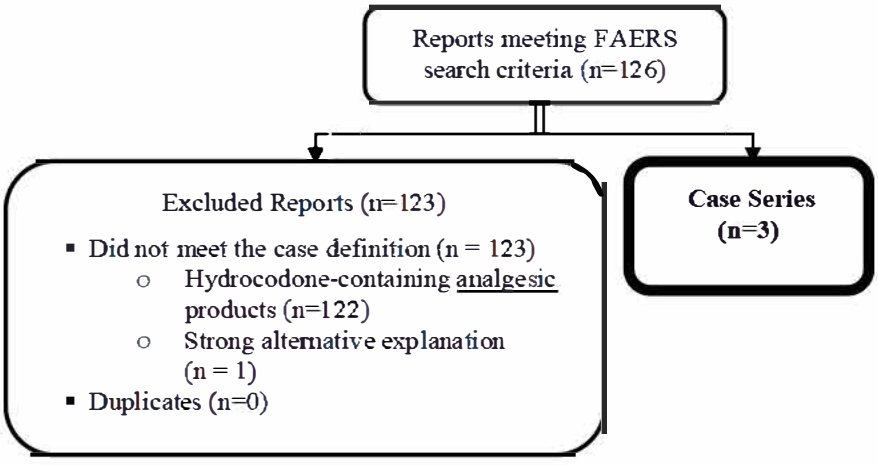
FAERS Case # 4815984, US, Death, 1991: A 3-year-old male experienced respiratory arrest and subsequently died while receiving therapeutic dose(s) of hydrocodone polistirex/ chlorpheniramine polistirex suspension. The patient's medical history and concomitant medications were not reported.

Reviewer Comment: *The case lacked some clinical detail. However, it is a noteworthy case with the following characteristics: therapeutic dose, domestic (US), and death outcome. In addition, the current product label for hydrocodone polistirex/chlorpheniramine polistirex suspension contraindicates use in pediatric patients less than 6 years of age.*

4.1.2 Designated Medical Events

The FAERS search retrieved 126 reports based on the search strategy described in Table 3. After applying the case definition in Section 2.1.2 and accounting for duplicate reports, three cases were included in the case series for DMEs reported with hydrocodone-containing cough and cold products in pediatric patients (see Figure 2).

Figure 2. FAERS Case Selection



Two of the three cases in this case series were captured within the respiratory depression case series.

Appendix D lists all the FAERS case numbers, FAERS version numbers and Manufacturer Control numbers for the three cases in this case series.

The remaining case is characterized below:

- Brain injury in a 5-month-old female as a result of overdose of hydrocodone polistirex/ chlorpheniramine polistirex suspension due to negligent administration

4.2 LITERATURE SEARCH RESULTS

The literature search, based on the search strategy in Table 4, Section 3.1, retrieved 28 articles. Of the 28 articles, only one article involved a case report associated with a hydrocodone-containing cough and cold product. This case was also received in FAERS and is discussed below.

FAERS Case # 7664715, Foreign, Death, 2010: This is a literature report[7] of a 5-year-old, Somolian female who was inadvertently administered high doses of hydrocodone for a respiratory tract infection. The patient went to her physician's office after having had a cold for several days. She was prescribed clarithromycin for an ear infection and hydrocodone bitartrate (1mg/ml) to be taken 1 teaspoonful three times daily for 5 days for cold symptoms. It was noted that the patient received 1 teaspoonful every 4 hours for a total of 30mg of hydrocodone in 24 hours. The patient was found dead the following morning. Other pertinent medical history for this patient included developmental delay and epilepsy. Other concomitant medication included valproic acid. Autopsy results revealed fatal hydrocodone blood concentrations, low hydromorphone levels, and therapeutic levels of valproic acid. CYP2D6 genetic testing found the patient to be a poor or intermediate metabolizer. The authors commented that in addition to the inadvertent increase in frequency of administration of hydrocodone, the patient's reduced CYP2D6 metabolism resulted in reduced hydrocodone clearance, and the CYP3A4 inhibition activity by clarithromycin may have also contributed to the toxic levels of hydrocodone.

Reviewer comment: This is the only case in the case series that mentioned CYP2D6 status. CYP2D6 testing may not be useful in predicting clinical outcome because hydrocodone and its metabolite, hydromorphone, are both pharmacologically active.[3] Furthermore, the primary metabolic pathway of hydrocodone is via CYP3A4 mediated N-demethylation to norhydrocodone with a lower contribution from CYP2D6 mediated O-demethylation to hydromorphone.[2]

5 DISCUSSION

The current labels for both codeine-containing and hydrocodone-containing cough and cold products have warnings in regard to respiratory depression. Additionally, codeine-containing products include a boxed warning regarding death related to ultra-rapid metabolism of codeine to morphine. Hydrocodone-containing products, however, do not include such warning. The purpose of this review is to analyze all serious pediatric respiratory depression cases and DMEs with hydrocodone-containing cough and cold products to identify any potential new safety signals.

This review identified 38 serious pediatric cases of respiratory depression with hydrocodone-containing cough and cold products. The most frequently reported product was hydrocodone

polistirex/chlorpheniramine polistirex suspension. A large majority of the cases (29/38 cases) were associated with inadvertent overdoses, especially in children less than 6 years of age. The inadvertent overdoses varied in nature and included cases of accidental ingestion, incorrect dose measurements, and prescription labeling errors. In March 2008, the FDA issued a public health advisory regarding the safe and appropriate use of hydrocodone polistirex/chlorpheniramine polistirex suspension in an effort to mitigate the potential for overdoses. The FDA has not received any additional pediatric reports involving hydrocodone polistirex/chlorpheniramine polistirex after 2008. Importantly, there are currently no hydrocodone-containing cough and cold products that are indicated for children less than 6 years of age.

There were two FAERS cases and one literature case report of co-administration of CYP3A4 inhibitors with hydrocodone-containing cough and cold products that may have increased hydrocodone plasma levels. Labeling for newly approved hydrocodone-containing analgesic products includes a box warning that states, "The concomitant use with all cytochrome P450 CYP3A4 inhibitors may result in an increase in hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression."[2] The current labeling for hydrocodone-containing cough and cold products does not include such warning with CYP3A4 inhibitors. Consideration should be given to the addition of this warning to all hydrocodone-containing cough and cold products.

Finally, the review of DME reports identified no new safety signals.

6 CONCLUSION

Based on a review of serious FAERS pediatric cases and medical literature of respiratory depression and DMEs with hydrocodone-containing cough and cold products, DPV identified a safety issue of drug interaction between hydrocodone-containing cough and cold products and CYP3A4 inhibitors.

7 RECOMMENDATIONS

DPV recommends the following for consideration:

- Include drug interaction with hydrocodone-containing cough and cold products and CYP3A4 inhibitors in the Warnings and Precautions section of all hydrocodone-containing cough and cold products for harmonization of labeling across all hydrocodone-containing products.

8 REFERENCES

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9 APPENDICES

9.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

9.2 APPENDIX B. LIST OF PREFERRED TERMS ASSOCIATED WITH HIGH LEVEL TERMS USED FOR RESPIRATORY DEPRESSION FAERS SEARCH

HLT	PT
Breathing abnormalities	Acute promyelocytic leukaemia differentiation syndrome, Apnoea, Apnoeic attack, Bradypnoea, Breath holding, Breathing-related sleep disorder, Cardiac asthma, Cardio-respiratory arrest, Central-alveolar hypoventilation, Cheyne-Stokes respiration, Congenital central hypoventilation syndrome, Dyspnoea, Dyspnoea at rest, Dyspnoea exertional, Dyspnoea paroxysmal nocturnal, Grunting, Hyperventilation, Hypopnoea, Hypoventilation, Kussmaul respiration, Mouth breathing, Nocturnal dyspnoea, Orthopnoea, Pickwickian syndrome, Platypnoea, Prolonged expiration, Psychogenic respiratory distress, Respiratory arrest, Respiratory depression, Respiratory depth decreased, Respiratory depth increased, Respiratory distress, Respiratory dyskinesia, Retinoic acid syndrome, Sleep apnoea syndrome, Tachypnoea, Transfusion-associated dyspnoea, Trepopnoea, Upper airway resistance syndrome
Respiratory failures (excl. neonatal)	Acute respiratory failure, Cardiopulmonary failure, Cardio-respiratory distress, Chronic respiratory failure, Postoperative respiratory distress, Postoperative respiratory failure, Respiratory failure, Respiratory paralysis
Death and sudden death	Accidental death, Agonal death struggle, Brain death, Cardiac death, Completed suicide, Death, Death neonatal, Decapitation, Drowning, Electrocution, Euthanasia, Foetal death, Maternal death affecting foetus, Maternal death during childbirth, Stillbirth, Sudden cardiac death, Sudden death, Sudden infant death syndrome, Sudden unexplained death in epilepsy
Tracheal therapeutic procedures	Endotracheal intubation, Mini-tracheostomy, Tracheal fistula repair, Tracheal lesion excision, Tracheal operation, Tracheal plastic repair, Tracheobronchial stent insertion, Tracheobronchial stent removal, Tracheo-oesophageal puncture, Tracheostomy, Tracheostomy closure, Tracheostomy tube removal
Disturbances in consciousness NEC	Adams-Stokes syndrome, Altered state of consciousness, Apallic syndrome, Consciousness fluctuating, Delayed recovery from anaesthesia, Depressed level of consciousness, Gasping syndrome, Hyperglycaemic unconsciousness, Hyperosmolar hyperglycaemic state, Hypoglycaemic unconsciousness, Lethargy, Loss of consciousness, Neonatal oversedation, Postictal state, Post-injection delirium sedation syndrome, Preictal state, Psychogenic pseudosyncope, Sedation, Somnolence, Somnolence neonatal, Sopor, Stupor, Syncope
Coma states	Coma, Coma acidotic, Coma blister, Coma hepatic, Coma neonatal, Coma uraemic, Diabetic coma, Diabetic hyperglycaemic coma, Diabetic hyperosmolar coma, Diabetic ketoacidotic hyperglycaemic coma, Hypercapnic coma, Hypoglycaemic coma, Hyponatraemic coma, Myxoedema coma, Traumatic coma

HLT	PT
Conditions associated with abnormal gas exchange	Alveolar aeration excessive, Anaemic hypoxia, Anoxia, Asphyxia, Brain hypoxia, Cyanosis, Cyanosis central, Hypercapnia, Hypercapnic coma, Hyperoxia, Hypocapnia, Hypoxia, Hypoxic-ischaemic encephalopathy, Respiratory acidosis, Respiratory alkalosis, Respiratory gas exchange disorder

9.3 APPENDIX C. LIST OF OSE DESIGNATED MEDICAL EVENTS AND ASSOCIATED MEDDRA PREFERRED TERMS

Designated Medical Event	MedDRA Preferred Terms (Version 18.0 – updated May 4, 2015)
Acute pancreatitis	Pancreatitis, Pancreatitis acute, Pancreatitis haemorrhagic, Pancreatitis necrotising, Pancreatic necrosis, Haemorrhagic necrotic pancreatitis
Acute respiratory failure	Acute respiratory failure, Respiratory failure, Acute respiratory distress syndrome
Agranulocytosis	Agranulocytosis, Neutropenia, Febrile neutropenia
Anaphylaxis and anaphylactoid reactions	Anaphylactic reaction, Anaphylactoid reaction, Anaphylactic shock, Anaphylactoid shock
Aplastic anemia	Aplastic anaemia, Bone marrow failure, Aplasia pure red cell
Blind	Blindness, Blindness transient, Blindness unilateral, Optic ischaemic neuropathy, Sudden visual loss
Congenital anomalies	Congenital anomaly
Deaf	Deafness, Deafness neurosensory, Deafness permanent, Deafness transitory, Deafness bilateral, Deafness unilateral, Sudden hearing loss
Disseminated intravascular coagulation	Disseminated intravascular coagulation
Endotoxic shock, confirmed or suspected	Endotoxic shock, Septic shock
Hemolytic anemia	Haemolytic anaemia, Coombs positive haemolytic anaemia, Coombs negative haemolytic anaemia
Haemolysis	Haemolysis, Intravascular haemolysis, Haemoglobinaemia, Haemoglobinuria, Haptoglobin decreased
Liver failure	Hepatic failure, Hepatic encephalopathy, Acute hepatic failure, Subacute hepatic failure
Liver necrosis	Hepatic necrosis, Hepatitis fulminant, Hepatitis acute
Liver transplant	Liver transplant
Pancytopenia	Pancytopenia
Pulmonary fibrosis	Pulmonary fibrosis
Pulmonary hypertension	Pulmonary hypertension, Cor pulmonale
Renal failure	Acute kidney injury, Renal failure, Renal impairment
Rhabdomyolysis	Rhabdomyolysis
Seizure	Seizure, Epilepsy, Generalised tonic-clonic seizure
Stevens-Johnson syndrome	Stevens-Johnson syndrome, Erythema multiforme
Sudden death	Sudden death, Sudden cardiac death
Torsade de Pointes	Torsade de pointes

Designated Medical Event	MedDRA Preferred Terms (Version 18.0 – updated May 4, 2015)
Toxic epidemal necrolysis	Toxic epidermal necrolysis, Dermatitis exfoliative
TTP	Thrombotic thrombocytopenic purpura
Ventricular fibrillation	Ventricular fibrillation
Suicide	Completed suicide
Neuroleptic malignant syndrome	Neuroleptic malignant syndrome
ALS - Amyotrophic lateral sclerosis	Amyotrophic lateral sclerosis
Serotonin syndrome	Serotonin syndrome
Colitis ischaemic	Colitis ischaemic, Intestinal infarction
PML - Progressive multifocal leukoencephalopathy	Progressive multifocal leukoencephalopathy
Product infectious disease transmission	Suspected transmission of an infectious agent via product, Transmission of an infectious agent via product, Product contamination microbial

9.4 Appendix D. FAERS Case Numbers, FAERS Version Numbers and Manufacturer Control Numbers

FAERS Case #	FAERS Version #	Manufacturer Control #
Respiratory Depression Cases		
7664715	1	GXKR2010CA12359
5222695	1	HYM950001
3147696	1	US01-18856
3267051	1	HYO980002
3987498	1	HYCD20030004
3244320	1	Direct report
4042229	1	2003-04187
4042268	1	2003-04185
7300312	1	CHPA2010US03750
3171954	1	MPI-1998-03096
3218194	3	MPI-982269(1)
3611389	1	MPI-2000-04670 (0)
3906417	1	CEL-2002-01508-ROC(1)
3928654	1	Direct report
4032085	1	CEL-2003-03663-ROC(0)
4042998	1	KII-2002-0005972
4289954	1	Direct report
4329489	1	Direct report

FAERS Case #	FAERS Version #	Manufacturer Control #
4358070	1	Direct report
4378882	1	0DER1112
4461044	1	DER1122
4577186	1	DER11/28
4577613	1	DER11/26
4577614	1	DER11/33
4592373	1	DER1136
4720428	1	TUD001M90
4815984	1	TUX001M91
4853093	1	TUD004M91
4858823	1	TUC001M87
4950202	1	TUD005M92
5662536	1	CEL-2004-01872-ROC
5754297	1	CEL-2004-01849-ROC(0)
5838116	1	PAR_0105_2005
5893560	1	US-KINGPHARMUSA00001-K200501284
6043154	4	8016409
6129939	1	CEL-2003-03485-ROC
6182008	1	CA-ROCHE-472863
6690749	1	Direct report
DME Cases		
4796046	1	TUC001M91
4858823	1	TUC001M87
4592373	1	DER1136

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/s/

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03/03/2016

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Adverse Opioid Analgesic-Related Outcomes in the Pediatric Population

Date:	September 12, 2016
Reviewer(s):	D. Tyler Coyle, M.D., M.S. Division of Epidemiology II
Team Leader:	Cynthia Kornegay, Ph.D. Division of Epidemiology II
Associate Director:	Judy Staffa, Ph.D., R.Ph. Office of Surveillance and Epidemiology
Drug Name(s):	Opioid analgesics
Subject:	Opioid analgesics in the pediatric population: a review of the epidemiologic literature examining the outcomes of misuse, abuse, addiction, overdose, and death
TSI #:	466
RCM #:	2016-1725

TABLE OF CONTENTS

EXECUTIVE SUMMARY

On August 13th 2015, the Food and Drug Administration (FDA) approved labeling for the use of Oxycontin® in select patients aged 11-17 years. This regulatory action highlighted the public health need for a better understanding of the risk of serious adverse outcomes associated with therapeutic medical opioid analgesic use in pediatric populations (≤21 years old). FDA scheduled an advisory committee (AC) to discuss appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients, including obtaining pharmacokinetic data and the use of extrapolation (docket number FDA-2016-N-0584). To inform this discussion, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Epidemiology (DEPI) to review the epidemiologic literature for studies examining adverse opioid analgesic-related outcomes related to misuse, abuse, addiction, overdose, and death in pediatric populations.

A question of particular interest is if legitimate medical use of opioid analgesics in pediatric patients increases these patients' risk of subsequently experiencing serious adverse opioid-related outcomes. The only longitudinal study to examine this question observed an increased risk of short-term future misuse of opioids among high school seniors previously exposed to opioids for legitimate medical purposes.[1] Additional prospective longitudinal studies are needed to confirm this study's results.

Much of the literature examines data drawn from large, nationally-representative surveys such as Monitoring the Future (MTF) and the National Survey on Drug Use and Health (NSDUH), which survey youths about non-medical use of prescription opioids (NMUPO). Both MTF and NSDUH data show that past-month and past-year NMUPO prevalence rates among persons aged ≤18 years have declined in the last five years compared to the mid-late 2000's. As of 2014, NSDUH data indicate that the prevalence of past-month NMUPO in persons aged 12-17 years and 18-25 years was 1.9% and 2.8%, respectively.[2]

Data from these surveys indicate that females aged 12-17 years are more likely to engage in NMUPO than males in this age group,[3] and whites and Native Americans have higher prevalence rates of past-year NMUPO than other racial/ethnic groups.[4] Depressive symptoms,[5] poor academic performance,[6] living in a single-parent home,[6] and annual family income <$20,000[5] are associated with increased odds of NMUPO in persons aged 12-17 years. Past-year alcohol, cigarette, marijuana, or cocaine/inhalant use is associated with increased odds of NMUPO in this age group as well.[6] Many youths reporting NMUPO obtain drugs from their own leftover prescriptions,[7] or for free from family and friends.[8]

1 INTRODUCTION

Opioid analgesic abuse and dependence have become increasingly common in the United States over the past two decades for several reasons, and represent major public health concerns due to the risk of death associated with opioid analgesic-associated respiratory depression.[9]

On August 13th 2015, the Food and Drug Administration (FDA) approved labeling for the use of long-acting opioid analgesic OxyContin® (oxycodone hydrochloride) in select patients aged 11 to 17 years.[a] It was the first approval of a long-acting oral opioid analgesic for pediatric patients. Because physicians can generally prescribe any approved drug to any patient for any condition as they see fit ("off-label use"), the approval aimed to provide prescribers with data-driven opioid analgesic dosing considerations for select pediatric patients.

This regulatory action underscored the need for a better understanding of the risk of serious adverse outcomes associated with opioid analgesic use in pediatric populations. The FDA scheduled an advisory committee (AC) to discuss appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients, including obtaining pharmacokinetic data and the use of extrapolation (docket number FDA-2016-N-0584).[b]

To provide context for this discussion, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) consulted the Division of Epidemiology (DEPI) to search the epidemiologic literature for studies examining opioid analgesic-related outcomes related to misuse, abuse, addiction, overdose, and death in pediatric populations. We sought to answer the following questions:

- Do pediatric patients who experience adverse opioid analgesic-related outcomes have a history of legitimate use of prescription opioid analgesics? Is there a differential risk of abuse between those patients who have a legitimate prescription and those who do not?
- What is known about the risk of misuse, abuse, addiction, overdose, and death in pediatric populations who are prescribed opioid analgesics? What is not known? What should FDA know in order to make sound regulatory decisions in this space?
- What data sources are available to research this topic? What types of study designs would be useful to better understand this issue in the future?

[a] Approval letter located at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/022272Orig1s027ltr.pdf, accessed 6/21/2016.

[b] Federal Register notice at https://www.federalregister.gov/articles/2016/02/19/2016-03468/anesthetic-and-analgesic-drug-products-advisory-committee-the-drug-safety-and-risk-management, accessed 8/8/2016.

The goal of this document is to provide an assessment of the available epidemiologic literature examining the adverse outcomes of misuse, abuse, addiction, overdose, and death in pediatric populations who are prescribed opioid analgesics.

2 REVIEW METHODS AND MATERIALS

DEPI worked with the FDA Library to search PubMed for peer-reviewed epidemiologic studies in the biomedical literature published from January 2000 to March 2016 that examined adverse opioid analgesic-related outcomes in persons aged <21 years. Our primary outcomes of interest were misuse, abuse, addiction, overdose, and death. The search string used in PubMed is shown in Appendix 1. We excluded case studies, case series, reviews, letters, editorials, animal studies, pharmacokinetic/pharmacodynamic studies, and commentaries. Article abstracts were reviewed for possible inclusion, with more detailed text analysis guiding final study selection.

Terminology in this area of study varies. FDA defines "pediatric patients" as persons aged 21 years or younger at the time of their diagnosis or treatment.[c] However, data sources used by researchers may define this term differently. This document typically includes the age range of interest for each study examined to provide as much specificity as possible. Additionally, for the purposes of this document, we assumed that the majority of opioid analgesic-related toxicities occurring in persons aged <12 years were due to unintentional poisonings associated with naivety (e.g., a toddler getting into a medicine cabinet) rather than with patterns of aberrant drug-related behaviors. Consequently this document focuses primarily on populations aged 12 to 21 years.

Adverse outcome definitions vary as well. FDA defines "abuse" as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect, and defines "misuse" as the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse.[10] Terms such as medical misuse, non-medical use, and extramedical use are also commonplace in this body of literature, each with its own specific definition depending on the data source. This document preserves the language used within each study in the study's analysis, and provides definitions as needed.

3 REVIEW RESULTS

DEPI identified 55 studies examining the adverse opioid-related outcomes of misuse, abuse, addiction, overdose, and death in pediatric populations using the methods described above.

Of the 55 studies, there were:

- 3 cohort studies;
- 1 randomized controlled trial;

[c] See final rule at 21 CFR 814.3(s) (79 FR 1740, January 10, 2014).

- 45 cross-sectional studies; and
- 6 ecologic[d] studies.

The following sections examine many of these studies in greater detail. Appendix 4 summarizes all the reviewed studies.

3.1 COHORT STUDIES

Three cohort studies examining adverse opioid analgesic-related outcomes in the pediatric population are reviewed below.

Miech et al. (2015)[1]

Authors analyzed data from 6,220 respondents who completed baseline Monitoring the Future (MTF; discussed in greater detail in Section 3.3.2) assessments between 1990 and 2012 as 12th graders and who responded to at least one of three follow-up surveys in the panel studies (a response rate of 71% for the follow-up surveys) to evaluate past-year opioid misuse as a function of therapeutic medical opioid use before 12th grade.[e] The analysis pool had 13,542 observations, and respondents, in general, contributed a mode of two follow-up survey observations.

The primary outcome measure was past-year opioid misuse, defined as "taking a narcotic other than heroin without a doctor telling you to on one or more occasions." Frequency of misuse and misuse to "get high or relax" were also assessed as independent outcome measures.

Results showed that 502 of the 6220 participants (8.1% cumulative incidence) reported any past-year opioid misuse in one of three follow-up intervals.

Adjusting for sex, race, parental education level, 12th grade academic performance, past-two week binge drinking, and pre-12th grade marijuana, cigarette, barbiturate/sedative, and opioid misuse, the legitimate medical use of opioids by the 12th grade was associated with a 33% (95% CI: 4%-70%) increased risk of future opioid misuse after the 12th grade. Twelfth graders reporting current opioid misuse, cigarette smoking, marijuana use, and sedative misuse also had a significantly increased risk of future opioid misuse in the multivariate models. Certain variables – such as racial minority status and high academic achievement – were protective against future opioid misuse.

Although the MTF panel study sample is a nationally representative probability sample, the sample used for this specific study may not be, as it only includes students who completed at least one follow-up assessment. Additionally, details of the initial (legitimate) opioid medical exposure are limited: data were not collected on duration of exposure, dose/strength, indication for use, or when the legitimate drug exposure occurred relative to 12th grade. Many of these factors could be residual confounders or

[d] Ecologic studies are observational epidemiologic studies in which at least one variable is measured at the population, rather than the individual, level.

[e] For additional information please see document authored by Alex Secora entitled *Review of Miech et al. 2015 article published in Pediatrics: "Prescription opioids in adolescence and future opioid misuse."* TSI #466.

effect modifiers in the association between prior opioid exposure and future misuse. Only risk for one to five years after graduation was assessed, leaving risk patterns beyond this timeframe unknown.

In sum, this study suggests an increased risk of future NMUPO among 12th graders previously exposed to opioids for legitimate medical purposes compared to 12th graders with no opioid exposure. Additional prospective studies are needed to confirm these findings and to characterize relevant adolescent risk factors for short-term and longer-term opioid misuse.

McCabe et al. (2013)[11]

The authors examined the prevalence and patterns associated with past-year medical use of opioids (using as prescribed), medical misuse of opioids (using more than prescribed), and non-medical use of prescription opioids (NMUPO; using drugs prescribed for someone else) among 7th-12th graders over a two year timeframe. The investigators administered the web-based Secondary Student Life Survey (SSLS) to 2,050 7th-12th graders in two southeastern Michigan school districts multiple times over two years, and analyzed data only from students who responded to the survey in both years. This survey assessed demographic characteristics and problem behaviors (e.g., bullying, gambling), and included questions drawn from the National Survey on Drug Use and Health (NSDUH) and Monitoring the Future (MTF) about alcohol and drug use. It also featured content from the Youth Self Report (YSR) questionnaire to collect data on sleeping and physical pain problems. The survey featured instruments called the Drug Abuse Screening Test, Short Form (DAST-10; sensitivity 0.70, specificity 0.80) and the adolescent-focused CRAFFT[f] survey (sensitivity 0.80, specificity 0.86) to screen for probable drug abuse or dependence.[g]

The authors observed that approximately 80% of 7th-12th graders prescribed opioids reported using their medications as prescribed. Of those respondents reporting past-year NMUPO in year 1, 25% continued this behavior in year 2. Appropriate medical use and NMUPO for pain relief were more prevalent among females than males.

Importantly, medical users of opioids in year 1 did not have statistically significantly increased odds of abnormal results on either the DAST-10 or CRAFFT instruments upon subsequent measurement. Adolescents who reported only medical misuse of opioids in year 1 had higher odds of abnormal screening results on CRAFFT (odds ratio [OR]=5.1,

[f] CRAFFT is a mnemonic acronym of first letters of key words in six screening questions that follow the first section of the screen, which asks about any drug use: Have you ever ridden in a CAR driven by someone (including yourself) who was "high" or had been using alcohol or drugs; do you ever use alcohol or drugs to RELAX, feel better about yourself, or fit in; do you ever use alcohol or drugs while you are by yourself, ALONE; do you ever FORGET things you did while using alcohol or drugs; do your FAMILY or FRIENDS ever tell you that you should cut down on your drinking or drug use; have you gotten into TROUBLE while you were using alcohol or drugs?

[g] The DAST-10 has been validated in adult psychiatric outpatients (Cocco et al. 1998), and a modified version of the DAST-10 has been validated by the author in college students (McCabe et al. 2006). DEPI is unable to identify a validation study for the DAST instrument in adolescents. The CRAFFT instrument has been validated in adolescent outpatients (Knight et al. 2002).

95% confidence interval [CI]:2.4-10.6) or DAST-10 (OR=4.7, CI:2.1-10.8) in year 2. Adolescents who reported NMUPO for non-pain relief in year 1 had higher odds of abnormal screening results on CRAFFT (OR=9.6, CI:3.9-23.6) or DAST-10 (OR=6.4, CI:2.4-16.9) in year 2 as well.

There are limitations that should be considered in interpreting these study results. The sample of adolescents was not nationally representative, and the follow-up assessment only assessed short-term risk (1-2 years after baseline). There was no assessment of longer-term risk or whether risk patterns were maintained over time. The screening instruments abstracted into the survey are not diagnostic, and DAST-10 may need further validation in the adolescent population; additional professional evaluation would be required to confirm the presence or absence of substance use disorders in respondents with abnormal screening results.

Despite these limitations, this cohort study provides evidence of an association between NMUPO and an increased risk of an abnormal screen for drug abuse or dependence in the near future. Importantly, it also suggests that medical use of opioid analgesics is not associated with subsequent (1-2 years after baseline) abnormal drug abuse screening results.

McCabe et al. (2014)[12]

The investigators used data from MTF's panel studies from 1976 to 2005 to examine NMUPO (use of a prescription opioid without a doctor's orders to do so) patterns during the transition from adolescence to adulthood. Each year, MTF selects approximately 2,400 high school seniors from the cross-sectional component of its data collection to follow in two year intervals as panel studies, effectively creating an annual cohort. This group is examined at a minimum of four time points (called "waves"): wave 1 is the initial survey in 12th grade, and data from waves 2, 3, and 4 are collected at roughly age 19/20, 21/22, and 23/24, respectively, through a mailed survey. MTF over-samples from 12th graders who report drug-related behaviors for inclusion in the panel studies.

The longitudinal sample examined consisted of over 27,000 individuals in 30 cohorts who participated in all four waves of data collection. Approximately 11.6% (CI:11.2-12.0%) of the sample reported past-year NMUPO in at least one of the four waves. Among those who reported past-year NMUPO in at least one wave, 69% (CI:67.6-70.4%), 20.5% (CI: 19.3-21.7%), 7.8% (CI:7.1-8.6%), and 2.7% (CI:2.3-3.1%) reported NMUPO in one, two, three, and four waves, respectively. The authors observed that participants who reported past-year marijuana use, past-two week binge drinking behavior, or graduated from 1992-2005 had greater odds of multiple waves of NMUPO compared to other panels.

Data were not available regarding quantity of opioid used on each occasion, or whether NMUPO was preceded by a legitimate prescription for opioids. Additionally, attrition analyses showed that those who reported NMUPO and other problem behaviors were less likely to participate in the study over time, potentially resulting in underestimation of the prevalence of health risk behaviors in the population of interest. This study assessed

short-term risk (one to five years after graduation). There was no assessment of longer-term risk or whether risk patterns are maintained over time.

These results indicate that most NMUPO among American high school seniors is self-limiting. However, approximately one third of those reporting NMUPO as 12th graders continue nonmedical use beyond age 18. This study does not suggest an association between legitimate use of opioids and future NMUPO; instead, its results indicate that 12th graders reporting NMUPO are more likely to engage in other drug-related behaviors in young adulthood.

3.2 RANDOMIZED CONTROLLED TRIAL STUDIES

One cluster randomized controlled study examined the effects of brief universal preventive interventions conducted in adolescents on long-term prescription drug misuse outcomes.

Spoth et al. (2013)[13]

In this group of three cluster randomized controlled studies, the investigators evaluated the effect of various interventions on Iowa and Pennsylvania middle school students' self-reported prescription opioid misuse (use of a prescription opioid not under a doctor's orders) in young adulthood .

In study 1 (1993), investigators randomized 6th graders in 33 Iowa schools in small (<8,500 residents) communities to one of three interventions (11 schools per intervention): Iowa Strengthening Families Program (ISFP), a control intervention, or a Preparing for the Drug-Free Years (PDFY) program.[h] The ISFP program is a 14-session parenting skills, children's social skills, and family life skills training program.[i] Parents and children participate in the program, both separately and together. In addition to a baseline survey in 6th grade, investigators evaluated responses to drug-related surveys in 7th, 8th, 10th, and 12th grades, as well as at ages 21 and 25. The authors observed that 13.5% of those assigned the control intervention reported lifetime prescription opioid misuse at age 25, while only 4.7% of those who received the ISFP intervention reported lifetime prescription opioid misuse at age 25 – a relative reduction of 65%.

In study 2 (1998), investigators randomized Iowa 7th graders in 36 schools in districts with enrollments of <1,200 students to one of three interventions (12 schools per intervention): Strengthening Families Program: For Parents and Youth 10-14 (SFP 10-14) with life skills training (LST), a control intervention, or solely LST. SFP 10-14 is a revised version of ISFP, and LST is a middle school substance abuse prevention program that teaches students social and self-management skills regarding peer- and media-pressure to use drugs, educating participants on the immediate consequences of substance

[h] The PDFY program is a skill-based, parent-oriented workshop that helps parents address risks that can contribute to drug abuse while strengthening family bonding by building protective factors. Findings from the PDFY cluster were not reported in the publication. For more information on PDFY, please visit http://www.strengtheningfamilies.org/html/programs_1999/05_PDFY.html.

[i] For more information on ISFP, please visit http://www.extension.iastate.edu/sfp10-14/.

abuse.[j] In addition to pre- and post-tests in the 7th grade, investigators followed participants with drug-related survey questions yearly in 8th through 12th grades, yearly from ages 19-22, and again at age 25. The authors observed that prescription opioid misuse rates were higher for the control condition across all time points: 8.8% of persons aged 25 years who received the control intervention reported lifetime prescription opioid misuse, while 6.0% of persons aged 25 years who received the SFP 10-14+LST intervention reported lifetime prescription opioid misuse – a relative reduction of approximately 32%.

In study 3 (2002), investigators randomized two consecutive cohorts of Iowa and Pennsylvania 6th graders and their families in 28 schools in districts with enrollments of 1,300-5,200 students to one of two interventions (14 schools per intervention): SFP 10-14 plus one of three school-based curricula,[k] or a control intervention. The three school-based curricula focused on fostering better understanding of the norms and behaviors regarding substance misuse, peer-resistance skills, and self-management. Investigators followed participants with surveys about drug-related questions yearly in 8th through 12th grades. The authors observed that 27.8% of 12th graders who received the control intervention reported lifetime prescription opioid misuse, while 22.1% of 12th graders who received the SFP 10-14 plus any school-based curricula reported lifetime prescription opioid misuse – a relative reduction of approximately 21%.

Overall this publication indicates that brief school- and family-based interventions during adolescence were associated with reductions in the likelihood of misusing opioids in early adulthood. However, combining three trials into a single publication resulted in a lack of granularity for any single trial; details such as the number of participants within each study are not easily identified. Similarly, it is unclear how many participants completed the entire curriculum for each intervention across all the studies, or whether partial curriculum completion was associated with meaningful risk reduction. School selection and cohort identification within the schools are not described in detail. is also unclear whether these results from predominantly small, non-urban settings would be generalizable to other communities; limited demographic detail is provided. Perhaps most importantly, this study provides no insight into the risk of future opioid misuse among pediatric patients prescribed opioid analgesics for legitimate medical purposes.

While this study suggests that brief school- and family-based interventions during adolescence were associated with reductions in the likelihood of misusing opioids in early adulthood, the lack of granularity in the publication makes it difficult to interpret the study's methodology. Further research confirming these results and better characterizing the relative effectiveness of the various interventions is warranted.

3.3 CROSS-SECTIONAL STUDIES

[j] Findings from the LST-only cluster were not reported in the publication.

[k] Curricula selected from the PROmoting School community-university Partnerships to Enhance Resilience (PROSPER) delivery model for evidence-based programs. For a description of the available school-based curricula, visit http://www.ppsi.iastate.edu/publicationsupplements/PF217/programs.pdf.

The majority of studies reviewed were cross-sectional studies, such as anonymous surveys and questionnaires. Cross-sectional studies are informative for describing prevalence trends.

DEPI reviewed 42 cross-sectional studies for this document; these studies are summarized in Appendix 4. Rather than describe each study's results, this document will summarize the findings of studies that may help answer the questions posed in the introduction that are relevant to this Advisory Committee meeting.

Additionally, this section describes of the major data sources used by these publications. Over half of these cross-sectional studies drew data from the same two sources: the National Survey on Drug Use and Health (NSDUH), and Monitoring the Future (MTF). These are two of the largest, most comprehensive, and longest-running nationally-representative surveys examining young populations' drug use patterns. An understanding of these data sources' methodologies and designs may allow for a better appreciation of the strengths and limitations of this body of research.

3.3.1 National Survey on Drug Use and Health (NSDUH)

NSDUH is an annual, nationally representative survey of the civilian, non-institutionalized population of individuals aged 12 and older (N=~70,000) supported by the Substance Abuse and Mental Health Administration (SAMHSA). Formerly called the National Household Survey on Drug Abuse (1971-2001), NSDUH is the largest and longest-running survey of its kind in the country, and its data provide details on drug use patterns in America. Data are collected through computer-assisted, in-person interviews conducted in English or Spanish with residents of households and non-institutional group quarters (e.g., shelters, rooming houses, dormitories, boarding houses, halfway houses), as well as civilians living on military bases. The survey excludes homeless, incarcerated, and institutionalized individuals, as well as individuals who are in nursing homes or are active duty military personnel. Respondents are paid $30 for their time and participation.[2]

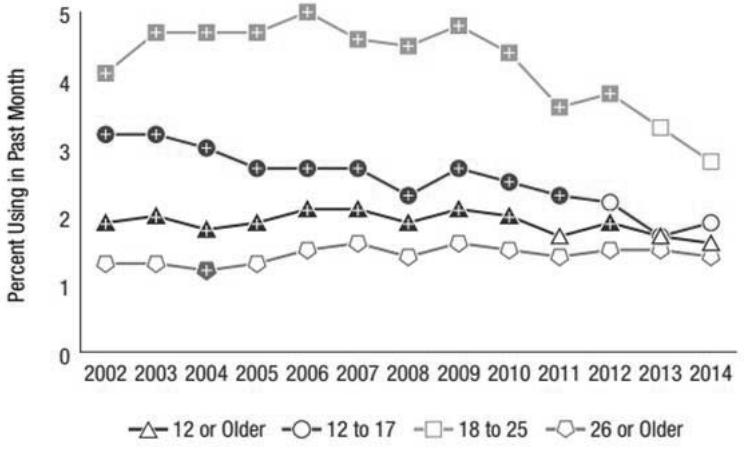
NSDUH uses a state-based, independent, multistage area probability sample to identify respondents. Each state is stratified into approximately equally populated state sampling regions (SSRs), from which census tracts are selected. Census block groups are then identified within census tracts, and area segments (i.e., a collection of census blocks) are selected within census block groups. Finally, dwelling units are selected within the area segments, and within each dwelling unit, up to two residents aged 12 or older are selected for interview. As of 2014, NSDUH allocates more interviews to more populous states, which improves the precision of the national estimates.

In addition to information about tobacco and alcohol use, NSDUH asks participants about use patterns for a variety of drugs, including non-medical use (NMU) of prescription pain relievers. The survey shows pictures of a variety of pills to help respondents respond accurately. NMU is defined as 1) use of the drug without a prescription belonging to the respondent, or 2) taking the drug for the experience or feeling the drug caused. NSDUH's definition of NMU thus incorporates elements from FDA's definitions of misuse (use of a drug not as prescribed) and abuse (use of the drug for its psychologically pleasurable

effects). NSDUH also asks questions that are components of diagnostic criteria for abuse based on the DSM-IV definition for substance use disorder.

A summary of the questions asked about prescription pain reliever NMU is included in Appendix 2, and results from the 2015 annual report describing pain reliever NMU are below.[2]

Figure 1. Past month nonmedical use of pain relievers among people aged 12 or older, by age group: Percentages, 2002-2014[2]



+ Difference between this estimate and the 2014 estimate is statistically significant at the .05 level.

Table 1. Past month nonmedical use of pain relievers among people aged 12 or older, by age group: Percentages, 2002-2014[2]

	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
12 or Older	1.9+	2.0+	1.8+	1.9+	2.1+	2.1+	1.9+	2.1+	2.0+	1.7	1.9+	1.7	1.6
12 to 17	3.2+	3.2+	3.0+	2.7+	2.7+	2.7+	2.3+	2.7+	2.5+	2.3+	2.2	1.7	1.9
18 to 25	4.1+	4.7+	4.7+	4.7+	5.0+	4.6+	4.5+	4.8+	4.4+	3.6+	3.8+	3.3	2.8
26 or Older	1.3	1.3	1.2+	1.3	1.5	1.6	1.4	1.6	1.5	1.4	1.5	1.5	1.4

* Difference between this estimate and the 2014 estimate is statistically significant at the .05 level.

In 2014, approximately 1.9% of Americans aged 12-17 reported past-month NMU of pain relievers, corresponding to approximately 467,000 adolescents. This represents a decline of 41% from 2002, when 3.2% of adolescents reported past-month NMU. The 2014 level (1.9%) of past-month NMU in this age group was similar to levels seen in 2012 (2.2%) and 2013 (1.7%).

In 2014, approximately 2.8% of Americans aged 18-25 reported past-month NMU of pain relievers, corresponding to approximately 978,000 adolescents. This represents a decline of 32% from 2002, when 4.1% of adolescents reported past-month NMU. The 2014 level (2.8%) of past-month NMU in this age group is lower than levels seen in 2012 (3.8%) and 2013 (3.3%).

3.3.2 Monitoring the Future (MTF)

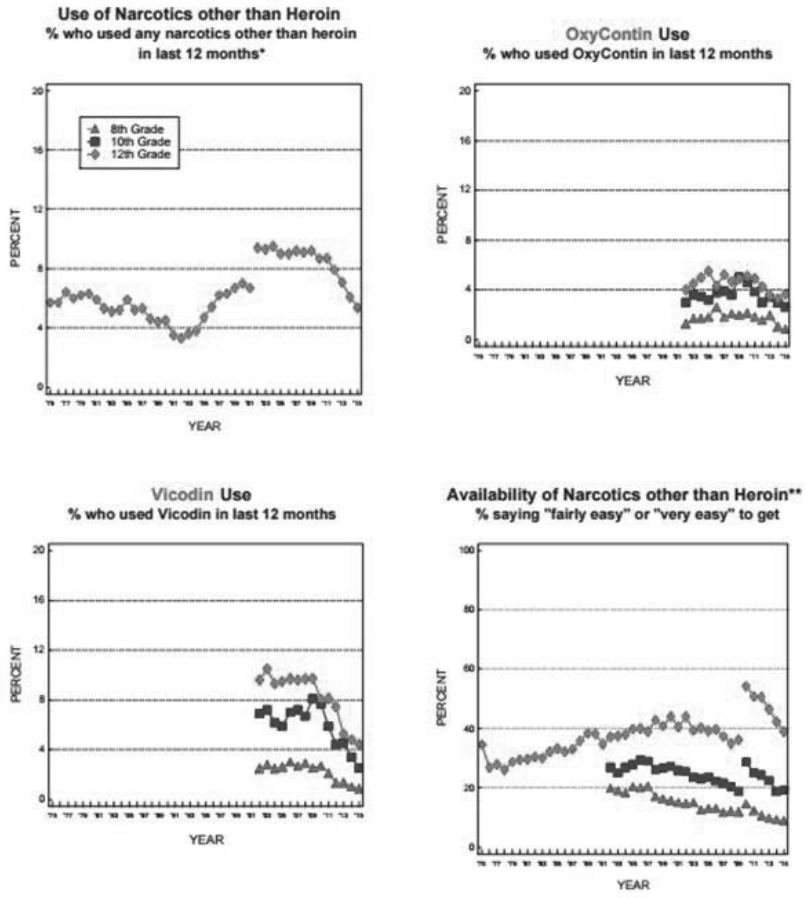
Monitoring the Future (MTF) is an annual survey examining drug use trends and related attitudes among America's secondary school students, college students, and adults through age 50. MTF is composed of three substudies: (a) an annual survey of high school seniors that was initiated in 1975; (b) ongoing panel studies of representative samples from each graduating class (i.e., 12th graders) that have been conducted by mail since 1976; and (c) annual surveys of 8th and 10th graders that began in 1991. Each spring, students in the 8th, 10th, and 12th grades complete a self-administered, paper-based, machine-readable questionnaire in a class period during school hours. In 2014, approximately 41,600 students in 377 public and private secondary schools were surveyed.[14] In addition, approximately 2,400 respondents who participate in the survey of 12th graders are followed longitudinally in the panel studies on a biennial basis, effectively creating a cohort drawn from the cross-sectional results.

To secure a nationally representative sample of high school seniors, the survey uses a three-stage sampling procedure:

- Stage 1: Geographic Areas. The geographic areas used are the primary sampling units (PSUs) developed by the Sampling Section of the University of Michigan's Institute for Social Research's Survey Research Center for use in the center's nationwide interview studies. Local field representatives can be assigned to administer the data collections in practically all included schools.
- Stage 2: Schools. In the major metropolitan areas, more than one high school is often included in the sampling design; in most other sampling areas, a single high school is sampled. In all cases, the selections of high schools are made such that the probability of drawing a school is proportionate to the size of its senior class. The larger the senior class (according to recent records), the higher the selection probability assigned to the high school. When a sampled school is unwilling to participate, a replacement school as similar to it as possible is selected from the same geographic area.
- Stage 3: Students. Within each selected school, up to 350 seniors may be included in the data collection. In schools with fewer than 350 seniors, the usual procedure is to include all of them in the data collection. In larger schools, a subset of seniors is selected either by randomly sampling classrooms or by some other random method that is convenient for the school and judged to be unbiased. Sample weights are assigned to each respondent so as to take into account variations in the sizes of samples from one school to another, as well as (smaller) variations in selection probabilities occurring at the earlier stages of sampling.

MTF asks questions about non-medical use (NMU; using the drugs without a doctor's order to do so) of non-heroin narcotics, as well as perceived risk, disapproval, and perceived availability of many types of drugs. Appendix 3 contains a summary of the questions included in MTF regarding non-heroin narcotic NMU. Figure 2 is a graphic from the 2015 annual report summarizing the prevalence of past-year non-heroin narcotic NMU.[14]

Figure 2. Trends in the annual use and availability of non-heroin narcotics – as well as OxyContin and Vicodin specifically – among 8th, 10th, and 12th graders through 2015[14]



Source. The Monitoring the Future study, the University of Michigan.
*Beginning in 2002, a revised set of questions on other narcotics use was introduced in which Talwin, laudanum, and paregoric were replaced as examples given with Vicodin, OxyContin, and Percocet.
**In 2010 the list of examples was changed from methadone, opium to Vicodin, OxyContin, Percocet, etc.

MTF data indicate that approximately 5.4% of 12th graders reported past-year NMU of non-heroin narcotics in 2015, with 3.7% and 4.4% reporting past-year Oxycontin® or Vicodin® NMU, respectively. The percentage of 12th graders reporting past-year or past-month NMU of non-heroin narcotics has decreased steadily from 2009 to 2015 (Tables 2 and 3).

Table 2. Trends in the <u>past-year</u> prevalence of non-medical use of non-heroin narcotics among 12th graders through 2015.[14]

Year	2008	2009	2010	2011	2012	2013	2014	2015
Prevalence (%)	9.1	9.2	8.7	8.7	7.9	7.1	6.1	5.4

Table 3. Trends in the past-month prevalence of non-medical use of non-heroin narcotics among 12th graders through 2015.[14]

Year	2008	2009	2010	2011	2012	2013	2014	2015
Prevalence (%)	3.8	4.1	3.6	3.6	3.0	2.8	2.2	2.1

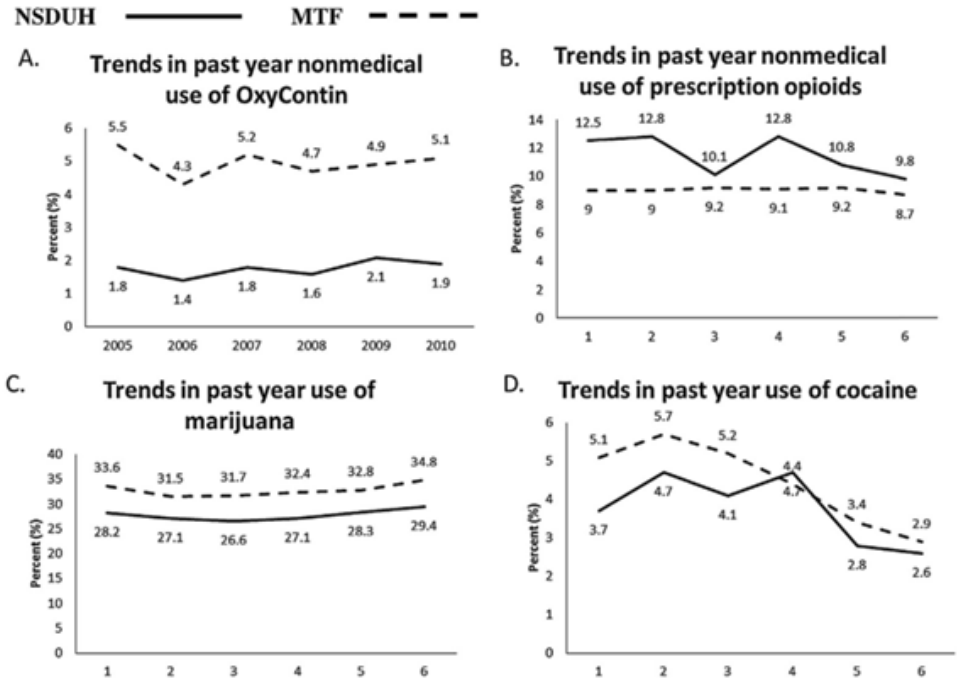
3.3.3 NSDUH vs. MTF

While often considered together, MTF and NSDUH have important differences. In contrast to MTF, NSDUH is household-based, uses a computer-assisted interview system, and shows respondents pill cards with pictures of specific drugs, which may increase identification accuracy of drugs used during the survey. MTF is school-based and uses paper-and-pencil surveys. One study suggests that school-based surveys tend to elicit higher prevalence rates of illicit behavior than household-based surveys, while computer-assisted methods tend to elicit higher prevalence rates of illicit behavior than paper-based methods.[15]

NSDUH's definition of NMU combines FDA's definitions of misuse and abuse (use not as prescribed or for the psychological effects), while MTF effectively captures misuse (use of a drug not as prescribed), but not abuse, of drugs in its questioning. NSDUH does not survey institutionalized individuals, and MTF does not survey high school dropouts. Dropouts tend to engage in riskier health behaviors than non-dropouts, so MTF may not capture data from a high-risk group, potentially underestimating health risk behavior prevalence.[16]

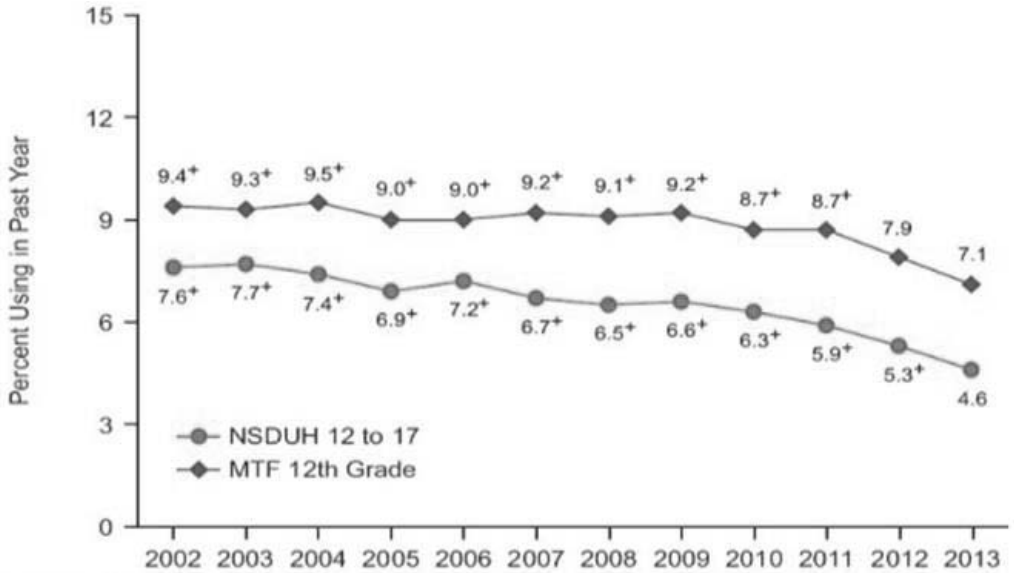
A study comparing 12th graders' MTF and NSDUH responses from 2005 to 2010 observed that prevalence estimates of past-year NMU of Oxycontin® were two-to-three times higher in MTF than in NSDUH. However, prevalence estimates of past-year NMU of any prescription opioids were consistently higher in NSDUH than in MTF (Figure 3).[17]

Figure 3. Trends in past-year prevalence of NMU of selected drugs among 12th graders in the 2005-2010: NSDUH and MTF estimates.[17]



An additional graphic confirms the variation in prevalence estimates for past-year NMUPO between the two surveys.[18] A possible explanation for some of the observed differences is a grouping effect: grouping 12 year olds with 17 year olds may lower NSDUH's observed prevalence of certain health risk behaviors compared to MTF's survey of solely high school seniors.

Figure 4. Past-year NMUPO among youths in NSDUH and MTF: 2002-2013.[18]



MTF = Monitoring the Future; NSDUH = National Survey on Drug Use and Health.
+ Difference between this estimate and the 2013 estimate is statistically significant at the .05 level.
Note: Data for MTF are for "narcotics other than heroin."

Although NSDUH and MTF have inherent limitations, these limitations do not represent a significant threat to the validity of either survey's findings. NSDUH data are informative because the data are detailed, the dataset is large, and data files are readily available. Likewise, MTF is a valuable data source for drug abuse researchers because of the population studied, the scale of the dataset, and its longitudinal panel studies.

3.3.4 RELEVANT NSDUH AND MTF STUDY RESULTS

Dozens of studies have used these data sources to examine associations between young people and prescription pain reliever abuse, misuse, and non-medical use of prescription opioids (NMUPO). While every reviewed study is summarized in the Appendix 4 table, the results of the most relevant studies for answering the questions posed in this document's introduction are outlined below, and are grouped by genre of association.

Please note that the below studies may have used different years' data for their analyses; owing to temporal variations in drug use, these results may have shifted since the time of data gathering analyses.

3.3.4.1 DEMOGRAPHY

- Persons aged 16 years are more likely to initiate NMUPO than any other persons aged 12-21 years.[19] Persons aged 15-18 years have higher odds (OR=2.75, CI:2.32-3.27) of reporting NMUPO than those aged 12-15 years.[6]
- Females aged 12-17 years are more likely than males to report NMUPO (OR=1.36, CI:1.26-1.47) or symptoms of opioid abuse/dependence (OR=1.39, OR:1.13-1.70).[3]
- Persons aged 12-17 years reporting an annual family income of <$20,000 have greater odds (OR=1.7, CI:1.4-2.0) of reporting NMUPO than respondents reporting an annual family income of >$75,000.[5]
- By ethnicity and race, the percentage of respondents aged 12-17 years indicating past-year NMUPO varies in prevalence from a low of 4.3% (CI:3.3-5.4%) among Asian or Pacific Islander respondents to a high of 9.7% (CI: 7.4-12.6%) among Native American respondents (summary table below).*[4]

Table 4: One-year prevalence of analgesic opioid misuse among 72,561 adolescents aged 12 to 17 years by race/ethnicity (percentage and 95% confidence interval)*[4]

	White (n=43,778)	**African American (n=10,109)**	**Native American (n=1122)**	**Asian or Pacific Islander (n=2481)**	**Multiple (n=2814)**	**Hispanic (n=12,257)**
Analgesic opioid misuse	**7.5 (7.2-7.8)**	**5.5 (4.9-6.1)**	**9.7 (7.4-12.6)**	**4.3 (3.3-5.4)**	**8.8 (7.2-10.8)**	**5.6 (5.0-6.4)**

*Adapted from Wu et al. (2011)

3.3.4.2 ACTIVITIES & CONTEXT

- Persons aged 12-17 years reporting the following social, educational, and home contexts have increased odds of reporting NMUPO:[6]
    - No mother (OR=1.38, CI:1.09-1.74) or father (OR=1.36, CI:1.16-1.60) in home
    - Grades of D or worse (OR=2.84, CI:2.29-3.51)
    - Past jail/detention (OR=2.00, CI:1.60-2.49)
    - Past-year move (OR=1.46, CI:1.24-1.73)
- 12th graders who participate in high-injury sports have increased odds (e.g., wrestling [OR=1.49, CI:1.01-2.19], football [OR=1.50, CI:1.12-1.99]) of NMUPO than those who do not participate in these sports.[20]
- Among 12th graders reporting past-year NMUPO, 45% reported pain relief as a motivation.[21]
- Nearly 50% of persons aged 12-17 years reporting past-year NMUPO got these drugs for free from friends or family.[8]
- Over 36% of 12th graders reporting NMUPO obtained the drugs from their own previous prescriptions from which they had leftover pills.[7]

3.3.4.3 MENTAL HEALTH

- Females aged 12-17 years had higher odds (OR=3.7, CI:2.7-5.2) of reporting both NMUPO and a major depressive episode (MDE) in the past year than males of the same age group.[5]
- Persons aged 12-17 years reporting past-year NMUPO had more than twice the prevalence of a past-year MDE than those who reported no past-year NMUPO.[5]
- Persons aged 12-17 years who received past-year mental health treatment had higher odds (OR=2.08, CI:1.78-2.43) of NMUPO than those who did not receive mental health treatment.[6]

3.3.4.4 OTHER DRUG USE

- Persons aged 12-17 years have increased odds of reporting NMUPO if they also report past-year marijuana (OR=9.4, CI:8.0-11.0), cigarette (OR=7.8, CI:6.6-9.0), alcohol (OR=7.0, CI:5.8-8.4), or cocaine/inhalant (OR=10.1, CI:8.4-12.1) use.[6]
- Alcohol use disorder among persons aged 12-17 years is associated with higher odds (OR=3.4, CI:2.5-4.6) of reporting past-year NMUPO.[5]
- Prior NMUPO among persons aged 12-21 years is associated with an increased risk (HR=13.1, CI:10.7-16.0) of subsequent heroin initiation.[22]

3.4 ECOLOGIC STUDIES

Seven ecologic studies[l] examining adverse opioid analgesic-related outcomes in the pediatric population are reviewed below.

Gilchrist et al. (2012)[23]

Using data from the national vital statistics system (NVSS) from 2000 to 2009, CDC researchers analyzed causes of unintentional injury deaths among persons aged 0 to 19 years in the United States. During this time period, the death rate due to unintentional poisoning among persons aged 10-14 years remained largely unchanged (0.1 to 0.2 per 100,000 population; p=0.116), while the rate among persons aged 15-19 years nearly doubled (1.7 to 3.3 per 100,000; p<0.001). Additionally, the percentage of poisoning deaths in this latter age group with prescription drugs as a contributing cause increased from 30% in 2000 to 57% in 2009.

This study did not feature individual-level data to allow for control of potential confounders such as prescription indication or clinical comorbidity. NVSS is a death certificate-based data system, and death certificates vary greatly in specificity. Cause of death is a clinical determination by a medical examiner or coroner (ME/C), which has a subjective component. While these data doubtless include poisonings due to opioid analgesic overdose, other poisoning etiologies are included as well. Although this analysis included all fatal poisonings – not solely opioid-related ones – it is reasonable to suspect that opioids played a significant role in this increase over this timeframe. However, this study provides no insight into the source of the drug implicated in the poisoning or the sequence of events leading to the adverse outcome, which are central concerns of this particular review.

Calcaterra et al. (2013)[24]

Using CDC WONDER multiple cause-of-death (MCOD) data to identify pharmaceutical opioid-related overdose fatalities from 1999 to 2009 by age strata and sex, the authors observed crude overdose death rates per 100,000 persons among females aged 15-24 years was 1.32 (CI: 1.25-1.39), and 4.69 (CI: 4.56-4.82) for males in the same age category.

This study did not stratify opioid-related overdose death rates over time by age group, which would have been valuable for this document's purposes. The study could not account for additional causes of death related to substance abuse – e.g., motor vehicle crashes while intoxicated on a substance – and did not feature individual-level data to allow for control of potential confounders such as prescription indication or clinical comorbidity. CDC WONDER MCOD is a death certificate-based data system, and death certificates vary greatly by cause of death specificity. Cause of death is a clinical determination by a ME/C, which has a subjective component.

This study's results indicate that between 1999 and 2009, the opioid-related overdose fatality rate was approximately 3.5 times higher among men than women aged 15-24 years. The age-adjusted overdose death rate due to pharmaceutical opioids rose during

[l] Ecologic studies are observational epidemiologic studies in which at least one variable is measured at the population, rather than the individual, level.

this same time period. This gender disparity in opioid overdose death rates may enable more targeted methods of risk reduction on a public health level: the knowledge that young men have over thrice the opioid-related fatality rate compared to young women may give a provider pause in considering his or her prescribing practices for certain patients. However, this study provides no insight into the source of the drug implicated in the poisoning or the sequence of events leading to the adverse outcome, which are central concerns of this review.

Rudd et al. (2014)[25]

Using state health department mortality data from 28 states solicited by CDC in 2014, the authors examined heroin and opioid pain reliever (OPR) death rates from 2010 to 2012 in a variety of populations. The authors observed that the death rate from heroin overdose across all age strata doubled in this timeframe, rising from 1.0 (n=1,779) to 2.1 (n=3,635) per 100,000 population. In contrast, the OPR death rate declined from 6.0 (n=10,427) to 5.6 (n=9,869) per 100,000 population during this timeframe. Within the 15-24 year old age stratum, fatal heroin overdose rates increased over this timeframe, rising from 1.2 to 2.3 per 100,000 population – an 86.3% increase. Over this period, fatal OPR overdoses decreased in the 15-24 year old age stratum, falling from 4.3 to 3.1 per 100,000 population – a 28.1% decrease.

These analyses are limited in that over 20% of death certificates do not specify the drug involved in fatal overdoses, so these numbers are likely an underestimate. Additionally, although these data cover a majority of the states in the union, the data are not necessarily nationally representative.

Although OPRs still account for many more deaths in the overall population than heroin, the uptick in heroin-related deaths among young people is disturbing. These data, in concert with the study published by Cerda et al. showing an association between prior NMUPO and an increased risk of heroin initiation, highlight the complex and potentially fluid relationship between licit and illicit drug use. However, this publication does not suggest that there is an association between legitimate opioid use in pediatric populations and future licit or illicit opioid misuse.

Tormoehlen et al. (2011)[26]

In 2001, the Joint Committee on Accreditation of Healthcare Organizations (JCAHO) established standards for pain assessment and treatment. Using data from a single poison center in Indiana, the authors examined the number of calls reporting opioid exposures involving persons aged 12-18 years from 1994 to 2007, using the JCAHO pain control initiative as a midpoint. The main outcome measure was the number of adolescent opioid cases reported for 1994-2000 compared to 2001-2007; secondary outcomes included outcome severity, analysis of case counts by specific opioid, and correlation of the number of cases and the amount of opioids distributed within the state. The authors observed that the opioid exposure rate per 1,000 adolescent cases increased from 20.1 in 1994-2000 to 36.2 in 2001-2007, and the opioid complication rate per 1,000 adolescent cases increased from 1.6 in 1994-2000 to 4.9 in 2001-2007.

Poison control centers do not consistently capture fatal events and rely on voluntary reports by patients or providers, and likely underestimate the actual public health burden

of opioid toxicity. Adolescents may be less likely to contact poison control centers in the context of a problematic drug reaction or overdose for fear of repercussions. Misclassification is a concern as well: poison control centers accept calls from lay-people who may misreport the ingested drug. It is unclear to what extent these results from a single poison control center can be generalized to a broader population. It is also difficult to establish the JCAHO initiative as causing the increase in exposure in this age group using this type of study design and data source.

This study's results show that the count and proportion of opioid-related calls to an Indiana poison control center involving persons aged 12-18 years increased when comparing data from 1994-2000 to data from 2001-2007. However, this study provides no insight into the source of the drug implicated in the poisoning or the sequence of events leading to the adverse outcome, both of which are central concerns of this review.

Warner et al. (2011)[27]

Using data from the National Vital Statistics System (NVSS), the authors examined trends in drug poisoning deaths nationwide over the past several decades. The investigators observed that from 1999 to 2008, the drug poisoning death rate per 100,000 population for persons under age 15 remained largely unchanged (0.1 in 1999 vs. 0.2 in 2008), while the rate for persons aged 15-24 increased from 3.2 in 1999 to 8.2 in 2008.

NVSS is a robust data source, but has limitations, as it is based on death certificate data. Death certificates vary in terms of specificity of drug identified and rely on the clinical expertise of the ME/C, which carries a subjective component. The age-stratified analysis did not restrict to deaths caused solely by opioid analgesics, instead analyzing all drug poisonings. Nevertheless, these data highlight a troubling rise in fatal drug poisonings in the pediatric population, and opioid analgesics can reasonably be assumed to contribute significantly to this burden. However, this study provides no insight into the source of the drug implicated in the poisoning or the sequence of events leading to the adverse outcome, which are central concerns of this review.

Zosel et al. (2013)[28]

RADARS® is a proprietary data system that collects poison center call data to provide information on prescription opioid and stimulant abuse and misuse in the American population. The authors used RADARS® data to describe adolescent (13-19 years) exposures to prescription opioids (oxycodone, fentanyl, hydrocodone, hydromorphone, morphine, methadone, buprenorphine, and tramadol) from 2007 to 2009. There were 10,966 opioid-related adolescent cases over this time period, and the most frequently reported drugs involved were hydrocodone, oxycodone, and tramadol.

The use of poison control center data has limitations. Poison control centers do not reliably capture fatal events, making these numbers an underestimate of the true burden on the population. The data are created through voluntary reports by patients or providers, and are therefore likely an underestimate of the true burden on the population. Adolescents may be less likely to contact poison control centers in the context of a problematic drug reaction or overdose for fear of repercussions. Misclassification is a concern as well: poison control centers accept calls from lay-people who may misreport the ingested drug.This study provides no insight into the source of the drug implicated in

the poisoning or the sequence of events leading to the adverse outcome, which are central concerns of this review.

4 DISCUSSION

This review summarizes the epidemiologic data on the adverse outcomes of misuse, abuse, addiction, overdose, and death in pediatric populations prescribed and using opioid analgesics. The introduction posed several questions of interest:

- What is known about the risk of misuse, abuse, addiction, overdose, and death in pediatric populations who are prescribed opioid analgesics? What is not known? What should FDA know in order to make sound regulatory decisions in this space?
- Do pediatric patients who experience opioid analgesic-related adverse outcomes have a history of either legitimate or nonmedical use of prescription opioid analgesics?
- What data sources are available to research this topic? What types of study designs would be useful to better understand this issue in the future?

The majority of the reviewed studies were cross-sectional or ecologic in nature, and many relied on one of two data sources: NSDUH or MTF. There were three longitudinal studies and a single clinical trial that had the potential to directly address these questions.

Overall, the most recent NSDUH data (2014) indicates that well under 5% of persons aged 12 to 25 years engaged in past-month NMUPO.[2] Both MTF and NSDUH data show that past-month and past-year NMUPO prevalence have declined in recent years in the pediatric population compared to the mid-late 2000's.[14] McCabe et al.'s 2014 study concluded that most NMUPO among high school seniors is a self-limiting phenomenon, perhaps associated with the transitional period from adolescence to adulthood where drug experimentation is not uncommon.[12]

Researchers observed several notable associations in this body of pediatric drug abuse research:

- Females are more likely to engage in NMUPO than males
- Whites and Native Americans have higher prevalence rates of past-year NMU than other racial/ethnic groups
- A history of a major depressive episode, poor academic performance, single-parent homes, and low annual family income are associated with increased odds of NMUPO
- Many who report NMUPO obtain the drugs from their own leftover prescriptions, or for free from family and friends
- Past-year use of alcohol, cigarette, marijuana, or cocaine/inhalants is associated with increased odds of NMUPO among adolescents; additionally, one particularly troubling report indicated that NMUPO in adolescence was associated with an increased risk of initiating heroin in young adulthood

Ecologic data provide insights into broader trends. From 2000 to 2009, the rate of fatal drug poisonings in persons aged 15-19 years nearly doubled, and heroin death rates

nearly doubled in persons aged 15-24 years from 2010 to 2012. However, these ecologic studies do not address the central question of interest, which is whether prescribing opioids to youths for legitimate medical purposes increases these persons' risk for future opioid misuse.

A central concern is whether a legitimate opioid analgesic prescription for a young person increases that person's risk for subsequent misuse and abuse of opioids. In contrast to McCabe et al.'s 2013 study which observed no association between legitimate opioid use and subsequent (one to two years after baseline) abnormal drug screening results among 7th-12th graders,[11] Miech et al.'s 2015 study observed an increased risk of short-term (one to five years after graduation) future misuse of opioids in 12th graders previously exposed to opioids for legitimate medical purposes.[1] The results of the study by Miech et al. are particularly troubling, and warrant confirmation through additional research.

Longitudinal studies provide valuable information on the risk of adverse opioid-related outcomes in pediatric patients, and additional studies are needed to better characterize drug safety concerns in this population. A useful study design would be to follow a cohort of adolescents prescribed opioid analgesics for legitimate medical purposes over time to observe the incidence of opioid-related adverse outcomes.

Current research indicates that NMUPO prevalence rates in the pediatric population are declining. However, a particularly striking area of continuing concern is the potential importance of reducing available drug supply: a large proportion of adolescents engaging in NMUPO obtain the drugs for free from friends or family, and from leftover medications in a medicine cabinet. Reducing availability of powerful opioid analgesics is critical to prevent temptation. Prescribers are the gatekeepers to prescription opioid analgesics, and should grant access to these drugs only to patients who truly need them and in as small a supply as necessary.

Like many of the studies reviewed for this document, our methods and analysis have limitations. Every effort was made to identify and review each relevant study in the literature; however, it is possible that some studies were not captured in our search.

5 CONCLUSION

It is possible that legitimate use of an opioid analgesic in adolescence increases an individual's risk of subsequent aberrant drug-related behaviors. However, the association between adolescent use of an opioid for legitimate medical purposes and future NMUPO is based on results from a single study, and needs confirmation through additional studies. Due to the paucity of longitudinal studies in this research space, little is known about the risk of long-term adverse opioid analgesic-related outcomes – such as misuse, abuse, addiction, overdose, and death – in pediatric patients who use opioids for legitimate medical purposes. Prospective cohort studies would be especially informative for these purposes.

Many adolescents reporting NMUPO report obtaining the drugs from leftover prescriptions or from family and friends. Reducing drug availability should be a public health priority to mitigate unnecessary exposure risk in this vulnerable population.

6 RECOMMENDATIONS

FDA should consider encouraging investigators to conduct prospective cohort studies in pediatric patients prescribed opioid analgesics for medical purposes to evaluate the risk of long-term adverse outcomes associated with opioid use, and factors associated with those risks.

FDA should promote proper disposal of leftover prescription opioid analgesics by patients, particularly in households where children are present. Additionally, FDA should consider working with clinicians and pharmacists to explore ways to reduce potential excess drug availability.

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APPENDICES

Appendix 1: PubMed search string conducted on March 4, 2016 with FDA Library to identify epidemiologic studies examining adverse opioid-related outcomes in the pediatric population

Search **(#37 AND #38)** Filters: **Publication date from 2000/01/01 to 2016/12/31; Adolescent: 13-18 years; Young Adult: 19-24 years**	2580	15:03:
Search **(("Analgesics, Opioid"[Mesh]) OR opioid*[tiab] OR opioid analgesic*[tiab] OR opiate*[tiab])** Filters: **Publication date from 2000/01/01 to 2016/12/31; Adolescent: 13-18 years; Young Adult: 19-24 years**	5572	15:01:
Search **((((((("Substance-Related Disorders"[Mesh]) OR substance abuse[tiab] OR abuse[tiab] OR "Prescription Drug Misuse"[Mesh]) OR misuse[tiab] OR aberrant[tiab] OR nonmedical[tiab] OR non-medical[tiab] OR "Opioid-Related Disorders"[Mesh]) OR "Drug Overdose"[Mesh]) OR overdos* [tiab] OR "Death"[Mesh] OR death*[tiab] OR morbid*[tiab] OR fatal*[tiab] OR mortal*[tiab])** Filters: **Publication date from 2000/01/01 to 2016/12/31; Adolescent: 13-18 years; Young Adult: 19-24 years**	143587	14:59:
Search **(#21 AND #32)** Filters: **Publication date from 2000/01/01 to 2016/12/31; Adolescent: 13-18 years; Young Adult: 19-24 years**	2164	14:54:
Search **(#21 AND #32)** Filters: **Publication date from 2000/01/01 to 2016/12/31; Child: birth-18 years; Adolescent: 13-18 years; Young Adult: 19-24 years**	2842	14:54:
Search **(#21 AND #32)** Filters: **Publication date from 2000/01/01 to 2016/12/31; Child: birth-18 years; Adolescent: 13-18 years**	2842	14:54:
Search **(#21 AND #32)** Filters: **Publication date from 2000/01/01 to 2016/12/31; Child: birth-18 years**	2842	14:53:
Search **((((("Substance-Related Disorders"[Mesh]) OR substance abuse OR abuse OR "Prescription Drug Misuse"[Mesh]) OR misuse OR aberrant OR nonmedical OR non-medical OR "Opioid-Related Disorders"[Mesh]) OR "Drug Overdose"[Mesh]) OR overdos* OR "Death"[Mesh] OR death* OR morbid* OR fatal* OR mortal*** Filters: **Publication date from 2000/01/01 to 2016/12/31; Child: birth-18 years**	221984	14:52:
Search **"Analgesics, Opioid"[Mesh]) OR opioid* OR opioid analgesic* OR opiate*** Filters: **Publication date from 2000/01/01 to 2016/12/31; Child: birth-18 years**	6586	14:43:
Search Filters: **Publication date from 2000/01/01 to 2016/12/31; Child: birth-18 years**	1339879	14:43:
Search **("Analgesics, Opioid"[Mesh]) OR opioid* OR opioid analgesic* OR opiate*)** Filters: **Publication date from 2000/01/01 to 2016/12/31**	59843	14:42:
Search **(("Analgesics, Opioid"[Mesh]) OR opioid* OR opioid analgesic* OR opiate*) AND ("Benzodiazepines"[Mesh] OR benzodiazepine*)) AND (co-prescription OR coprescription OR concomitant OR concurrent OR polypharmacy)** Filters: **Publication date from 2000/01/01 to 2016/12/31**	201	14:40:

Appendix 2: NSDUH Prescription Pain Reliever Question Summary

(abstracted by DEPI)[m]

Screening:
Have you ever used any prescription pain reliever? [Y/N]
Which of the following prescription pain relievers have you used in the last 12 months? [Pill cards shown here]

If yes to either screening question:
Have you ever used any prescription pain reliever in any way a doctor did not direct you to use it? [Y/N]
Examples include:

- Using it without a prescription of your own
- Using it in greater amounts, more often, or longer than you were told to take it

How old were you when you first used [DRUG]* in a way not directed by doctor? What month?

*[DRUG] includes every major opioid analgesic category, including methadone and buprenorphine.

Past year use: How have you used [DRUG] in a way other than prescribed?

- Greater amount than directed
- Without a prescription
- Other

Most recent use: What [DRUG] did you use most recently? Why did you use [DRUG]?

- Relieve pain
- Relieve tension / relax
- Experimentation
- To feel good or get high
- Sleep aid
- Help with feelings/emotions
- Increase/decrease effect of another drug
- Because I'm "hooked"
- Other reason

Information on past month use:

- Did you use [DRUG] in a manner other than prescribed? [Y/N] On how many days (estimate)?
- Did you mix with alcohol within a couple of hours of using [DRUG]? [Y/N]

[m] Substance Abuse and Mental Health Services Administration, National Survey on Drug Use and Health 2016. Final Approved CAI Specifications for Programming (English Version), accessed from http://www.samhsa.gov/data/sites/default/files/NSDUHmrbCAIquex2016v2.pdf on 6/27/2016.

How did you obtain [DRUG] that you used non-medically:

- Prescription from 1 doctor
- Prescription from >1 doctor
- Stole from healthcare facility
- Got from a friend/relative for free
- Bought from friend/relative
- Took without asking from friend/relative
- Bought from dealer/stranger
- Some other way

If you got [DRUG] from a friend/relative for free, how did they obtain [DRUG]:

- Prescription from 1 doctor
- Prescription from >1 doctor
- Stole from healthcare facility
- Got from a friend/relative for free
- Bought from friend/relative
- Took without asking from friend/relative
- Bough from stranger/dealer
- Some other way

If "YES" to past year prescription pain reliever non-medical use:

- Was there a month or more where you spent lots of time getting or using prescription pain relievers? [Y/N]
- Was there a month or more where you spent lots of time getting over the effects of prescription pain relievers? [Y/N]
- Did you try to set limits on how often / how much you would use? [Y/N]
    - Were you usually able to keep limits, or did you often use more than you intended to? [Y/N]
- Did you need to use more prescription pain reliever than previously needed to get desired effect? [Y/N]
    - Did you notice that the same amounts of prescription pain relievers had less effect than previously? [Y/N]
- Did you want to or try to cut down or stop using prescription pain relievers? [Y/N]
    - Were you able to cut down or stop using prescription pain relievers every time you wanted to or tried to? [Y/N]
    - Did you cut down or stop using prescription pain relievers at least one time? [Y/N]
- Did you ever have 3 or more of the following symptoms after cutting back or stopping? [Y/N]
    - Feeling kind of blue or down
    - Vomiting/nausea
    - Cramps/muscle aches
    - Teary eyes, runny nose
    - Sweaty, enlarged pupils, or body hair standing up on skin

    - Diarrhea
    - Yawning
    - Fever
    - Difficulty sleeping
- Same question as above, but did the symptoms last longer than a day? [Y/N]
- Did you have any problems with your emotions, nerves, or mental health that were probably caused or made worse by use of prescription pain relievers? [Y/N]
    - Did you continue to use prescription pain relievers even though you thought this was causing you to have problems with your emotions, nerves, or mental health? [Y/N]
- During past 12 months, did you have any physical health problems that were probably cause or made worse by use of prescription pain relievers? [Y/N]
    - Did you continue to use prescription pain relievers even though you thought this was causing you to have physical problems? [Y/N]
- Did using prescription pain relievers cause you to give up or spend less time doing activities like work, school, taking care of children, hobbies/sports, spending time with friends/family? [Y/N]
- Sometimes people who use prescription pain relievers have serious problems at home/school, such as neglecting their children; missing work/school; doing poorly at work/school; losing a job or dropping out of school. Did using prescription pain relievers cause you to have serious problems like this at home, work, or school? [Y/N]
- Did you regularly use prescription pain relievers and then do something where using prescription pain relievers might have put you in physical danger? [Y/N]
- Did using prescription pain relievers cause you to do things that repeatedly got you in trouble with the law? [Y/N]
- Did you have problems with family or friends that were probably caused by your use of prescription pain relievers? [Y/N]
- Did you continue to use prescription pain relievers even though you thought this caused problems with family or friends? [Y/N]
- Have you needed additional treatment or counseling for prescription pain relievers? [Y/N]

Appendix 3: MTF Non-Heroin Narcotics Question Summary

Description of the monitored variables in the survey (abstracted by DEPI)[n]

Exposure and availability of [DRUG]:

- Exposure to people who use [DRUG]
    - Exposure at parties to [DRUG]
- Proportion of friends who use [DRUG]
- Perceived availability

Use:

- Lifetime/annual/monthly prevalence and frequency of use
- Quantity consumed
- Indirect measures of quantity used per occasion (i.e., degree & duration of high)
- Mode of administration
- Injection of any drug for nonmedical use
- Patterns of multiple drug use: concurrent and not concurrent
- Age at first use
- Attempts to quit
- Felt need to quit or cut back
- Expected future use
- Prescribed use of psychotherapeutic drugs
- Use of OTC psychoactive drugs

Attitudes of significant others:

- Parental awareness of use
- Perceived friends' disapproval of use
- Perceived status attached to use in the school
- Perceived social connotations of use by respondent's acquaintances
- Perceived pressure to use

Exposure to drug education:

- Types
- Rated helpfulness
- Effect on use

Frequency of use in different settings:

- While alone
- With a few friends
- At parties

[n] Johnston L, O'Malley P, Miech R, Bachman J, Schulenberg J. Monitoring the Future: National Survey Results on Drug Use, 1975-2015: Overview, Key Findings on Adolescent Drug Use. Ann Arbor: Institute for Social Research, The University of Michigan. Accessed from http://www.monitoringthefuture.org/pubs/monographs/mtf-overview2015.pdf on 6/27/2016.

- With spouse/date
- With adults
- At home
- At school
- In a car
- During the daytime

Source of substance:
- Where acquired

Drug-related problems:
- Checklist of 15 problems
- Having "bad trips"
- Auto crashes and violations under the influence
- Driving after drinking

Reasons for use, abstention, and termination of use

Attitudes and beliefs regarding the use of various drugs:
- Perceived harmfulness
- Personal disapproval
- Social connotations attached to use
- Preferred legal status
- Preferences re: marijuana decriminalization

Exposure to drug treatment:
- Inpatient
- Outpatient

Exposure to drug testing:
- Pre-employment
- Post-employment

Exposure to antidrug ads:
- Level of recalled exposure
- Credibility of ads
- Judged impact of ads

Appendix 4: Literature review summary table. Epidemiologic studies examining the adverse opioid-related outcomes of misuse, abuse, addiction, overdose, and death in the pediatric (<21 years) population, January 1, 2000 – March 4, 2016. Updated July 21, 2016

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
2015	Ali	The mental health consequences of nonmedical prescription drug use among adolescents	Journal of Mental Health Policy and Economics	Cross-sectional	NSDUH 2008-2012 (84,800 12-17 yo)	Major depressive episode	12-17 year olds reporting NMUPO were 33-35% more likely to experience major depressive episodes than those who did not report NMUPO	
2013	Biondo	Discrepancies in prevalence estimates in two national surveys for nonmedical use of a specific opioid product versus any prescription pain reliever	Drug and Alcohol Dependence	Cross-sectional	NSDUH 2005-2010 (n=approximately 3,020 12th graders per year); MTF 2005-2010 (n=approximately 15,127 12th graders per year)	Discrepancies in NMU estimates	Prevalence of past-year oxycodone nonmedical use was relatively steady over the time period in both surveys, but was 2.5-3 times higher in MTF compared to NSDUH. Possible explanations include NSDUH pill cards, setting (household vs. school), mode of administration (computer vs. pencil/paper)	
2014	Bonar	Prescription drug misuse and sexual risk behaviors among adolescents and emerging adults	Journal on Studies of Alcohol and Drugs	Cross-sectional	Electronically-administered survey of adolescents seen in Michigan academic ER (n=2,127 14-20 yo), 2010-2012	SRB (inconsistent condom use, multiple partners, intercourse following drug/EtOH use); AUDIT-C and ASSIST surveys; adapted questions from National Longitudinal Study of Adolescent Health for SRB	Opioid misuse was positively associated with inconsistent condom use, multiple partners, and substance use before sex in this demographic	
2006	Boyd	Adolescents' motivations to abuse prescription medications	Pediatrics	Cross-sectional	Electronically-administered survey of 7-12th graders in MI (n=1,086), 2005	Motivations for Rx nonmedical use / abuse (including opioids); positive DAST score	12% of respondents engaged in NMUPO in the past year; main motivations were pain relief, sleep aid, anxiety, and psychoactive effects. Increasing number of motivations to abuse opioids corresponded to an increased likelihood of a positive DAST score when compared to respondents whose primary NMUPO was self-treatment of pain	Defined NMUPO as using to get high or not as prescribed
2014	Boyd	Psychological and drug abuse symptoms associated with non-medical use of opioid analgesics among adolescents	Substance Abuse	Cross-sectional	SSLS electronically administered to 7-12th graders in MI (n=2,627), 2009-2010	Psychological (assessed by YSR version of CBCL) and DAST score; motivations for Rx nonmedical use / abuse	3.5% of respondents were nonmedical users of opioids, and 1.6% screened positive for opioid abuse. Abusers had greater odds of having psychological (affective, anxiety, somatic, attention-deficit	Defined nonmedical misuse as using someone else's Rx

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
						including NYS battery about pain symptoms	hyperactivity, and conduct) symptoms than non-abusers	
2010	Brands	Nonmedical use of opioid analgesics among Ontario students	Canadian Family Physician	Cross-sectional	Electronically-administered survey of 7-12th graders in Ontario (n=2,914), 2007	NMUPO	20.6% respondents reported nonmedical use in last year, female (16.6%) > male (12.0%). Most (72%) got the drugs from home; 6% reported obtaining drugs from friends. NMUPO users had higher past-year prevalences of alcohol use, daily smoking, and other illicit drugs compared to non-users	Defined NMUPO as taking pills without a prescription
2013	Calcaterra	National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999-2009	Drug and Alcohol Dependence	Ecologic	CDC WONDER MCOD data, 2005-2009	Unintentional pharmaceutical opioid-related death	Crude overdose death rates per 100,000 persons, 15-24 yo: female 1.32 (CI: 1.25-1.39), male 4.69 (CI: 4.56-4.82). Overall age-adjusted pharmaceutical opioid-related death rate for 15-64 yo over this timeframe was 5.47 (CI:5.42-5.51) per 100,000 person-years	
2015	Cerda	Nonmedical prescription opioid use in childhood and early adolescence predicts transitions to heroin use in young adulthood: a national study	Journal of Pediatrics	Cross-sectional	NSDUH 2004-2011 (n=223,534 12-21 yo)	Heroin initiation with previous NMUPO; age of first NMUPO as a risk function for later heroin initiation	Prior nonmedical use of Rx opioids strongly associated w/ heroin initiation (HR 13.12, CI: 10.73-16.04) in young adulthood. Younger age of NMU of opioids associated with higher risk of heroin initiation (10-12 had highest risk). Black respondents had lowest risk of heroin initiation of all ethnicities. Peak heroin initiation occurs at 17-18 years old. No one who reported zero NMUPO initiated heroin	
2012	Currie	Adolescent use of prescription drugs to get high in Canada	Canadian Journal of Psychiatry	Cross-sectional	Canadian Youth Smoking Survey 2008-2009 (n=44,344 7th-12th graders)	Past-year NMUPO	5.9% overall prevalence; females had higher odds of reporting NMUPO compared to males. Native / First Nations population had higher prevalence as well. Students with high "school connectedness" scores had lower prevalence of abuse	
2013	DeAndrea	Toward primary prevention of extra-	Preventive Medicine	Cross-sectional	NSDUH 2004-2008 (135,552 12-21 yo who had	Incident Oxycontin® abuse	Peak incidence of initiating extra-medical use of Oxycontin® is age	

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
		medical Oxycontin use among young people			not used Oxycontin® extra-medically in year prior to survey assessment)		16-18 yo. Pooled estimation vs. meta-analysis approaches yielded similar results	
2015	Edlund	Opioid abuse and depression in adolescents: Results from the NSDUH	Drug and Alcohol Dependence	Cross-sectional	NSDUH 2008-2012 (n=112,600 12-17 yo total sample; n=7,100 12-17 yo reporting past-year NMUPO)	MDE and NMUPO	6% reported past-year NMUPO and 8% reported past year MDE. When NMUPO and MDE were comorbid, respondents reported MDE typically preceded NMUPO. Past-year MDE associated with increased risk for reporting NMUPO	
2015	Fink	Patterns of major depression and nonmedical use of prescription opioids in the United States	Drug and Alcohol Dependence	Cross-sectional	NSDUH 2011-2012 (36,663 12-17 yo)	MDE and NMUPO	Comorbid MDE and NMUPO cluster in lower socioeconomic strata; female adolescents have higher odds (OR 3.7, CI:2.7-5.2) of comorbid NMUPO and MDE than male adolescents. Adolescents reporting EtOH use disorder, any drug use other than NMUPO also had increased odds of comorbid NMUPO and MDE	
2015	Ford	Racial/ethnic differences in factors that place adolescents at risk for prescription opioid misuse	Prevention Science	Cross-sectional	NSDUH 2012 (n=17,399 12-17 yo)	Prevalence of NMUPO by race	Black adolescents (6.08%) have highest prevalence of NMUPO, not statistically significant vs. whites (5.39%) or Hispanics (5.60%). Whites had greatest odds of NMUPO	
2012	Gilchrist	Vital signs: Unintentional injury deaths among persons aged 0-19 years – US, 2000-2009	MMWR	Ecologic	NVSS MCOD file; unintentional injury deaths from 2000-2009 (0-19 yo)	Unintentional injury death	From 2000-2009, poisoning rate among 15-19 year olds nearly doubled (1.7 to 3.33 per 100,000). Percentage of poisoning deaths in this age group w/ Rx drugs as a contributing cause increased from 30% in 2000 to 57% in 2009	
2015	Johnston	Monitoring the Future: Key Findings on Adolescent Drug Use, 2015 Findings	MTF	Cross-sectional	MTF 2015 (n=approximately 13,700 12^{th} graders)	Non-heroin narcotic use without being instructed to take by a doctor	Annual prevalence of 12^{th} grader use of non-heroin narcotics without being instructed to do so: 4.4% used Vicodin, 3.7% used Oxycontin. 2.1% report using any non-heroin narcotic in past 30 days. 39% report obtaining non-heroin narcotic would be "fairly easy" or	

Year	First Author	Title	Journal	Study Design	Data & Population	Outcome	Main Findings	Comments
							"easy"	
2008	McCabe	Screening for drug abuse among medical and nonmedical users of prescription drugs in a probability sample of college students	Archives of Pediatric and Adolescent Medicine	Cross-sectional	Web survey of college students at a "large, Midwestern 4-year university" (n=3,639), 2005	Medical and nonmedical use of prescription drugs; "probable drug abuse" measured using DAST-SF	Non-medical users of Rx drugs are at elevated risk of screening positive for drug abuse; medical users without a Hx of non-medical use are not at increased risk	
2005	McCabe	Sources of prescription drugs for illicit use	Addictive Behaviors	Cross-sectional	Web survey of college students (n=9,161), 2003	Identification of sources for Rx drugs	Broadly, categories are peer (57%) family (12%), and other (30%) for opioid sources. Peer sources were associated with higher rates of all other drug use than other sources	
2009	McCabe	Motives for nonmedical use of prescription opioids among high school seniors in the United States	Archives of Pediatric and Adolescent Medicine	Cross-sectional	MTF 2002-2006 (n=12,441 12th graders)	Identification of motivations for nonmedical Rx	45% of past-year nonmedical users reported pain relief as a primary motivation. Odds of heavy drinking and other drug use were lower among users seeking solely pain relief vs. those seeking highs	
2005	McCabe	Illicit use of opioid analgesics by high school seniors	Journal of Substance Abuse and Treatment	Cross-sectional	MTF 2002 (n=4,522 12th graders)	Identification of correlates for illicit opioid use (using Rx opioid without a prescription)	Illicit users were more likely to be male, white, and have a lower GPA; also have higher rates of tobacco use, EtOH use, MJ use, other illicit drug use, and problematic behaviors	
2007	McCabe	Medical and nonmedical use of prescription drugs among secondary school students	Journal of Adolescent Health	Cross-sectional	Web survey in MI (n=1,086 7-12th graders), 2005	Rx opioid use – medical or nonmedical – and association with positive DAST-SF screen, MJ use, or other illicit drug use	Adolescents reporting [medical or nonmedical] or nonmedical use were significantly more likely to report illicit abuse and screen positive on DAST-SF for probable drug abuse than nonusers	
2014	McCabe	Non-medical use of prescription opioids during the transition to adulthood: a multi-cohort national longitudinal study	Addiction	Cohort	MTF 1976-2005 panel studies (n=27,268 18-25 year olds)	Characteristics of persistent NMUPO users by positive NMUPO reports at any of a series ("wave") of 2-year follow-up surveys following graduation	Majority of wave 1 + users did not continue to use; majority of wave 1-2-3-4 + users (~3% of all NMUPO users) had associations with binge drinking, MJ, and other substance abuse behaviors	
2005	McCabe	Nonmedical use of prescription opioids	Addictive Behaviors	Cross-sectional	CAS 2001 (n=10,904 college students)	NMUPO (use without a doctor's Rx)	Students attending less competitive schools, HBCU had lower	

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		among U.S. college students: prevalence and correlates from a national survey					prevalence of NMUPO. Black, Asian, Hispanic respondents had lower prevalence of NMUPO; higher GPA had lower prevalence of NMUPO; living in off-campus or Greek housing had higher prevalence of NMUPO	
2013	McCabe	Motives for medical misuse of prescription opioids among adolescents	Journal of Pain	Cross-sectional	2011-2012 SSLS (n=2,964 Detroit 7^{th}-12^{th} graders)	Listed motivation for past-year misuse (taking more of one's own pills than prescribed or to get high, e.g.) and nonmedical use (using pills prescribed to someone else)	Misuse: pain relief (84%), to get high (20%) are most common motivations NMU: pain relief (87%), to get high (13%) are most common motivations	
2013	McCabe	Medical use, medical misuse, and nonmedical use of prescription opioids: results from a longitudinal study	Pain	Cohort	2009-2011 SSLS (n=2,050 7^{th}-11^{th} graders at 2 schools in MI)	Past year use; nonmedical use; DAST-10 score for probable drug abuse	Of those reporting past-year NMUPO in year 1, 25% continued in year 2. Odds of a positive DAST in year 2 were greater for adolescents who reported medical misuse or NMUPO for non-pain-relief motives in Year 1 compared to those who did not use Rx opioids	
2013	McCabe	Leftover prescription opioids and nonmedical use among high school seniors: a multi-cohort national study	Journal of Adolescent Health	Cross-sectional	MTF 2007-2010 (n=8,888 12^{th} graders)	Past year NMUPO and sources	36.9% of past year NMUPO users obtained Rx from their own previous prescriptions; 55% received for free from a friend or relative; those who obtained Rx from another source had higher odds of abuse-type behaviors. Most commonly reported motivation was pain relief (72%)	
2007	McCabe	Does early onset of non-medical use of prescription drugs predict subsequent prescription drug abuse and dependence? Results from a national study	Addiction	Cross-sectional	NESARC 2001-2002 (n=43,093 $\geq$18 yo)	Self-report age of onset of non-medical use of Rx pain reliever; current drug use d/o based on validated AUDADIS-IV instrument	A higher percentage of individuals who began using Rx drugs nonmedically at or before age 13 years had developed Rx drug abuse and dependence compared to those who began using at or after 21 years of age	

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2012	McCabe	Co-ingestion of prescription opioids and other drugs among high school seniors: results from a national study	Drug and Alcohol Dependence	Cross-sectional	MTF 2002-2006 (n=12,441 12th graders)	Report of NMUPO and co-ingestion of other drugs simultaneously	Overall prevalence of NMUPO co-ingestion with other drugs is 4.9%; MJ (58%), alcohol (52%) most commonly reported. Among those who report NMUPO, prevalence of co-ingestion is 70%. Nonmedical users who co-ingested were more likely to snort, use recreationally, and had higher subjective high experiences	
2014	McCabe	Trends in medical use, diversion, and nonmedical use of prescription medications among college students from 2003 to 2013: Connecting the dots	Addictive Behaviors	Cross-sectional	CSLS, conducted odd years inclusive 2003-2013 (n=21,771 undergraduate college students)	Prevalence of past year, lifetime use NMUPO	8.8-16.4% of respondents had used NMUPO in the lifetimes, depending on the year. Past year prevalence of medical use, diversion, and nonmedical use of prescription opioids decreased from 2003-2013. White, male, Greek member, lifetime hx of receiving an Rx have higher odds for nonmedical use	
2012	McCabe	Adolescent nonmedical users of prescription opioids: Brief screening and substance use disorders	Addictive Behaviors	Cross-sectional	SSLS 2009-2010 (n=2,744 7th-12th graders)	Positive CRAFFT screen with h/o NMUPO	35% of NMUPO users screen positive for CRAFFT. Odds of buying, obtaining from multiple sources, snorting, and abusing were higher among those with positive CRAFFT screen	
2014	McCabe	Social contexts of substance use among U.S. high school seniors: a multicohort national study	Journal of Adolescent Health	Cross-sectional	MTF 2002-2011 (n=24,809 12th graders)	Social context of drug use	Alcohol, MJ, and polydrug use most often occur at parties; stimulants, tranquilizers, and opioid use occur most often at home	
2007	McCabe	Trends and college-level characteristics associated with the non-medical use of prescription drugs among US college students from 1993 to 2001	Addiction	Cross-sectional	CAS 1993-2001 inclusive odd years (n=approximately 10,000-15,000 undergraduate college students annually)	Prevalence trends and college-level characteristics of NMUPO	Past-year and lifetime prevalence of NMUPO increased from 1993-2001	
2012	Meier	Extramedical use of prescription pain relievers by youth	Archives of Pediatric and Adolescent Medicine	Cross-sectional	NSDUH 2004-2008 (n=138,729 12-21 yo)	Estimated age-specific risk of initiating extramedical use of	16 years of age is peak year for initiating extramedical use (2-3% become newly incident users);	

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		aged 12 to 21 years in the United States				prescription pain relievers, year by year, and confirmation of peak age risk	smaller risk estimates above and below that age	
2015	Miech	Prescription opioids in adolescence and future opioid misuse	Pediatrics	Cohort	MTF 1990-2012 (n=6,220 who answered questions in at least one of the three follow-up panel surveys)	Past-year opioid misuse at subsequent follow-up	Among 12th graders with little experience with illegal drug use and who strongly disapprove of illegal drugs, a legitimate opioid Rx predicts opioid misuse after HS (RR 1.33, CI: 1.04-1.7)	
2015	Mitra	Drug use patterns predict risk of non-fatal overdose among street-involved youth in a Canadian setting	Drug and Alcohol Dependence	Cohort	Street-involved (homeless or semi-homeless) youth in BC, Canada (At Risk Youth Study) who self-report no history of OD (n=615 14-26 yo)	Self-report of non-fatal OD in past 6 months; aim to determine factors associated with non-fatal OD from 9/2005 – 5/2012. Time to OD event as survival analysis	98 participants (16%) reported non-fatal OD from 2005-2012. Binge drug use, injection Rx opioid use, non-injection meth use, injection heroin use were associated with shorter time to non-fatal overdose	Defined non-fatal OD as "negative reaction from using too much drugs"
2015	Murphy	Opioid misuse among adolescents: new evidence from a misclassification analysis	Applied Health Economics and Health Policy	Cross-sectional	2008 WA State Healthy Youth Survey (n=9,990 8th, 10th, and 12th graders)	Non-medical prescription opioid use; misusing own vs. someone else's prescription, likelihood of misreporting of prescription source	35% of respondents who said they had never misused prescription opioids "most likely had [done so]". 17% claimed to have misused a diverted prescription, but probably had misused their own	
2014	Murphy	Non-medical prescription opioid use and violent behavior among adolescents	Journal of Child and Adolescent Mental Health	Cross-sectional	2008 WA State Healthy Youth Survey (n=10,623 8th, 10th, 12th graders)	Opioid abuse and association with violent behavior or thoughts	Rx opioid abuse associated with violent behavior, attitude, and thoughts	
2012	Nakawaki	Predicting adolescents' persistence, non-persistence, and recent onset of nonmedical use of opioids and stimulants	Addictive Behaviors	Cross-sectional	NSDUH 2003-2009 (n=126,764 12-17 yo)	Persistent, non-persistent, and nonmedical use of Rx opioids	Persistent nonmedical users of MJ/inhalants had greater risk of nonmedical opioid and stimulant use. Non-persistent use of MJ/inhalants was strong predictor of non-persistent opioid and stimulant use	Non-persistent user is someone who used in the past 2 years w/o repeat use; persistent user is someone who used in past 2 years with use in past year
2015	Parker	Epidemiological evidence on extra-medical use of prescription pain	PeerJ	Cross-sectional with pooled meta-analysis	NSDUH 2002-2013 (n=330,983 12-21 yo)	Opioid dependence within 12 months of initiating extramedical use of prescription	Peak risk of transitioning from extramedical use of opioids to opioid dependence seen among 14-15 yo, which is earlier than peak	

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		relievers: transitions from newly incident use to dependence among 12-21 year olds in the United States using meta-analysis, 2002-13				pain relievers	risk for extramedical use initiation, which is typically 16-19 yo. Projected one adolescent transition to adolescent-onset opioid dependence within 12 months for every 11-16 newly incident extramedical users	
2014	Rudd	Increases in heroin overdose deaths – 28 states, 2010 to 2012	MMWR	Ecologic	28 state health department mortality files, 2008-2012	Heroin overdose death	Heroin OD death rate in 15-24 yo stratum increased 86% from 2010 to 2012 ; opioid pain reliever death rate in same stratum decreased 28% in same timeframe	
2008	Schepis	Characterizing adolescent prescription misusers: a population-based study	Journal of the American Academy of Child and Adolescent Psychiatry	Cross-sectional	NSDUH 2005 (n=18,678 12-17 yo)	Predictors of opioid Rx misuse	Predictors of Rx opioid misuse include poor academic performance, past year depression, past-year MJ, EtOH, Tob, cocaine/inhalant use (Table 2)	
2009	Schepis	Sources of prescriptions for misuse by adolescents: Differences in sex, ethnicity, and severity of misuse in a population-based study	Journal of the American Academy of Child and Adolescent Psychiatry	Cross-sectional	NSDUH 2005-2006 (n=36,992 12-17 yo)	Sources of misused Rx opioids	47% of all misusers got Rx opioid for free from friend/relative; 22% from a physician; 13% purchased	
2013	Spoth	Longitudinal effects of universal preventive intervention on prescription drug misuse: three randomized controlled trials with late adolescents and young adults	American Journal of Public Health	Randomized controlled trial	IA, PA 6-12th graders	Self-reported Rx opioid misuse and lifetime Rx drug misuse after randomization to either control group or family-, community-, and peer pressure resisting-related programming	Brief universal interventions – ISFP, SFP 10-14 + LST, SFP + 1 of 3 school-based curricula – were associated with significant reductions in likelihood of misusing opioid Rx in young adulthood	
2010	Subramania m	The added risk of opioid problem use among treatment-seeking youth with marijuana and/or	Addiction	Cross-sectional	Youth recruited from Baltimore-area drug treatment sites (n=475)	Opioid problem use in youth with MJ/EtOH problem use already	Individuals with opioid problem use in conjunction with MJ/EtOH problem use more likely to be older teens (15-17 yo), white, have higher SUD diagnoses, have	

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		alcohol problem use					greater psychiatric symptom severity, engage in higher rates of illegal behaviors	
2005	Sung	Nonmedical use of prescription opioids among teenagers in the United States: trends and correlates	Journal of Adolescent Health	Cross-sectional	2002 NSDUH (n=17,709 12-17 yo) as well as trended NSDUH data from 1965-2001	Past year prevalence of opioid misuse	Highest prevalence groups include females, blacks, lower SES, have favorable attitudes towards illicit drugs, have detached parents, or have friends who use illicit drugs	
2011	Tormehlen	Increased adolescent opioid use and complications reported to a poison control center following the 2000 JCAHO pain initiative	Clinical Toxicology	Ecologic	Poison control center in Indiana from 1994-2000, 2001-2007 (n=1,634 12-18 yo)	Number of opioid calls from the two timeframes involving 12-18 yo	In 2001-2007, there was an increase in the number of calls involving adolescents	
2012	Vaughn	Risk profiles among adolescent nonmedical opioid users in the United States	Addictive Behaviors	Cross-sectional	2008 NSDUH (n=17,842 12-17 yo)	Latent class analysis risk stratification	Four classes of risk exist in this age group: low delinquency/low substance use, high delinquency / low substance use, high substance use / low delinquency, high delinquency/high substance use	
2014	Veliz	Painfully obvious: a longitudinal examination of medical use and misuse of opioid medication among adolescent sports participants	Journal of Adolescent Health	Cross-sectional	SSLS 2009-2012 (n=1,540 14-19 yo)	Misuse of Rx opioids and playing organized sports	Male adolescents who participate in organized sports have higher odds of medical use (OR=1.86, CI:1.23-2.82) and misuse of opioids (OR=10.5, CI:2.42-45.5)	
2013	Veliz	Playing through pain: sports participation and nonmedical use of opioid medications among adolescents	American Journal of Public Health	Cross-sectional	MTF 2010-2011 (n=21,135 8^{th}, 10^{th}, and 12^{th} graders)	Nonmedical use of opioids and participation in an organized sport	Adolescents participating in high-injury sports (wrestling OR1.49, CI:1.01-2.19; football OR=1.50, CI:1.12-1.99) had greater odds of NMUPO than those who did not participate in these sports	
2011	Warner	Drug poisoning deaths in the United States, 1980-2008	NCHS data brief	Ecologic	NVSS	Poisoning deaths; opioid-related poisonings	From 1999-2008, opioid-related poisoning rate in 15-24 yo rose from 3.2 per 100,000 to 8.2 per 100,000	
2013	Whiteside	Nonmedical prescription opioid	Pediatrics	Cross-sectional	Adolescents who presented to Univ. Michigan ED	Prevalence of past-year nonmedical	~10% reported nonmedical prescription opioid use in past year.	

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		and sedative use among adolescents in the emergency department			(n=2,135)	prescription opioid use	Correlates included other substance use, drinking and driving, receiving IV opioids in ED	
2011	Wu	Treatment use and barriers among adolescents with prescription opioid use disorders	Addictive Behaviors	Cross-sectional	NSDUH 2005-2008 (n=1,788 12-17 yo who met at least one of the past-year criteria for Rx opioid abuse or dependence)	Prevalence of treatment use and perceived need by opioid use status; perceived barriers to Tx	About 17% of adolescents with opioid dependence used treatment in the past year for their condition. Under-used among adolescents who would benefit from it, especially black adolescents	
2008	Wu	Prescription pain reliever abuse and dependence among adolescence: a nationally representative study	Journal of the American Academy of Child and Adolescent Psychiatry	Cross-sectional	NSDUH 2005-2006 (n=2,675 12-17 yo who reported past-year nonprescribed prescription pain reliever use)	Opioid misuse, nonmedical use, and subthreshold dependence	Increased odds of abuse among females, those who buy pills, those who report fair/poor health, nonstudents	
2011	Wu	Racial/ethnic variations in substance-related disorders among adolescents in the United States	Archives of General Psychiatry	Cross-sectional	NSDUH 2005-2008 (n=72,561 12-17 yo)	Substance-related disorders by ethnicity/race	Rx opioid misuse prevalence highest among Native Americans (9.7%), lowest among Asian/Pacific Islanders (4.3%)	
2012	Young	Nonmedical use of prescription opioids among adolescents: subtypes based on motivation for use	Journal of Addictive Diseases	Cross-sectional	Web-based survey administered to MI middle and high school students from 2009-2010 (n=2,597)	Profiles of users by those who want to get high or those who are treating themselves	Sensation-seeking nonmedical users were characterized by rule-breaking and aggressive behaviors. Medical and nonmedical self-treating users were characterized by somatic complaints, anxiety/depressive symptoms, and history of sexual victimization	
2013	Zosel	Characterization of adolescent prescription drug abuse and misuse using the RADARS system	Journal of the American Academy of Child and Adolescent Psychiatry	Ecologic	RADARS (n=16,209 poison control center calls involving 13-18 yo and opioids or stimulants)	Opioid-related adolescent calls	10,966 opioid-related adolescent cases, and the most frequently reported drugs were hydrocodone, oxycodone, and tramadol	

ASSIST – Alcohol, Smoking, and Substance Involvement Screening Test
AUDADIS-IV – Alcohol Use Disorder and Associated Disabilities Interview Schedule – DSM-IV version
AUDIT-C – Alcohol Use Disorders Identification Test
CAS – Harvard School of Public Health College Alcohol Study
CBCL – Child Behavior Checklist

CDC – Centers for Disease Control and Prevention
CRAFFT – Adolescent drug survey screen
CSLS – College Student Life Survey
DAST / DAST-10 / DAST-SF – Drug and Alcohol Screening Test
d/o – Disorder
EtOH – Alcohol
h/o – History of
MCOD – Multiple Cause of Death
MDE – Major depressive episode
MI – Michigan
MTF – Monitoring the Future
NESARC – National Epidemiologic Study on Alcohol and Related Conditions
NHAMCS – National Hospital Ambulatory Medical Care Survey
NSDUH – National Survey on Drug Use and Health
NVSS – National Vital Statistics System
NYS – National Youth Survey
Rx – Prescription
SRB – Sexual risk behaviors
SSLS – Secondary Student Life Survey
WONDER – Wide-ranging Online Data for Epidemiologic Research
Yo – Years old
YSR – Youth Self Report

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/s/

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