



Codeine: Time to Say “No”

Joseph D. Tobias, MD, Thomas P. Green, MD, Charles J. Coté, MD, SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE, COMMITTEE ON DRUGS

Codeine has been prescribed to pediatric patients for many decades as both an analgesic and an antitussive agent. Codeine is a prodrug with little inherent pharmacologic activity and must be metabolized in the liver into morphine, which is responsible for codeine’s analgesic effects. However, there is substantial genetic variability in the activity of the responsible hepatic enzyme, *CYP2D6*, and, as a consequence, individual patient response to codeine varies from no effect to high sensitivity. Drug surveillance has documented the occurrence of unanticipated respiratory depression and death after receiving codeine in children, many of whom have been shown to be ultrarapid metabolizers. Patients with documented or suspected obstructive sleep apnea appear to be at particular risk because of opioid sensitivity, compounding the danger among rapid metabolizers in this group. Recently, various organizations and regulatory bodies, including the World Health Organization, the US Food and Drug Administration, and the European Medicines Agency, have promulgated stern warnings regarding the occurrence of adverse effects of codeine in children. These and other groups have or are considering a declaration of a contraindication for the use of codeine for children as either an analgesic or an antitussive. Additional clinical research must extend the understanding of the risks and benefits of both opioid and nonopioid alternatives for orally administered, effective agents for acute and chronic pain.

abstract

FREE

This document is copyrighted and is property of the American Academy of Pediatrics and its Board of Directors. All authors have filed conflict of interest statements with the American Academy of Pediatrics. Any conflicts have been resolved through a process approved by the Board of Directors. The American Academy of Pediatrics has neither solicited nor accepted any commercial involvement in the development of the content of this publication.

Clinical reports from the American Academy of Pediatrics benefit from expertise and resources of liaisons and internal (AAP) and external reviewers. However, clinical reports from the American Academy of Pediatrics may not reflect the views of the liaisons or the organizations or government agencies that they represent.

The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

All clinical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

DOI: 10.1542/peds.2016-2396

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2016 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they do not have a financial relationship relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: 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

INTRODUCTION

Effective pain management for pediatric patients remains problematic, with studies showing that significant improvements and alterations in practice may be needed to provide safe and adequate analgesia.¹⁻³ These issues are further complicated by the limited number of child-appropriate pain formulations and medications, parental perceptions about the need for such analgesics, and differences in metabolism and oral bioavailability between children and adults.^{1,4} Similarly, there are few evidence-based therapies for children with cough.⁵ The purpose of this clinical report is to present up-to-date information regarding risks related to pharmacogenetic variations in codeine metabolism and to

outline the therapeutic and safety implications in the treatment of pain or cough in children.

BACKGROUND

Codeine (3-methylmorphine) is a naturally occurring methylated morphine that has seen widespread clinical use for >50 years as an analgesic and an antitussive agent. Historically, codeine was considered an optimal oral analgesic for the outpatient treatment of acute pain of various etiologies in children, partly because of the perception that it was a safe opioid analgesic with a wide therapeutic index and a limited risk of respiratory depression.⁶ It was the primary agent used for outpatient analgesia after adenotonsillectomy in children and was recommended as a step 2 medication in the World Health Organization Pain Ladder for the treatment of moderate pain.⁷ However, codeine itself has no analgesic effect; it is a prodrug that must be metabolized to morphine to be effective. Furthermore, increased understanding of pharmacogenetics and ongoing safety investigations have shown a large variation in the conversion of codeine to morphine. This genetics-based interpatient variation produces considerable variability in the therapeutic response to recommended codeine dosing, ranging from a lack of effect because of low morphine levels to fatalities related to excessive morphine levels.⁸

Despite these concerns and the potential hazards, codeine continues to be widely available from many pharmacies and inpatient hospital formularies for use in outpatient pediatric settings and is commonly prescribed to pediatric patients.^{9,10} One study from 2011 reported that, among dispensed prescriptions for selected opioids, codeine was prescribed to >800 000 patients younger than 11 years, more than any other opioid in the study.¹¹

During the years 2007–2011, otolaryngologists were the most frequent prescribers of codeine/acetaminophen liquid formulations (19.6%), followed by dentists (13.3%), pediatricians (12.7%), and general practice/family physicians (10.1%).¹¹ Two other studies reported the use of opioids in pediatric emergency departments in the period 2001–2010. In 1 study, the frequency of codeine administration in emergency departments both for pain associated with injury and for cough remained unchanged during this period.⁹ The other longitudinal study covering the same time period showed that overall codeine use remained constant in adolescents but has decreased in younger age groups.¹²

In the last 5 years, various organizations and regulatory bodies have promulgated warnings regarding adverse responses associated with codeine, as follows:

1. March 2011: The World Health Organization deleted codeine from its list of essential medications for children because of concerns that its “efficacy and safety were questionable in an unpredictable portion of the paediatric population.”¹³
2. August 2012: The US Food and Drug Administration (FDA) issued a safety alert regarding the use of codeine in children after tonsillectomy, adenoidectomy, or adenotonsillectomy.¹⁴
3. February 2013: An update from the FDA added a “black box warning” to the drug label of codeine and codeine-containing preparations. The warning advises health care professionals “to prescribe an alternative analgesic [to codeine] for postoperative pain control in children undergoing tonsillectomy and/or adenoidectomy.” A contraindication was added to restrict codeine use in such

patients. The “Warnings/Precautions,” “Pediatric Use,” and “Patient Counseling Information” sections of the label were also updated.¹⁵

4. June 2013: The European Medicines Agency issued a report recommending the restriction of codeine for the treatment of pain to children older than 12 years as well as a contraindication to its use in children younger than 18 years undergoing tonsillectomy and/or adenoidectomy. In addition, it recommended against codeine use in breastfeeding women.¹⁶
5. June 2013: Health Canada announced that it had reviewed the safety of prescription pain and cough medications containing codeine and recommended against their use in children younger than 12 years.¹⁷
6. March 2015: The European Medicines Agency completed a review of the use of codeine for cough and cold and recommended against its use in children younger than 12 years as well as children and adolescents between 12 and 18 years who have problems with breathing.¹⁸

GENETIC VARIABILITY IN CODEINE METABOLISM

Codeine is a prodrug that has limited affinity for the μ -opioid receptor and no analgesic effects. After an oral dose, the majority of codeine undergoes hepatic glucuronidation or N-demethylation to inactive metabolites. The analgesic properties result from hepatic metabolism and conversion of the parent compound (codeine) to morphine and the active metabolite morphine-6-glucuronide. The conversion from codeine to morphine is regulated by the cytochrome P450 2D6 (CYP2D6) enzyme system.^{19,20}

The activity of *CYP2D6* varies significantly as a function of genetic polymorphisms. More than 70 different alleles have been identified, with individuals inheriting 1 allele from each parent. The level of enzyme activity from each allele has been broadly classified according to the following scheme: normal function = 1, reduced function = 0.5, and no function = 0. The enzyme activity for an individual is the sum of activity from each parent's allele. On the basis of these additive scores, individuals can be classified as extensive (score of 1–2), intermediate (0.5), or poor (0) metabolizers. It has also been increasingly recognized that some individuals may have significantly more activity related to gene duplication.

The prevalence of the different levels of activity varies among ethnic backgrounds, with poor metabolizers overrepresented in people of northern European Caucasian descent. Poor metabolizers initially received the greatest attention because of codeine's lack of efficacy in such patients.^{21–23} As our understanding of the influence of genetic variations on pharmacokinetics has improved, attention has become more focused on individuals who are ultrarapid metabolizers secondary to gene duplications. This latter group has ≥ 2 copies of the *CYP2D6* gene, which can result in an enzyme activity score ≥ 3 , indicating a very high level of enzyme activity. The result in these patients is the production of large amounts of morphine that can cause respiratory depression or apnea, even after normal therapeutic doses of oral codeine.^{19,23,24} The frequency of the ultrarapid metabolizer genotype has been estimated at $\sim 29\%$ of patients of African/Ethiopian heritage, $\sim 21\%$ of those from Saudi Arabia and other Middle Eastern countries, and $\sim 3.4\%$ to 6.5% of African-American and white persons.^{19,20,23,24}

Intermediate metabolism tends to be more common in Asians than in whites,²⁵ but poor metabolism is less common.²⁶

REPORTS OF ADVERSE EFFECTS

The evidence linking the use of codeine with life-threatening or fatal respiratory depression is based on a series of case reports that have appeared in the literature regularly since 2004.^{27–34} The publication of these reports initiated an evaluation by the FDA, which included a review of the literature as well as reports submitted to the FDA Adverse Event Reporting System from 1969 through May 2012.³⁵ The search revealed 13 cases of pediatric deaths ($n = 10$) or respiratory depression ($n = 3$) attributed to the therapeutic use of codeine, 7 of which had been published in the medical literature. The age range was slightly wider than the initial reports (21 months to 9 years of age). The majority occurred during the postoperative period after adenoidectomy or adenotonsillectomy with the recommended codeine dose and dosing interval. However, 1 clinical study proposed that repeated episodes of hypoxemia result in altered μ -opioid receptors and greater analgesic potency of opioids in this setting.³⁶

Three additional pediatric deaths related to codeine were reported in 2013.³⁷ These included a 10-year-old child who had undergone orthopedic surgery, a 4-year-old treated after tonsillectomy, and a third child who received codeine as a cough suppressant, albeit in a higher dose than was prescribed.

Most recently, a review by the FDA of the Adverse Event Reporting System data from 1965 to 2015 in children who had used codeine or any codeine-containing products revealed a total of 64 cases of severe respiratory depression and 24 codeine-related deaths, 21 of which

were in children younger than 12 years.³⁸

USE OF CODEINE AND ITS ALTERNATIVES FOR ANALGESIA

Even before these reports of adverse events, many physicians had concerns regarding the efficacy of codeine, mostly related to its lack of effect in a significant proportion of the population (poor metabolizers). Although *CYP2D6* genotyping that could identify patients at higher risk is available (although currently expensive), patients with normal metabolism are also at theoretical risk of high morphine levels. Therefore, further investigation is required to determine the value of such testing, which will depend on the population in whom it is applied. As such, physicians are faced with considering alternative analgesic agents to use when oral administration is needed postoperatively or in the outpatient setting.

In the United States, many physicians have switched to prescribing oxycodone for analgesia. Oxycodone is a semisynthetic opioid that is an active analgesic, not a prodrug like codeine. Metabolism is via *N*-demethylation by the *CYP3A4* enzyme system to inactive metabolites. A minor percentage of oxycodone is metabolized by the *CYP2D6* enzyme system to the active metabolite noroxymorphone, so ultrarapid metabolizers may be at some risk of opiate toxicity. Oxycodone is available in a liquid formulation both alone and in combination with acetaminophen. However, data are currently insufficient to unequivocally endorse the widespread use of oxycodone in infants and children. One study has shown considerable variability in absorption and oral bioavailability in children.³⁹ Another recent preliminary pharmacokinetic study in children younger than 6 years

showed significant differences in onset of absorption and peak levels of oxycodone and plasma concentrations of noroxycodone on the basis of *CYP2D6* genotypes.⁴⁰

Hydrocodone is also a potential alternative for analgesia, but *CYP2D6* is responsible for the conversion of hydrocodone to an active metabolite, hydromorphone. Ultrarapid metabolizers may have up to an eightfold greater plasma concentration of hydromorphone, whereas poor metabolizers receive minimal analgesia.⁴¹

Given the problems with codeine and potential concerns with the other available agents, the use of an oral morphine elixir has been suggested by some as an alternative.^{20,42}

However, although there is extensive experience with intravenous morphine in children, there is little clinical experience and very limited comparative clinical data on safety and efficacy available for the oral formulation.

Additional options for pain relief include less familiar and less commonly used medications, such as tramadol. Tramadol has a longer half-life (6–7 hours) than other oral agents as well as an active metabolite with a half-life of 10 to 11 hours. Unlike other weak opioids, it has a unique dual mechanism of action, including agonism at the μ -opioid receptor, and inhibits reuptake of neurotransmitters (norepinephrine and serotonin) within the central nervous system. Primary metabolism occurs through hepatic *N*-demethylation by the cytochrome *CYP3A4* enzyme system to an inactive metabolite. A smaller percentage is metabolized by *o*-demethylation (*CYP2D6* enzyme) to the active metabolite desmethyltramadol. Although preliminary studies in the pediatric population have shown effective analgesia,^{43–46} there are reasons to be concerned about potential problems with tramadol that are similar to those encountered

with codeine. Although tramadol is not dependent on metabolism for its analgesic effect, it is partially dependent on the *CYP2D6* enzyme system for metabolism, which could lead to drug accumulation in poor metabolizers.⁴⁷ In addition, the *o*-demethylated (*CYP2D6*-dependent) metabolite has a much higher affinity for the μ -opioid receptor, and a case report of administration of tramadol to a child with ultrarapid metabolism and subsequent respiratory depression was recently published.⁴⁸ Furthermore, many other drugs, including selective serotonin reuptake inhibitors, tricyclic antidepressants, and some antiepileptic drugs, inhibit the metabolism of tramadol, leading to undesirable tramadol accumulation. As such, further investigation must be conducted before the widespread use of tramadol in children for pain relief.

A similar agent, tapentadol, is a centrally acting analgesic with a dual mode of action as an agonist at the μ -opioid receptor and as a norepinephrine reuptake inhibitor within the central nervous system. In contradistinction to tramadol, it has only weak effects on the reuptake of serotonin and is a significantly more potent opioid agonist. It has no active metabolites. It was approved by the FDA in 2011 for use in adults; to date, there are no data regarding its use in the pediatric population. There is 1 report from a poison control center review of 124 unintended exposures, one of which resulted in coma and respiratory depression in a 9-month-old child.⁴⁹

Concerns regarding opioids in children with sleep-disordered breathing have led to a reevaluation of postoperative nonopioid analgesics, such as acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen, for children with mild to moderate pain.^{50–54} In addition, there are intravenous formulations of

acetaminophen and an NSAID (ketorolac).^{55,56} Although previously thought to potentially increase the incidence of postoperative bleeding, some evidence suggests that NSAIDs can be incorporated into the postoperative regimen without adversely affecting the postoperative course in most children without underlying bleeding diatheses.^{53,54} The effective use of these nonopioid agents may significantly reduce or, in some cases, eliminate the need for opioids. Further studies of other nonopioid analgesics, including dextromethorphan and dexmedetomidine, are also needed.

It is clear that one of the keys to improving analgesia and reducing opioid-related adverse effects is both provider and parental education regarding the effective use of nonopioid analgesics.^{1,57} The answer may not lie in using more medication or different medications but merely using more effectively other options that are currently available.

USE OF CODEINE AS AN ANTITUSSIVE AGENT IN CHILDREN

Codeine is also prescribed as an antitussive agent and is still available in over-the-counter cough and cold formulations without a prescription from outpatient pharmacies in 28 US states and the District of Columbia.³⁸ However, neither the value of suppressing cough nor the effectiveness of codeine in children with acute illnesses has been shown,^{58–60} and the risks of codeine administration described previously also apply to children receiving this agent as an antitussive agent. In April 2015, the European Medicines Agency announced that codeine must not be used to treat cough and cold in children younger than 12 years¹⁸ and further cautioned that codeine is not recommended in children and adolescents between 12 and 18 years of age with compromised respiratory function, including those with

asthma and other chronic breathing problems. On July 1, 2015, the FDA issued a drug safety communication stating that it is investigating the possible risks of using codeine-containing medicines to treat coughs and colds in children younger than 18 years because of the potential for serious adverse effects, including slowed or difficult breathing.⁶¹ An FDA advisory panel met in December 2015³⁸ and, by an overwhelming majority vote, recommended that the use of codeine in the treatment of cough in all children up to 18 years of age should be contraindicated. Final agency action on this recommendation is pending at this time. Alternative therapies for cough have recently been reviewed.⁶²

SUMMARY

Published reports and clinical evidence have shown the potential dangers of codeine as an analgesic or as an antitussive. Although these concerns have been emphasized by the FDA, the European Medicines Agency, Health Canada, and the American Academy of Pediatrics, regular codeine administration to children continues.^{9,10,63} The life-threatening events and deaths in these reports share a number of common features in that the majority of the children (1) were relatively young, (2) were placed on a postoperative pain regimen of scheduled acetaminophen and codeine, and (3) had undergone adenotonsillectomy for sleep-disordered breathing. However, physicians cannot assume that such problems will occur only after adenotonsillectomy. Given the increasing prevalence of obesity in the United States, it is likely that some patients presenting for nonotolaryngologic procedures may have undiagnosed sleep-disordered breathing and may also be at risk if they require extended postoperative analgesia.

Additional measures are needed to prevent future problems with the use of codeine in the pediatric population. Improved education of parents and more formal restrictions regarding its use in children, regardless of age, are necessary. The evolving information about the genetic variability in drug metabolism will yield important insights to guide physicians in the safe and effective treatment of their patients. Additional clinical research must extend the understanding of the risks and benefits of both opioid and nonopioid alternatives for orally administered, effective agents for acute pain.

LEAD AUTHORS

Joseph D. Tobias, MD, FAAP
Thomas P. Green, MD, FAAP
Charles J. Coté, MD, FAAP

SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE EXECUTIVE COMMITTEE, 2014–2015

Joseph D. Tobias, MD, FAAP
Rita Agarwal, MD, FAAP
Corrie T.M. Anderson, MD, FAAP
Courtney Alan Hardy, MD, FAAP
Anita Honkanen, MD, FAAP
Mohamed A. Rehman, MD, FAAP

LIAISONS

Carolyn Bannister, MD
Randall Flick, MD
Constance S. Houck, MD
Carolyn Bannister

STAFF

Jennifer Riefe

COMMITTEE ON DRUGS, 2014–2015

Kathleen Neville, MD, MS, FAAP, Chairperson
Thomas P. Green, MD, FAAP
Constance S. Houck, MD, FAAP
Bridgette Jones, MD, MSc, FAAP
Ian M. Paul, MD, MSc, FAAP
Janice E. Sullivan, MD, FAAP
John N. Van Den Anker, MD, PhD, FAAP

LIAISONS

John J. Alexander, MD, FAAP – *Food and Drug Administration*
R. Phillip Heine, MD – *American College of Obstetricians and Gynecologists*
Janet D. Craigan, MD, MPH, FAAP – *Centers for Disease Control and Prevention*

Michael J. Rieder, MD, FAAP – *Canadian Paediatric Society*

Adelaide S. Robb, MD – *American Academy of Child and Adolescent Psychiatry*

Hari Cheryl Sachs, MD, FAAP – *Food and Drug Administration*

Anne Zajicek, MD, PharmD, FAAP – *National Institutes of Health*

STAFF

Raymond J. Koterak, MHA

ABBREVIATIONS

FDA: Food and Drug Administration

NSAID: nonsteroidal antiinflammatory drug

REFERENCES

- Fortier MA, MacLaren JE, Martin SR, Perret-Karimi D, Kain ZN. Pediatric pain after ambulatory surgery: where's the medication? *Pediatrics*. 2009;124(4):e588–e595
- Shum S, Lim J, Page T, et al. An audit of pain management following pediatric day surgery at British Columbia Children's Hospital. *Pain Res Manag*. 2012;17(5):328–334
- Stewart DW, Ragg PG, Sheppard S, Chalkiadis GA. The severity and duration of postoperative pain and analgesia requirements in children after tonsillectomy, orchidopexy, or inguinal hernia repair. *Paediatr Anaesth*. 2012;22(2):136–143
- Rony RY, Fortier MA, Chorney JM, Perret D, Kain ZN. Parental postoperative pain management: attitudes, assessment, and management. *Pediatrics*. 2010;125(6):e1372–e1378
- Paul IM. Therapeutic options for acute cough due to upper respiratory infections in children. *Lung*. 2012;190(1):41–44
- Ewah BN, Robb PJ, Raw M. Postoperative pain, nausea and vomiting following paediatric day-case tonsillectomy. *Anaesthesia*. 2006;61(2):116–122
- Tremlett M, Anderson BJ, Wolf A. Pro-con debate: is codeine a drug that still

- has a useful role in pediatric practice? *Paediatr Anaesth*. 2010;20(2):183–194
8. Madadi P, Koren G. Pharmacogenetic insights into codeine analgesia: implications to pediatric codeine use. *Pharmacogenomics*. 2008;9(9):1267–1284
 9. Kaiser SV, Asteria-Penalzoza R, Vittinghoff E, Rosenbluth G, Cabana MD, Bardach NS. National patterns of codeine prescriptions for children in the emergency department. *Pediatrics*. 2014;133(5):e1139–e1147
 10. Cartabuke RS, Tobias JD, Taghon T, Rice J. Current practices regarding codeine administration among pediatricians and pediatric subspecialists. *Clin Pediatr (Phila)*. 2014;53(1):26–30
 11. Racoosin JA. Death and respiratory arrest related to ultra-rapid metabolism of codeine to morphine. Available at: www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM343601.pdf. Accessed January 6, 2016
 12. Mazer-Amirshahi M, Mullins PM, Rasooly IR, van den Anker J, Pines JM. Trends in prescription opioid use in pediatric emergency department patients. *Pediatr Emerg Care*. 2014;30(4):230–235
 13. World Health Organization. Unedited report of the 18th Expert Committee on the Selection and Use of Essential Medicines. Geneva, Switzerland: World Health Organization; 2011. Available at: www.who.int/selection_medicines/Complete_UNEDITED_TRS_18th.pdf. Accessed February 1, 2016
 14. US Food and Drug Administration. Drug safety communication. Codeine use in certain children after tonsillectomy and or adenoidectomy may lead to rare but life threatening adverse events or death. Rockville, MD: US Food and Drug Administration; 2012. Available at: www.fda.gov/Drugs/Drugsafety/ucm313631.htm. Accessed February 23, 2016
 15. US Food and Drug Administration. Drug safety communication. Safety review update of codeine use in children: a new boxed warning and contraindication on use after tonsillectomy and or adenoidectomy. Rockville, MD: US Food and Drug Administration; 2013. Available at: www.fda.gov/Drugs/Drugsafety/ucm339112.htm. Accessed February 23, 2016
 16. European Medicines Agency. Codeine-containing medicines. 2013. Available at: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeinecontaining_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f. Accessed February 23, 2016
 17. Health Canada. Health Canada's review recommends codeine only be used in patients aged 12 and over. Ottawa, Canada: Health Canada; 2013. Available at: www.healthycanadians.gc.ca/recall-alert-rappel-avis/hcsc/2013/33915aeng.php. Accessed February 23, 2016
 18. European Medicines Agency. Codeine not to be used in children below 12 years for cough and cold. London, United Kingdom: European Medicines Agency; 2015. Available at: www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine_containing_medicinal_products_for_the_treatment_of_cough_and_cold_in_paediatric_patients/human_referral_prac_000039.jsp&mid=WC0b01ac05805c516f. Accessed February 23, 2016
 19. Cascorbi I. Pharmacogenetics of cytochrome p4502D6: genetic background and clinical implication. *Eur J Clin Invest*. 2003;33(suppl 2):17–22
 20. Tremlett MR. Wither codeine? *Paediatr Anaesth*. 2013;23(8):677–683
 21. May DG. Genetic differences in drug disposition. *J Clin Pharmacol*. 1994;34(9):881–897
 22. Poulsen L, Riishede L, Brøsen K, Clemensen S, Sindrup SH. Codeine in post-operative pain: study of the influence of sparteine phenotype and serum concentrations of morphine and morphine-6-glucuronide. *Eur J Clin Pharmacol*. 1998;54(6):451–454
 23. VanderVaart S, Berger H, Sistonen J, et al. CYP2D6 polymorphisms and codeine analgesia in postpartum pain management: a pilot study. *Ther Drug Monit*. 2011;33(4):425–432
 24. de Leon J, Dinsmore L, Wedlund P. Adverse drug reactions to oxycodone and hydrocodone in CYP2D6 ultrarapid metabolizers. *J Clin Psychopharmacol*. 2003;23(4):420–421
 25. Dean L. Codeine therapy and the CYP2D6 genotype. *Med Genet Summ* [online]. September 20, 2012. Available at: www.ncbi.nlm.nih.gov/books/NBK100662/. Accessed January 6, 2016
 26. Sohn DR, Shin SG, Park CW, Kusaka M, Chiba K, Ishizaki T. Metoprolol oxidation polymorphism in a Korean population: comparison with native Japanese and Chinese populations. *Br J Clin Pharmacol*. 1991;32(4):504–507
 27. Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet*. 2006;368(9536):704
 28. Gasche Y, Daali Y, Fathi M, et al. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. *N Engl J Med*. 2004;351(27):2827–2831
 29. Madadi P, Koren G, Cairns J, et al. Safety of codeine during breast feeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. *Can Fam Physician*. 2007;53(1):33–35
 30. Ferner RE. Did the drug cause death? Codeine and breastfeeding. *Lancet*. 2008;372(9639):606–608
 31. Voronov P, Przybylo HJ, Jagannathan N. Apnea in a child after oral codeine: a genetic variant—an ultra-rapid metabolizer. *Paediatr Anaesth*. 2007;17(7):684–687
 32. Ciszkowski C, Madadi P, Phillips MS, Lauwers AE, Koren G. Codeine, ultrarapid-metabolism genotype, and postoperative death. *N Engl J Med*. 2009;361(8):827–828
 33. Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American children. *Pediatrics*. 2012;129(5):e1343–e1347
 34. Lynn AM, Nespeca MK, Opheim KE, Slattery JT. Respiratory effects of intravenous morphine infusions in neonates, infants, and children after cardiac surgery. *Anesth Analg*. 1993;77(4):695–701

35. Racoosin JA, Roberson DW, Pacanowski MA, Nielsen DR. New evidence about an old drug—risk with codeine after adenotonsillectomy. *N Engl J Med*. 2013;368(23):2155–2157
36. Brown KA, Laferrière A, Lakheeram I, Moss IR. Recurrent hypoxemia in children is associated with increased analgesic sensitivity to opiates. *Anesthesiology*. 2006;105(4):665–669
37. Friedrichsdorf SJ, Nugent AP, Strobl AQ. Codeine-associated pediatric deaths despite using recommended dosing guidelines: three case reports. *J Opioid Manag*. 2013;9(2):151–155
38. Seymour S. Briefing document, Joint Pulmonary-Allergy Drugs and Drug Safety and Risk Management Advisory Committee Meeting; December 10, 2015. Available at: www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm433815.htm. Accessed February 23, 2016
39. Kokki H, Rasanen I, Reinikainen M, Suhonen P, Vanamo K, Ojanperä I. Pharmacokinetics of oxycodone after intravenous, buccal, intramuscular and gastric administration in children. *Clin Pharmacokinet*. 2004;43(9):613–622
40. Sriswasdi P, Dube C, Perieira L, et al. Population Pharmacokinetics and Pharmacogenomics of Oral Oxycodone in Pediatric Surgical Patients. In: Proceedings from the Annual American Society of Anesthesiologist Meeting; October 24-28, 2015; San Diego, CA. Abstract 3200.
41. Stauble ME, Moore AW, Langman LJ, et al. Hydrocodone in postoperative personalized pain management: pro-drug or drug?. *Clin Chim Acta*. 2014;429:26–29
42. Anderson BJ. Is it farewell to codeine? *Arch Dis Child*. 2013;98(12):986–988
43. Payne KA, Roelofse JA, Shipton EA. Pharmacokinetics of oral tramadol drops for postoperative pain relief in children aged 4 to 7 years—a pilot study. *Anesth Prog*. 2002;49(4):109–112
44. Rose JB, Finkel JC, Arquedas-Mohs A, Himmelstein BP, Schreiner M, Medve RA. Oral tramadol for the treatment of pain of 7-30 days' duration in children. *Anesth Analg*. 2003;96(1):78–81
45. Finkel JC, Rose JB, Schmitz ML, et al. An evaluation of the efficacy and tolerability of oral tramadol hydrochloride tablets for the treatment of postsurgical pain in children. *Anesth Analg*. 2002;94(6):1469–1473
46. Tobias JD. Tramadol for postoperative analgesia in adolescents following orthopedic surgery in a third world country. *Am J Pain Manage*. 1996;6:51–53
47. Xu J, Zhang XC, Lv XQ, et al. Effect of the cytochrome P450 2D6*10 genotype on the pharmacokinetics of tramadol in post-operative patients. *Pharmazie*. 2014;69(2):138–141
48. Orliaguet G, Hamza J, Couloigner V, et al. A case of respiratory depression in a child with ultrarapid CYP2D6 metabolism after tramadol. *Pediatrics*. 2015;135(3):e753–e755
49. Borys D, Stanton M, Gummin D, Drott T. Tapentadol toxicity in children. *Pediatrics*. 2015;135(2):e392–e396
50. Mattos JL, Robison JG, Greenberg J, Yellon RF. Acetaminophen plus ibuprofen versus opioids for treatment of post-tonsillectomy pain in children. *Int J Pediatr Otorhinolaryngol*. 2014;78(10):1671–1676
51. Merry AF, Edwards KE, Ahmad Z, Barber C, Mahadevan M, Frampton C. Randomized comparison between the combination of acetaminophen and ibuprofen and each constituent alone for analgesia following tonsillectomy in children. *Can J Anaesth*. 2013;60(12):1180–1189
52. Kelly LE, Sommer DD, Ramakrishna J, et al. Morphine or ibuprofen for post-tonsillectomy analgesia: a randomized trial. *Pediatrics*. 2015;135(2):307–313
53. Bedwell JR, Pierce M, Levy M, Shah RK. Ibuprofen with acetaminophen for postoperative pain control following tonsillectomy does not increase emergency department utilization. *Otolaryngol Head Neck Surg*. 2014;151(6):963–966
54. Yaman H, Belada A, Yilmaz S. The effect of ibuprofen on postoperative hemorrhage following tonsillectomy in children. *Eur Arch Otorhinolaryngol*. 2011;268(4):615–617
55. Sucato DJ, Lovejoy JF, Agrawal S, Elerson E, Nelson T, McClung A. Postoperative ketorolac does not predispose to pseudoarthrosis following posterior spinal fusion and instrumentation for adolescent idiopathic scoliosis. *Spine*. 2008;33(10):1119–1124
56. Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. *Anesthesiology*. 2005;102(4):822–831
57. Jenkins BN, Fortier MA. Developmental and cultural perspectives on children's postoperative pain management at home. *Pain Manag*. 2014;4(6):407–412
58. American Academy of Pediatrics Committee on Drugs. Use of codeine- and dextromethorphan-containing cough remedies in children. *Pediatrics*. 1997;99(6):918–920
59. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. *Cochrane Database Syst Rev*. 2008;4:CD001831
60. Goldman RD. Codeine for acute cough in children. *Can Fam Physician*. 2010;56(12):1293–1294
61. Drug Safety Communication. FDA evaluating the potential risks of using codeine cough-and-cold medicines in children. Rockville, MD: US Food and Drug Administration; July 1, 2015. Available at: www.fda.gov/Drugs/DrugSafety/ucm453125.htm. Accessed February 23, 2016
62. Lowry JA, Leeder JS. Over-the-counter medications: update on cough and cold preparations. *Pediatr Rev*. 2015;36(7):286–297, quiz 298
63. Woolf AD, Greco C. Why can't we retire codeine? *Pediatrics*. 2014;133(5). Available at: www.pediatrics.org/cgi/content/full/133/5/e1354

Codeine: Time To Say "No"

Joseph D. Tobias, Thomas P. Green, Charles J. Coté, SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE and COMMITTEE ON DRUGS *Pediatrics*; originally published online September 19, 2016;
DOI: 10.1542/peds.2016-2396

Updated Information & Services	including high resolution figures, can be found at: /content/early/2016/09/15/peds.2016-2396.full.html
References	This article cites 51 articles, 15 of which can be accessed free at: /content/early/2016/09/15/peds.2016-2396.full.html#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Anesthesiology/Pain Medicine /cgi/collection/anesthesiology:pain_medicine_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: /site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2016 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Codeine: Time To Say "No"

Joseph D. Tobias, Thomas P. Green, Charles J. Coté, SECTION ON
ANESTHESIOLOGY AND PAIN MEDICINE and COMMITTEE ON DRUGS

Pediatrics; originally published online September 19, 2016;

DOI: 10.1542/peds.2016-2396

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

</content/early/2016/09/15/peds.2016-2396.full.html>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2016 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

