

Why Can't We Retire Codeine?

Some remedies have long outlived their usefulness and have thankfully been relegated to historical archives, supplanted by safer, more effective drugs. We no longer prescribe mercury loop diuretics or antisyphilitic arsenicals. Yet, the use of codeine-containing products persists for cough relief and analgesia in children. As Kaiser et al¹ report in their study "National Patterns of Codeine Prescriptions for Children in the Emergency Department" in this month's issue, prescriptions for codeine-containing products barely edged down in frequency between 2001 and 2010, despite convincing studies documenting their lack of benefit and serious adverse effects. Using data from the National Hospital and Ambulatory Medical Care Survey database, they found codeine prescribed in the pediatric emergency department at the incredible rate of 558 805 to 876 729 prescriptions per year with only a small statistical decline over that period. Additionally, the US Food and Drug Administration reported that >1.7 million children aged 17 years and younger had a prescription for a codeine product filled at a pharmacy in 2011.² These high numbers continue despite guidance from professional societies discouraging the use of codeine in children. Why do pediatric practitioners continue to write prescriptions for codeine? Kaiser et al¹ observed wide practice variations, with fewer prescriptions written in the Northeast compared with other locales and fewer written by non-physicians. There are good reasons why we should encourage all pediatric clinicians to give up their codeine-prescribing habit.

CODEINE'S ADVERSE SIDE EFFECTS

Codeine is a drug with an inordinately high number of adverse effects. Children often suffer allergic reactions and urticarial rashes, or constipation and/or hyperemesis. Codeine is a "prodrug"; that is, it requires hepatic metabolism to its pharmacologically active metabolite, morphine. And up to 29% of some ethnic/racial groups are of the "ultra-rapid metabolizer" *CYP2D6* genotype, converting the prodrug into morphine at a much faster rate, leading to unanticipated, sometimes life-threatening, opiate overdose, especially in young children. Breastfed infants are at risk of overdose when their lactating mothers, having been prescribed codeine-containing products for postpartum analgesia, are ultrarapid metabolizers.³

LACK OF EFFICACY

There is no evidence that codeine shortens the duration or reduces the severity of pediatric coughs.⁴ As the American Academy of Pediatrics stated in 1997 (reaffirmed in 2006): "no well-controlled scientific studies were found that support the efficacy and safety of narcotics (including codeine) or dextromethorphan as antitussives in children."⁵ Yet, Kaiser et al¹ could not detect changes in the frequency of codeine prescriptions for pediatric coughs and colds, ranging from 69 057 to 145 857 annually.

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Codeine is an ineffective analgesic in many pediatric patients.⁶ Yet, we are still reporting childhood deaths from codeine use as a postoperative analgesic.^{7,8} There are safer regimens. For postoperative analgesia in infants, unless specifically contraindicated, an approach that avoids respiratory risks is to prescribe round-the-clock dosing of acetaminophen and ibuprofen and to regard opioid analgesia as a rescue medication. Oxycodone is an active opiate, not a prodrug like codeine. It is metabolized via *CYP3A4* to inactive metabolites, although a secondary pathway involving *CYP2D6* generates potent oxycodone, which has been associated with increased risks among ultrarapid metabolizers.⁹ Morphine itself is a second pediatric analgesic alternative to codeine. It is easier to titrate to an effective dose and undergoes glucuronidation during metabolism, bypassing the *CYP* enzyme system. There is a prevailing impression that genetic variation produces less dramatic effects on either over- or

underdosing for both oxycodone and morphine relative to codeine.

CODEINE POISONINGS AND DIVERSION

Codeine is diverted for recreational use by substance abusers. There are also high rates of inadvertent poisoning. In 2011 alone, US poison control centers reported >900 poisonings by codeine among children <12 years old, with an additional 1400 poisonings associated with analgesics or cough and cold preparations containing codeine.¹⁰

CHANGING PRESCRIBING PRACTICES

There is a movement toward greater scrutiny of the value of specific therapeutic interventions in pediatric medicine. At Boston Children's Hospital, we have eliminated codeine-containing products from our formulary; our electronic medical record prescribing software does not list codeine-containing products. It may be time for hospital formularies

throughout the country to eliminate codeine-containing products, as Kaiser et al¹ suggest. Removing the products from routine Medicaid and private health insurer reimbursement schedules may be effective in reducing the drug's everyday use in children. Professional continuing education and resident and student curricular content initiatives are also needed to inform present and future pediatric health care providers. Such measures will engender inevitable pushback from practitioners who want to maintain the status quo. As economist John Kenneth Galbraith observed: "Faced with the choice of changing one's mind or proving there is no need to do so, almost everybody gets busy with the proof."¹¹ There may be reasons why clinicians are still attached to the use of codeine in everyday practice; and they will howl with dismay when it is gone. But we must find novel ways to convince them that there is a need to change and that the time to retire this drug is today.

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