

# Codeine Pharmacogenetics as a Proof of Concept for Pediatric Precision Medicine

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Codeine is a prodrug whose analgesic efficacy derives from a 5% to 10% metabolic conversion to the active drug morphine by the polymorphic cytochrome P450 CYP2D6 enzyme system. Among individuals, codeine metabolism varies in proportion to the number and function of gene alleles. Dosing recommendations achieve therapeutic drug exposures in the great majority of the general population, who are “extensive metabolizers” possessing the wild type phenotype of 1 to 2 fully functional alleles. But codeine fails to provide adequate analgesia in many patients with reduced CYP2D6 function; of greater concern, “ultra-rapid metabolizers” (UMs), who have >3 functional genes due to gene copying, are at risk for serious adverse events including respiratory arrest and death. UMs make up 1% to 2% of the general population but as many as 28% in certain Arab, Ethiopian, and North African populations.<sup>1</sup>

In the past decade, multiple reports have recounted deaths in children receiving standard dosages of codeine for analgesia. Most of the children who had genomic analysis were found to demonstrate a UM phenotype, although 1 child was determined to be an extensive metabolizer.<sup>2</sup> The American Academy of Pediatrics has recommended that codeine should be contraindicated for use in all children and replaced by safer and more or equally effective medications. Appropriate alternatives for relief of short-term pain include

nonsteroidal antiinflammatory drugs, acetaminophen, and short courses of immediate-release preparations of oxycodone or hydrocodone at the lowest effective dosage. In 2013, the US Food and Drug Administration (FDA) added a label boxed warning highlighting the increased risk of death in UM patients treated with codeine after tonsillectomy or adenoidectomy. Through 2014, the FDA had identified 24 codeine-related deaths in children <18 years of age by using multiple surveillance tools. Some hospitals have responded by eliminating codeine from their formularies. Still, codeine use remains high: It is the most commonly prescribed opioid in children <18 years of age.<sup>3</sup> Codeine, compounded with a second nonnarcotic active ingredient, is available over the counter in 28 states.

In this month’s issue, Gammal et al<sup>4</sup> describe how they used pharmacogenetic data to ensure safe codeine prescription at St Jude Children’s Research Hospital in their report “Pharmacogenetics for Safe Codeine Use in Sickle Cell Disease.” St Jude offers eligible patients entry into a clinical research trial, Pharmacogenetics for Kids, which genotypes 230 pharmacogenes and integrates selected test results into the electronic health record to guide individualized pharmacy prescription by using clinical decision support tools. CYP2D6 genotype information, including copy number information, was available for 621, or 75%, of all active patients with sickle cell disease.

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In this large group, 7% were UM or possible UM phenotypes, 1.5% were poor metabolizers, and 4% had an indeterminate phenotype. Embedded tools in the medication order process enabled the practice of precision medicine by notifying providers of the CYP2D6 genotype status and suggesting alternative drugs. Only 1 “possible UM” among these 78 patients received codeine when a provider overrode the recommendation because of that patient’s previous history of codeine tolerance.

In December 2015, a joint FDA advisory committee recommended amendment of the codeine label to contraindicate codeine treatment of pain and cough in all children <18 years of age and to remove codeine from the Over-the-Counter monograph. The FDA is not obliged to adopt these recommendations, but substantial concurrence would probably induce many children’s hospitals to eliminate codeine from their formularies.

The significance of this report is less related specifically to improving the safety of codeine prescription than it is more generally to the successful demonstration of a proof of concept implementation of precision pharmacogenetic principles in children. Many drug exposures (as quantitated by the integrated area under the drug concentration versus time curve, or area under the curve) are affected substantially by individual variation in multiple polymorphic enzyme systems that determine the time course of concentrations of the drug and its active metabolites. For instance, a recent report has shown that area under the curve exposures for atomoxetine, a selective

norepinephrine reuptake inhibitor used to treat attention-deficit/hyperactivity disorder, varied 30-fold across a study cohort of children 6 to 17 years of age as a function of the CYP2D6 genotype.<sup>5</sup> Therefore, safe and effective use of this medication will require dosing adjustment based in part on pharmacogenetic data.<sup>6</sup>

Hospital research networks are beginning to test broader incorporation of pharmacogenomic data into pediatric electronic health records and clinical decision support.<sup>7,8</sup> Of the ~1000 drugs approved by the FDA, nearly 100 are candidates for pharmacogenetic testing in light of population variability in 12 genes.<sup>8</sup> The FDA package label includes pharmacogenetic data for 135 drugs (<http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>). At St Jude, 48% of pediatric patients over a period of 1 year were treated with  $\geq 1$  pharmacogenetic high-risk drug.<sup>8</sup>

Advances in pharmacogenomics and information science have brought us thus far to base camp of the mountain we still need to summit. Further ascent on behalf of our patients will occur as we fully embrace the application of current knowledge and better understand the developmental trajectories of key enzyme systems and protein expression that influence drug–target and drug–nontarget interactions, which in turn affect efficacy and adverse risk.

#### ABBREVIATIONS

FDA: US Food and Drug Administration

UM: ultrarapid metabolizer

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