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The case for pharmacogenetics-guided prescribing of codeine in children

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CONFLICTS OF INTEREST/DISCLOSURE

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INTRODUCTION:

In April 2017, the U.S. Food and Drug Administration (FDA) issued a contraindication to the drug label of codeine, alerting prescribers that codeine should not be used to treat pain or cough in children younger than 12 years old. These regulatory actions may have negative consequences for certain pediatric patient populations who, if *CYP2D6* genotype is known, could otherwise potentially safely receive and benefit from codeine as an analgesic (e.g., patients with sickle cell disease [SCD]).

It is well-established that CYP2D6 phenotype predicts codeine toxicity and therapeutic failure (1). Codeine is a prodrug that requires bioactivation to morphine via CYP2D6 for analgesic effect. The body of evidence in support of this association clearly demonstrates that, at standard doses of codeine, CYP2D6 ultra-rapid metabolizers (UMs) are at risk for toxicity and CYP2D6 poor metabolizers (PMs) are at risk for therapeutic failure (1). No opioid is without adverse effects in at least some patients, whether children or adults, but based on genotype, codeine is predicted to be safe and effective in the nearly 90% of the North American population who are CYP2D6 normal metabolizers (NMs) or intermediate metabolizers (IMs) (1).

The FDA decision to contraindicate codeine in children less than 12 years old broadened the previous contraindication issued in 2013 that stated codeine should not be used to treat pain in children post-tonsillectomy or adenoidectomy (post-AT) due to the risk of severe respiratory depression and death (2). However, the current FDA contraindication cuts a wide swath against the use of codeine in all children in the United States younger than 12 years old, regardless of CYP2D6 phenotype, and the indication for cough was removed for patients less than 18 years old in January 2018. We believe that if available, *CYP2D6* genotype results can be reasonably used to identify children at the highest risk for codeine-related adverse events and to allow codeine use in children at lower risk for adverse events.

According to the Code of Federal Regulations, 21 CFR 201.57c(5), a drug should be contraindicated only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit (3). Only known hazards, and not theoretical possibilities, can be the basis for a contraindication. Available evidence suggests that pediatric patients who are CYP2D6 NMs and IMs as determined by an appropriate *CYP2D6* genotyping method including copy number or gene duplication detection are not at high risk for adverse events from codeine use, provided that they are not post-AT (1, 4). For some pediatric patient populations who require acute or chronic analgesia (e.g., patients with SCD or osteogenesis imperfecta), it may be important to retain acetaminophen with codeine – the only Schedule III opioid – as a therapeutic option. For these patients, the benefit of codeine use may outweigh the risks. We believe that the FDA could modify the current

contraindication as follows: “Codeine should not be used to treat pain in children younger than 12 years with the following exception: outside the setting of post-adenotonsillectomy, codeine may be prescribed for pain management in children younger than 12 years old who are known CYP2D6 NMs or CYP2D6 IMs based on pharmacogenetic testing that includes *CYP2D6* copy number or gene duplication detection.” This modification acknowledges the utility of precision medicine to preserve the potential use of codeine in those patients for whom the therapeutic benefit may outweigh the risks, while avoiding the drug in patients with an unknown or high-risk CYP2D6 phenotype.

It is important to note that other factors, such as drug-drug interactions, can affect CYP2D6 phenotype. For example, a patient who is genotypically a CYP2D6 NM who is taking a strong CYP2D6 inhibitor (e.g., fluoxetine, paroxetine) will be phenotypically a CYP2D6 PM. For this reason, the ultimate decision to prescribe codeine must take into consideration all clinical factors (e.g., co-morbid conditions, drug-drug interactions) that could tip the harm to benefit balance.

Removing codeine as an option for the treatment of pain in pediatric patients under 12 has necessitated the use of alternative analgesics, which in many cases may be other opioid analgesics that also carry risks of adverse effects. For example, using tramadol instead of genotype-directed codeine could result in toxicity (in CYP2D6 UMs) or therapeutic failure (in CYP2D6 PMs), as tramadol, like codeine, requires activation via CYP2D6 for its opioid analgesic effect.

While *CYP2D6* testing is not yet standard of care, it is available and currently performed for pediatric patients (4). *CYP2D6* testing is available from numerous Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratories. In 2017, 119 clinical laboratories participated in the College of American Pathologists (CAP) proficiency testing for *CYP2D6*. With ever-increasing improvements in technology and decreasing genotyping costs (5), pharmacogenetic testing is expected to become more widespread over time. Although *CYP2D6* genotyping is not without limitations, pre-emptive *CYP2D6* testing has already been shown to inform the safe and effective use of codeine to treat pain in children under the age of 12. Gammal *et al.* demonstrated that using *CYP2D6* to guide codeine prescribing for pediatric pain outside the setting of post-AT (e.g., in SCD) is feasible and enables the safe and effective use of codeine in patients who are most likely to benefit and least likely to experience toxicity (i.e., CYP2D6 NMs and IMs) (4). Of the 830 patients with SCD included in this cohort, 621 (75%) had a *CYP2D6* genotype result; 7.1% were UMs, and 1.4% were PMs. Codeine was avoided in 100% of patients at risk for toxicity (i.e., CYP2D6 UMs) and in 100% of patients at high risk for therapeutic failure (i.e., CYP2D6 PMs). A *CYP2D6* genotype test should ideally interrogate all known alleles in the patient population of interest. If an allele of unknown function is reported, the CYP2D6 phenotype cannot be reliably ascertained and thus, codeine use should be avoided in these patients.

The Health and Medicine Division of the National Academy of Sciences, Engineering, and Medicine published a consensus study report on “Pain Management and the Opioid Epidemic” (6). In addressing strategies to reduce the national opioid epidemic, it suggests “the FDA should explicitly consider specific subpopulations (…) that may present distinct

benefit-risk profiles" while making opioid regulatory decisions related to public health considerations. We believe that children who are CYP2D6 NMs and IMs represent such a subpopulation, and we have petitioned the FDA to amend the current contraindication against codeine use in children to include an exception for patients who are CYP2D6 NMs and IMs.

Available data from the previous 20 years suggests that between 1 and 3 million children received a codeine prescription each year (7). A search of the FDA Adverse Event Reporting System (FAERS) from inception (1969) to May 2015 yielded 64 cases of codeine-related fatal and non-fatal severe respiratory depression in children less than 18 years old. A subsequent search of the medical literature revealed two additional cases not reported in FAERS. Events reported through FAERS do not necessarily reflect a causal relationship with the product in question, and some reports may not contain enough information to fully evaluate an event (e.g., CYP2D6 phenotype). Using a conservative estimate of 1 million pediatric codeine prescriptions each year for just the past 20 years and assuming that 100% of the abovementioned cases of respiratory depression were caused by codeine, this indicates a negligible event rate (66 events/20 million prescriptions = 0.0000033) and is certainly far below adverse event rates, including severe adverse events, for many commonly used medications (note that a caveat to this estimate is that this system under-reports events). The risk of adverse events in patients without high-risk *CYP2D6* genotypes applies to all opioids, not just codeine. Moreover, objections based on concerns for "number needed to test" do not account for the situation in which *CYP2D6* genotype is already known (e.g., through a pre-emptive genotyping model, the use of which is increasing with array-based genotype tests and decreasing test costs (5)). The National Institutes of Health-funded Clinical Pharmacogenetics Implementation Consortium (CPIC®) offers an evidence-based, international consensus guideline on the use of *CYP2D6* test results to inform codeine prescribing (1).

Codeine may be an important analgesic for pediatric patients, including those with SCD. Approximately 1 in 375 African Americans and 1 in 1100 Hispanic individuals suffer from SCD in the U.S., including 36,000 children. These patients, who frequently live in poverty, suffer from recurrent, debilitating episodes of pain called vaso-occlusive crises (8). For these individuals, opioids are often the backbone of pain management, and using opioids at home means they can avoid emergency room and urgent-care visits. Until recent restrictions, acetaminophen with codeine was a commonly used analgesic for these patients. As a Schedule III medication, acetaminophen with codeine can be dispensed without a written prescription in most states, in contrast to prescriptions for Schedule II analgesics with comparable efficacy (9) which require a written or electronic prescription, and which cannot be refilled. Given the well-documented racial and economic disparities in access to care (8), requiring caregivers of children in pain to obtain new prescriptions for Schedule II drugs would be an unfortunate consequence of these new restrictions on codeine use, rather than having their physician call in a codeine prescription to their local pharmacy as part of a specified home pain management plan.

In the setting of post-AT, we support the codeine contraindication regardless of *CYP2D6* genotype due to patients' increased risk of respiratory depression. Pediatric patients who are

post-AT often suffer from obstructive sleep apnea, which is characterized by an increase in upper airway resistance and/or prolonged airway obstruction that leads to a disruption in ventilation and breathing patterns during sleep, which may not be fully corrected post-AT. Post-AT, inflammation in the airways may also impede air flow. Furthermore, children with obstructive sleep apnea are thought to have increased opioid sensitivity due to up-regulation of central opioid receptors consequent to recurrent hypoxemia and therefore have reduced opioid requirements for analgesia (10). However, outside the post-AT setting, and in the absence of other high-risk factors such as sleep apnea, we propose that codeine can be used to treat pain in children who are known to be CYP2D6 NMs or IMs.

There has been much consideration given to reducing the harms that can result from the use and misuse of opioid medications. In the midst of this public health crisis, there must also be sufficient consideration given to ensuring that those who may benefit from opioid medications can receive them. There is ample precedence for using genetic testing to minimize drug toxicity by directing the use of medications to genetic subsets, and there is no reason that children should be excluded from the benefit of using precision medicine to improve the use of medications. Taking into account an individual patient's inherited ability to metabolize codeine, if known, can – and should – be an element of an evidence-based approach to pain management.

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