Clinical Perspective on the Clinical Pharmacogenetics Implementation Consortium Updated 2014 Guidelines for CYP2D6 and Codeine

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As pharmacogenomics makes further advances into clinical practice, the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines provide considerable assistance in clinical decision making. The new 2014 CPIC guidelines on CYP2D6 and codeine (1) have an update on considerations for clinicians and healthcare providers. The previous CPIC guidelines provided recommendations primarily on codeine and tramadol. The new guidelines maintain the dosing recommendations for codeine—specifically, to avoid codeine in both CYP2D6 poor and ultrarapid metabolizers; however, the guidelines take another step forward by noting that, not only may tramadol be problematic, but hydrocodone and oxycodone are also not considered good analgesic alternatives when metabolic concerns exist with CYP2D6. Additionally, this update recommends alternatives with the following statement: “To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone, along with nonopioid analgesics, may be considered as alternatives for use in CYP2D6 poor metabolizers and in ultrarapid metabolizers...” Although appropriate from a CYP2D6 metabolic standpoint, these recommendations may present some challenges to healthcare providers when applied to some clinical settings.

Pain is one of the leading reasons a patient presents to healthcare providers, which includes physicians, dentists, physician assistants, and nurse practitioners in both inpatient hospital and outpatient clinic community settings. Many healthcare providers follow a WHO ladder “type” approach for the treatment of pain (2). In this paradigm, depending on the severity of the pain, a nonopioid drug is considered as a first step in pain management (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs). The second step employs an opioid commonly used for moderate pain (e.g., tramadol, codeine, hydrocodone, and possibly oxycodone), often in combination with acetaminophen or nonsteroidal anti-inflammatory drugs. The third step includes the use of an opioid usually reserved for severe pain presentation (e.g., morphine, oxymorphone, fentanyl, methadone, and hydromorphone). Of concern, the new CPIC considerations advise increased restrictions for the second step in pain management for CYP2D6 poor and ultrarapid metabolizers.

Several problems are presented to healthcare providers when avoiding all of the common analgesic agents in the second step of pain management. First, analgesics including morphine, oxymorphone, fentanyl, methadone, and hydromorphone are usually reserved for opioid-tolerant patients currently receiving opioid therapy. These agents are readily used in nontolerant patients not currently receiving opioid therapy, within an inpatient hospital setting under the direct supervision of a healthcare provider for severe, acute pain (e.g., surgery, postoperative pain). In contrast, within the outpatient clinic setting, these analgesic agents would not be usually used except in cases of more severe chronic pain (e.g., oncological pain). Second, many outpatient clinic healthcare providers are unfamiliar with the use of these drugs, and their inappropriate use greatly increases the risk of medication toxicity. Evidence demonstrating toxicity is abundant in the literature, including inadvertent drug overdoses when opioids for severe pain, such as morphine, oxymorphone, fentanyl, hydromorphone, and methadone, are used inappropriately. Because of its complex pharmacokinetic profile, methadone alone is responsible for one third of the drug deaths from opioids (3). A third consideration is the availability of proper analgesic dosage forms. These drugs usually require alternative formulations such as intravenous administration, extended release/duration, or transdermal dosage forms. These drug formulations are inappropriate for the treatment of acute, moderate pain. One should note that the CPIC guidelines state that a healthcare provider’s clinical judgment should be used and that the recommended alternatives should be used in the appropriate manner based on type, severity, and chronicity of the pain that requires treatment. However, when consideration is given to the many outpatient clinic uses for moderate pain where an opioid might be required (e.g., musculoskeletal pain, toothache), it is unlikely that the provided alternatives would be an appropriate opioid choice for routine use.
The 2014 CPIC guidelines provide an excellent review of the available evidence regarding tramadol, codeine, hydrocodone, and oxycodone. Codeine provides its analgesic clinical effects following metabolism to morphine. Codeine toxicity is well documented in several case reports in CYP2D6 ultrarapid metabolism phenotypes. Because codeine metabolism demonstrates a large amount of variability, the 2014 guidelines continue to recommend avoiding codeine and use an alternative agent in CYP2D6 poor and ultrarapid metabolism phenotypes. Tramadol is also extensively metabolized by CYP2D6 to its more potent active metabolite, O-desmethyltramadol. Although toxicity has not been as clearly documented in CYP2D6 ultrarapid metabolizers as in the case of codeine, studies have indicated that poor metabolizers are more likely to have inadequate analgesia compared with extensive metabolizers. In many cases, because of the large variability between CYP2D6 metabolic phenotypes, tramadol avoidance should be considered.

The avoidance of hydrocodone or oxycodone recommendation is less clear based on the evidence presented in the guidelines. Hydrocodone with acetaminophen is currently the most prescribed drug for the treatment of pain. Because it has multiple manufacturers (Actavis, Mallinckrodt, and Qualitest Products), hydrocodone with acetaminophen was the number 1, 3, and 5 drug in total prescriptions in 2012 (4). Hydrocodone is metabolized to its more potent active metabolite, hydromorphone, by CYP2D6. Both hydrocodone and hydromorphone have analgesic activity and, although some metabolic variability would be anticipated with different CYP2D6 phenotypes, the guidelines state: “there is insufficient evidence to conclude whether poor metabolizers can be expected to have decreased analgesia or whether ultrarapid metabolizers have an increased risk of toxicity with normal doses of hydrocodone.” The lack of evidence likely is due to the limited number of studies and clinical evidence obtained to date. However, with millions of prescriptions of hydrocodone and acetaminophen dispensed per year, there also appears to be a current lack of reported systematic documentation of pharmacogenomics problems in the literature related to the use of hydrocodone.

Oxycodone is another analgesic agent frequently prescribed for moderate to severe pain. A small amount of oxycodone is metabolized by CYP2D6 to the more potent compound oxymorphone. Here again, both compounds have analgesic activity. In experimental pain studies in healthy volunteers, different analgesic responses were observed between different phenotypes. However, in clinical studies in postoperative or oncological pain, there was no significant difference among CYP2D6 phenotypes with adverse effects and analgesia. The guidelines concluded with the following statement: “Due to these conflicting data, it is difficult to conclude whether CYP2D6 metabolizer phenotype affects oxycodone analgesia or risk of toxicity.”

Two key points must be kept in mind when considering opioid substitution within the framework of the CPIC guidelines. First, the setting in which the patient is located (e.g., outpatient, inpatient) must be clear. Second, the type of pain that requires treatment (e.g., acute, chronic) must also be clear. In keeping with the WHO pain treatment recommendations, if the pain is mild to moderate, then a nonopioid drug can be used, and, if appropriate, can also be reconsidered instead of an opioid. In hospital inpatient settings, it is common to receive a question from a provider about using fentanyl during a surgical procedure in a patient with CYP2D6 metabolism issues. Here, it is clear the fentanyl use would not be an issue with respect to CYP2D6. However, rather than complete avoidance of hydrocodone or oxycodone where it would be otherwise appropriate, the possible metabolic variability might be considered along with the patient. Often drug doses can be titrated or adjusted (e.g., amount, frequency of administration) to overcome metabolic variability. It is important to remember that there are many reasons for interpatient variability (e.g., age, organ function, pathology) with drugs requiring dose adjustments, in addition to pharmacogenomics considerations. By viewing drug metabolism on a continuum, a better therapeutic decision can be made for the patient who might have a specific genotype that codes for an extensive to ultrarapid phenotype when the different CPIC treatment recommendations are given for either extensive or ultrarapid phenotypes. Working as a team with medicine, pharmacy, and laboratory medicine is likely going to yield the best patient outcomes for management of difficult pharmacogenomics issues.

Laboratory medicine is likely to be at the forefront of inquiries by practitioners when pharmacogenomics test results are reported. It is important to recognize, since pharmacogenomics is a new science to many healthcare providers, that CPIC guideline recommendations for analgesic alternatives may be readily accepted without consideration of the complex interplay between clinical care and the proper application of pharmacogenomics. This unfortunately might result in the inadequate treatment of pain due to the healthcare providers’ fear of prescribing the recommended pain medication or toxicity as a result of the healthcare providers’ overconfidence in prescribing an unfamiliar analgesic drug.

When recommending against the use of codeine in a patient with CYP2D6 poor or ultrarapid metabolism status in a situation of moderate pain, it may be appropriate to avoid tramadol as recommended by the guidelines. However, caution should be used in interpreting the new CPIC guidelines to completely avoid the use of hydrocodone with acetaminophen, and instead substitute one of the recommended analgesic alternatives. Because not all opioids are interchangeable from a practice stand-
point, the use of an unfamiliar drug in the inappropriate situation is likely to carry a greater risk.

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**References**


