

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of *Cytochrome P450 2D6* (*CYP2D6*) Genotype

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Codeine is bioactivated to morphine, a strong opioid agonist, by the hepatic cytochrome P450 2D6 (*CYP2D6*); hence, the efficacy and safety of codeine as an analgesic are governed by *CYP2D6* polymorphisms. Codeine has little therapeutic effect in patients who are *CYP2D6* poor metabolizers, whereas the risk of morphine toxicity is higher in ultrarapid metabolizers. The purpose of this guideline (periodically updated at <http://www.pharmgkb.org>) is to provide information relating to the interpretation of *CYP2D6* genotype test results to guide the dosing of codeine.

FOCUSED LITERATURE REVIEW

A systematic literature review was conducted that focused on *CYP2D6* and its relevance in codeine use (see **Supplementary Data** online). This guideline was developed based on interpretation of the literature by the authors and by experts in the field.

GENE: *CYP2D6*

Background

More than 80 *CYP2D6* alleles have been defined by the Cytochrome P450 Nomenclature Committee at <http://www.cypalleles.ki.se>. Clinical phenotype data are available for many common alleles (see **Supplementary Tables S1–S5** online); however, many alleles are not typically tested for in clinical trials. Their clinical phenotype is predicted on the basis of the expected functional impact of their defining genetic variation or is extrapolated from results of *in vitro* functional studies using different substrates.

Interpretation of genetic test results

Most clinical laboratories report *CYP2D6* genotype using the star (*) allele nomenclature and may provide interpretation of the patient's predicted metabolizer phenotype. Single-nucleotide polymorphisms (SNPs) and other sequence variations, including insertions and deletions, are determined by genetic laboratory tests. The reference SNP number (rs number) for a given SNP defines the specific genomic nucleotide alteration. Each star (*) allele (or haplotype) is defined by the presence of a specific combination of SNPs and/or other sequence alterations within the *CYP2D6* gene locus. The key alleles are shown in **Supplementary Table S1** online and the key allele-defining SNPs and their respective impacts on *CYP2D6* enzyme function are provided in **Supplementary Table S2** online. Genetic results are reported as a diplotype, which includes one maternal and one paternal allele (e.g., *CYP2D6**1/*4; **Supplementary Table S3** online). In some cases, patients have more than two copies of the *CYP2D6* gene. Those alleles are denoted by an "xN" following the allele designation (e.g., *CYP2D6**2xN; *duplication*) (see **Supplementary Data** online for details). Additional details about allele nomenclature and definitions can be found at <http://www.cypalleles.ki.se/cyp2d6.htm>, and information regarding the effects of allelic variation on *CYP2D6* substrates can be found at <http://www.pharmgkb.org/search/annotatedGene/cyp2d6/haplotype.jsp>. *CYP2D6* allele frequencies differ substantially between racial and ethnic groups. **Supplementary Table S1** online summarizes the most important allele frequencies for the major races and Hispanics.

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The combination of alleles is used to determine a patient's diplotype. *CYP2D6* alleles are characterized as wild-type (normal function), reduced-function, or nonfunctional based on the expected activity level of the enzyme for which they encode. Each functional group is assigned an activity value ranging from 0 to 1.0 (e.g., 0 for nonfunctional, 0.5 for reduced function, and 1.0 for fully functional).¹ **Supplementary Table S4** online describes the activity score values assigned to selected alleles. If multiple copies of the *CYP2D6* gene are detected, the activity score is multiplied by the number of copies of each allele present. The total *CYP2D6* activity score is the sum of the values assigned to each allele, which typically ranges from 0 to 3.0 but may exceed 3.0 in rare cases.^{1,2}

The *CYP2D6* activity score relates to the phenotype classification system as follows (**Table 1**): patients with an activity score of 0 are poor metabolizers, those with a score of 0.5 are considered intermediate metabolizers, and those with a score of 1.0, 1.5 or 2.0 represent a range of extensive metabolizers. Patients with a score >2.0 are classified as ultrarapid metabolizers. The extensive metabolizer phenotype represents normal (wild-type) enzyme activity.^{1–3} The incidence of poor and ultrarapid metabolizers varies greatly (0–10% and 0–29%, respectively) among various populations. Selected *CYP2D6* activity scores are provided in **Supplementary Table S3** online, and predicted phenotypes of common diplotypes are summarized in **Supplementary Table S5** online.

It is noted that subjects with genotypes giving rise to an activity score of 1.0, caused by a diplotype containing one functional and one nonfunctional allele or containing two reduced-function alleles, are classified by some investigators as “intermediate metabolizers.” Regardless of the term used to describe such

individuals (extensive metabolizers or intermediate metabolizers), they have lower *CYP2D6* activity than subjects with two fully functional alleles (activity score of 2.0) and higher activity as compared with subjects with one reduced and one nonfunctional allele (with an activity score of 0.5). Given that there is no gold standard for phenotype classification, genotypes that result in *CYP2D6* activity scores of 1.0, 1.5, and 2.0 are grouped together as extensive metabolizers in this guideline, which is based on data specific for codeine metabolism (**Supplementary Table S6** online).

It should be noted that reference laboratories providing clinical *CYP2D6* genotyping may use varying methods to assign phenotypes. Therefore it is advisable to note a patient's *CYP2D6* diplotype and to calculate an activity score before making therapeutic decisions about codeine therapy.

AVAILABLE GENETIC TEST OPTIONS

Several academic and commercial clinical laboratories offer genetic testing for *CYP2D6*. Specific information (on several of these laboratories, on the assays, and links to the product labels) can be found in the supplementary information and at http://www.pharmgkb.org/resources/forScientificUsers/pharmacogenomic_tests.jsp.

Incidental findings

Currently, there are no diseases or conditions known to be linked to variations in the *CYP2D6* gene independent of drug metabolism and response. Although there are some isolated reports of *CYP2D6* genetic effects on phenotypes other than in relation to drug response,^{4,5} these findings have not been consistently reproduced in other studies.

Other considerations

Modification of the predicted phenotype by drug interactions. The *CYP2D6* metabolizer phenotype may undergo alteration in a patient who is taking drugs that inhibit *CYP2D6* activity. A list of *CYP2D6* inhibitors can be found at <http://medicine.iupui.edu/clinpharm/ddis/table.aspx>. For this purpose, drugs are classified as strong, moderate, or weak inhibitors, based on the US Food and Drug Administration (FDA) guidance on drug interaction studies (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm081177.htm#classInhibit>). Borges *et al.* demonstrated that incorporating the impact of drug interactions by *CYP2D6* inhibitors improves the ability of the activity score to predict the extent of tamoxifen metabolism by *CYP2D6*.² For patients on strong inhibitors, the *CYP2D6* activity score is adjusted to 0 and the predicted phenotype is that of a poor metabolizer. For patients who are on weak or moderate *CYP2D6* inhibitors, the activity score is multiplied by 0.5 and then converted to the predicted phenotype.²

CYP2D6 does not appear to be induced by concurrent medications; however, there are limited data showing that *CYP2D6* enzyme activity increases during pregnancy. Wadelius *et al.* demonstrated that *CYP2D6* activity increases during pregnancy by showing that the value of the dextromethorphan/dextrophan metabolic ratio was reduced by 53%; Heikkinen *et al.*

Table 1 Assignment of likely codeine metabolism phenotypes based on *CYP2D6* diplotypes

Likely phenotype ^a	Activity score	Genotypes	Examples of diplotypes
Ultrarapid metabolizer (~1–2% of patients)	>2.0	An individual carrying more than two copies of functional alleles	*1/*1xN, *1/*2xN
Extensive metabolizer (~77–92% of patients)	1.0–2.0 ^b	An individual carrying two alleles encoding full or reduced function or one full function allele together with either one nonfunctional or one reduced-function allele	*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10
Intermediate metabolizer (~2–11% of patients)	0.5 ^b	An individual carrying one reduced and one nonfunctional allele	*4/*10, *5/*41
Poor metabolizer (~5–10% of patients)	0	An individual carrying no functional alleles	*4/*4, *4/*5, *5/*5, *4/*6

^aThe frequency estimates are based on data from Caucasians and may differ substantially for other ethnicities. See **Supplementary Data** online for estimates of phenotype frequencies among different ethnic/geographic groups. ^bNote that some investigators define patients with an activity score of 0.5 and 1.0 as intermediate metabolizers and define patients with an activity score of 1.5 and 2.0 as extensive metabolizers. Classifying patients with an activity score of 1.0 as extensive metabolizers in this guideline is based on data specific for formation of morphine from codeine in these patients.¹³

demonstrated that the norfluoxetine/fluoxetine metabolic ratio increased 2.4-fold.^{6,7} The apparent oral clearance of metoprolol was shown to increase four- to fivefold during pregnancy.⁸ Although mean CYP2D6 activity appears to increase during pregnancy, the large interindividual variability in the increase, and the limited number of subjects studied, make it difficult to make any recommendations regarding adjustment of the activity scores of functional alleles during pregnancy. The CYP2D6 activity scores of nonfunctional alleles are not affected by pregnancy.

CODEINE

Background

Codeine is an opioid analgesic indicated for the relief of mild to moderately severe pain. The analgesic properties of codeine stem from its conversion to morphine and morphine-6-glucuronide because codeine's affinity for μ -opioid receptors is 200-fold weaker than that of morphine.^{9,10} Both codeine and morphine also have antitussive effects.

O-Demethylation of codeine into morphine by CYP2D6 represents a minor pathway in extensive metabolizers, accounting for only 5–10% of codeine clearance in such individuals; however, this pathway is essential for its opioid activity (**Figure 1**). The percentage of codeine converted into morphine can be affected by drug interactions and can be much higher in ultrarapid metabolizers.¹¹ Morphine is further glucuronidated to morphine-3-glucuronide and morphine-6-glucuronide. Morphine-6-glucuronide is known to have analgesic activity in humans, whereas morphine-3-glucuronide is generally not considered to possess analgesic properties. Approximately 80% of an administered dose of codeine is converted to inactive metabolites by glucuronidation to codeine-6-glucuronide via UDP-glucuronosyltransferase (UGT) 2B7, and by N-demethylation to norcodeine via CYP3A4. The analgesic activity of codeine-6-glucuronide in humans is unknown, whereas norcodeine is thought to have no analgesic properties.

Codeine analgesia is closely related to CYP2D6 pharmacogenetics. The association between CYP2D6 metabolizer phenotype and the formation of morphine from codeine is well defined. Pharmacokinetic and pharmacodynamic studies show a decrease in morphine levels and a decrease in analgesia in

poor metabolizers receiving codeine as compared with extensive metabolizers.^{12,13} Mikus *et al.* reported a decreased incidence of gastrointestinal side effects (i.e., constipation) in poor metabolizers as compared with extensive metabolizers;¹⁴ a later study by the same group of investigators found that central side effects (e.g., sedation, nausea, and dry mouth) did not differ between poor metabolizers and extensive metabolizers.¹² Further studies are needed to fully investigate the impact of the CYP2D6 poor metabolizer phenotype on the adverse-effect profile of codeine.

On the other hand, increased conversion to morphine in CYP2D6 ultrarapid metabolizers can result in toxic systemic concentrations of morphine¹¹ even at low codeine doses. The most common adverse reactions to codeine include drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, and sweating. Serious adverse reactions include respiratory depression and, to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest. Pharmacokinetic studies show increased conversion of codeine to morphine in ultrarapid metabolizers as compared with extensive metabolizers.¹⁵ Case reports detail the occurrence of severe or life-threatening side effects following standard doses of codeine in ultrarapid metabolizers.^{11,16,17}

Despite these data, codeine continues to be widely used, and most patients receive codeine without prior CYP2D6 genotyping. This guideline recommends using alternative analgesics in patients who are CYP2D6 poor metabolizers or ultrarapid metabolizers. It is important to recognize that, in addition to codeine, several other opioids are metabolized, at least in part, by CYP2D6. The opioids tramadol, hydrocodone, and oxycodone are O-demethylated by CYP2D6 to O-desmethyltramadol, hydromorphone, and oxymorphone, respectively.

Tramadol in its available racemic form is extensively metabolized via several pathways, including CYP2D6-mediated oxidation to O-desmethyltramadol, which has a 200-fold greater affinity for μ -opioid receptors than the parent drug does.^{10,18} Consequently, (+)-O-desmethyltramadol is principally responsible for opioid receptor-mediated analgesia, whereas (+)- and (–)-tramadol contribute to analgesia by inhibiting reuptake of the neurotransmitters serotonin and noradrenaline. As compared with CYP2D6 extensive metabolizers, poor metabolizers have been shown to have much lower median values of area under the concentration–time curves for the active metabolite after a dose of tramadol.^{19,20} In addition, several prospective clinical trials have shown that, as compared with CYP2D6 extensive metabolizers, poor metabolizers more often fail to exhibit analgesia in response to tramadol.^{18,19,21} Judging from this evidence, it is likely that tramadol has reduced clinical efficacy in CYP2D6 poor metabolizers.

Pharmacokinetic studies showed higher peak plasma concentrations of (+)-O-desmethyltramadol after a dose of tramadol, and also greater analgesia, stronger miosis, and higher incidence of nausea in ultrarapid metabolizers as compared with extensive metabolizers.²² There is one case report of respiratory depression in a CYP2D6 ultrarapid metabolizer with renal impairment after postsurgical tramadol treatment.²³ On the basis of these data, the use of analgesics other than tramadol may be

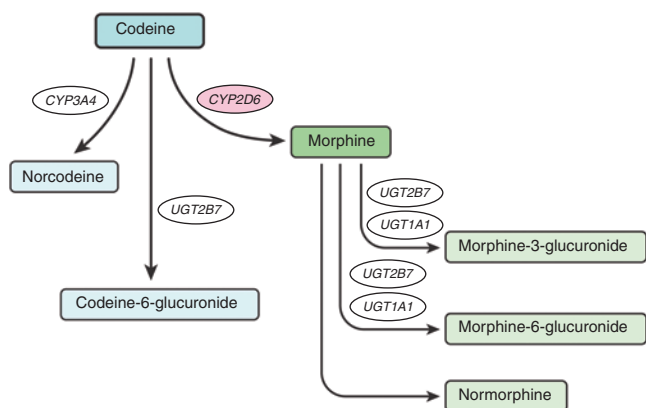


Figure 1 Codeine metabolism pathway.

preferable in CYP2D6 poor metabolizers and also in ultrarapid metabolizers.

Hydrocodone is biotransformed by CYP2D6 into hydromorphone, which has a 10- to 33-fold greater affinity for μ -opioid receptors as compared with the parent drug. Relative to extensive metabolizers, poor metabolizers have been shown to have lower peak concentrations of hydromorphone after a dose of hydrocodone²⁴; however, CYP2D6 metabolizer status does not appear to affect response to hydrocodone.^{24,25} To date, there is no information on the pharmacokinetics of hydrocodone in CYP2D6 ultrarapid metabolizers. Therefore, there is insufficient evidence as to whether poor metabolizers can be expected to have decreased analgesia when treated with hydrocodone, and whether ultrarapid metabolizers have an increased risk of toxicity with normal doses of hydrocodone.

Approximately 11% of an oxycodone dose is *O*-demethylated by CYP2D6 to the minor metabolite oxymorphone, which has a 40-fold higher affinity and eightfold higher potency for μ -opioid receptors as compared with the parent drug.^{10,26} As compared with extensive metabolizers, poor metabolizers have been shown to have lower peak concentrations of oxymorphone after a dose of oxycodone.^{27,28} However, prospective clinical studies have produced conflicting data pertaining to the associations between CYP2D6 metabolizer phenotype and the analgesic effect and toxicity of oxycodone. In two studies in healthy volunteers, differential analgesia response to experimental pain stimuli was observed between extensive and poor metabolizers and also between ultrarapid and extensive/poor metabolizers.^{29,30} However, clinical studies in postoperative patients and in patients with cancer failed to demonstrate a significant difference in analgesia or side effects in response to oxycodone across CYP2D6 phenotypes.^{27,28} Physiologic alterations (e.g., miosis) after dosing with oxycodone correlate best with exposure to the parent compound.³¹ It is therefore premature to recommend routine therapy adjustment for oxycodone on the basis of *CYP2D6* genotype.

The differing levels of evidence for the association of *CYP2D6* phenotype with hydrocodone and oxycodone analgesia as compared with codeine and tramadol may be because of the difference in the relative roles of the parent drug and circulating metabolites in analgesia among these *CYP2D6* substrates.³¹

To avoid treatment complications, opioids that are not metabolized by CYP2D6, including morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone,³² along with nonopioid analgesics, may be considered as alternatives for use in *CYP2D6* poor metabolizers and in ultrarapid metabolizers, depending on the type and chronicity of the pain being treated.

Other genes affecting codeine

Glucuronidation of codeine and of morphine is mediated by the polymorphic UGT2B7 enzyme.³³ Although the production of morphine-6-glucuronide is almost exclusively catalyzed by UGT2B7, several isoforms of the UGT1A subfamily are also involved in the formation of morphine-3-glucuronide. Conflicting evidence exists regarding the impact of the *UGT2B7*2*

variant on the glucuronidation of codeine.³⁴ Polymorphisms in the MDR1 transporter (*ABCB1*) gene also appear to have a modest association with opioid dose requirements.³⁵ The response to codeine may also be influenced by polymorphisms in drug response genes including, but not limited to, the opioid receptor μ_1 gene *OPRM1*; however, the importance of this gene to clinical outcome is not yet fully appreciated.³⁵

LINKING GENETIC VARIABILITY TO VARIABILITY IN DRUG-RELATED PHENOTYPES

There is substantial evidence linking *CYP2D6* genotype to variability in codeine efficacy and toxicity (see **Supplementary Table S6** online). Decreased codeine analgesia has been observed in poor metabolizers, whereas severe or life-threatening toxicity after normal doses of codeine has been documented in ultrarapid metabolizers. This body of evidence, rather than randomized clinical trials involving pharmacogenetic testing, provides the basis of the therapeutic recommendations in **Table 2**.

Table 2 Codeine therapy recommendations based on CYP2D6 phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy ^a
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol. ^b	Strong
Extensive metabolizer	Normal morphine formation	15–60 mg every 4 h as needed for pain (label recommendation)	Strong
Intermediate metabolizer	Reduced morphine formation	Begin with 15–60 mg every 4 h as needed for pain. If no response, consider alternative analgesics such as morphine or a nonopioid. Monitor tramadol use for response.	Moderate
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy. Consider alternative analgesics such as morphine or a nonopioid. Consider avoiding tramadol. ^b	Strong

^aRating scheme is described in **Supplementary Data** online. ^bAlthough detailed recommendations for using *CYP2D6* phenotype in tramadol therapy are beyond the scope of this guideline, there is strong evidence for decreased efficacy of tramadol in poor metabolizers and a single case report of toxicity in an ultrarapid metabolizer with renal impairment following tramadol postsurgery. Use of other analgesics in *CYP2D6* poor metabolizers and ultrarapid metabolizers may therefore be preferable.^{18,19,21,23}

CYP2D6 GENETIC TEST INTERPRETATION AND SUGGESTED CLINICAL ACTION

Table 2 summarizes the therapeutic recommendations for codeine based on CYP2D6 phenotype. A standard starting dose of codeine, as recommended in the product label, is warranted in patients with an extensive metabolizer phenotype (i.e., a CYP2D6 activity score of 1.0 to 2.0). Likewise, a standard starting dose of codeine is warranted in patients with an intermediate metabolizer phenotype (i.e., a CYP2D6 activity score of 0.5); these patients should be monitored closely for less than optimal response and should be offered an alternative analgesic if required. If the CYP2D6 substrate tramadol is selected as alternative therapy in intermediate metabolizers, close monitoring should be carried out because of the possibility of low response.

If clinical genotyping identifies a patient as a CYP2D6 poor metabolizer (i.e., a CYP2D6 activity score of 0), current evidence suggests that the use of codeine be avoided because of the possibility of lack of effect, and that an alternative analgesic should be used. That is, it may be preferable to use an analgesic other than the CYP2D6 substrate tramadol in poor metabolizers. There is insufficient evidence in the literature to recommend a higher dose of codeine in poor metabolizers, especially given that adverse effects do not differ between poor metabolizers and extensive metabolizers.¹²

In a patient identified as a CYP2D6 ultrarapid metabolizer (i.e., a CYP2D6 activity score of >2.0), the choice of an alternative analgesic should be made to avoid the risk of severe toxicity associated with a “normal” dose of codeine. That is, it may be preferable to use an analgesic other than the CYP2D6 substrate tramadol in ultrarapid metabolizers.

OTHER CONSIDERATIONS: BREASTFED INFANTS

Codeine and its metabolites, including morphine, are secreted in human breast milk, but the amount is typically low and dose dependent. However, breastfeeding women with an ultrarapid metabolizer phenotype may achieve high serum levels of morphine on standard codeine therapy.³⁶ This may lead to high concentrations of morphine in breast milk and dangerously high serum morphine levels in their breastfed infants.³⁷ Notably, there was a reported case of fatal opioid poisoning in a breastfed neonate as a result of the codeine treatment taken by the mother, an ultrarapid metabolizer.³⁸ Case reports such as this prompted the FDA to change the codeine product label to include information on the increased risk of morphine overdose in breastfed infants whose mothers are taking codeine and are ultrarapid metabolizers. Additional information about codeine use in breastfeeding mothers can be found elsewhere.³⁹ Codeine is not recommended in children less than 2 years of age and presumably would carry similar dangers in other neonates and young children who are themselves ultrarapid metabolizers.¹⁷

POTENTIAL BENEFITS AND RISKS FOR THE PATIENT

The potential benefit of CYP2D6 genotype testing is that patients with genotypes that are associated with a higher

risk of ineffective analgesia or of an adverse event may be identified, and alternative analgesics may be administered to these patients. CYP2D6 genotyping is reliable when performed in qualified laboratories. However, as with any laboratory test, a possible area of risk is an error in genotyping, which could have long-term adverse health implications for the patient.

CAVEATS: APPROPRIATE USE AND/OR POTENTIAL MISUSE OF GENETIC TESTS

One of the challenges with using clinical pharmacogenetic testing for codeine dosing is the need for results at the time an analgesic regimen is chosen. The ideal situation is to preemptively genotype patients who may need pain control in the future. For instance, preemptive CYP2D6 genotyping has been implemented in patients treated for acute lymphoblastic leukemia, who often require pain control medication during their therapy.⁴⁰ Like all diagnostic tests, the CYP2D6 genotype test is one of multiple pieces of information that clinicians should consider in guiding their therapeutic choice for each patient.

Disclaimer

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SUPPLEMENTARY MATERIAL is linked to the online version of the paper at <http://www.nature.com/cpt>

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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