Codeine Therapy and *CYP2D6* Genotype

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Codeine is used to relieve mild to moderately severe pain, and it belongs to the drug class of opioid analgesics.

The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, including codeine. Some individuals have multiple functional copies of the *CYP2D6* gene, making them "ultrarapid metabolizers". They are able to metabolize codeine to morphine more rapidly and more completely. As a result, even with normal doses of codeine, these individuals may experience the symptoms of morphine overdose, which include extreme sleepiness, confusion, and shallow breathing. Nursing mothers may also produce breast milk containing higher than expected levels of morphine that can lead to severe adverse events in their infants ([1]).

The FDA advises that codeine should be prescribed in the lowest effective dose for the shortest period of time, and patients should be informed about the risks and the signs of morphine overdose ([2]). The Clinical Pharmacokinetics Implementation Consortium (CPIC) recommends avoiding the use of codeine in patients who are either ultrarapid or poor metabolizers (see Table 1) ([3]).

Table 1.

CYP2D6 phenotypes and recommendations for codeine therapy

Phenotype	Activity score	Phenotype details	Genotype	Examples of diplotypes	Recommendations for codeine therapy[1]
Ultrarapid metabolizer	>2.0	Increased enzyme activity. Increased formation of morphine following codeine administration and increased risk of adverse events.	More than two copies of functional alleles	**1/*1xN* **1/*2xN*	Avoid codeine. Consider an alternative analgesic, e.g., morphine or a nonopioid. Consider avoiding tramadol.
Extensive metabolizer	1.0-2.0*	Normal enzyme activity. Normal morphine formation.	Two functional alleles, or two reduced function alleles, or one functional allele and one reduced or nonfunctional allele	**1/*1* **1/*2* **2/*2* **1/*41* **1/*4* **2/*5* **10/*10*	Dose recommended by drug label.
Intermediate metabolizer	0.5*	Intermediate enzyme activity. Reduced morphine formation.	One reduced function allele and one nonfunctional allele	**4/*10* **5/*41*	Dose recommended by drug label. If no response, consider an alternative analgesic, e.g., morphine or a nonopioid. Monitor tramadol use for response.

Phenotype	Activity score	Phenotype details	Genotype	Examples of diplotypes	Recommendations for codeine therapy[1]
Poor metabolizer	0	Low or absent enzyme activity. Greatly reduced morphine formation and risk of insufficient pain relief.	Two nonfunctional alleles	**4/*4* **4/*5* **5/*5* **4/*6*	Avoid codeine. Consider an alternative analgesic, e.g., morphine or a nonopioid. Consider avoiding tramadol.

[*]Activity scores are based on the formation of morphine from codeine. Other investigators may define extensive metabolizers with a score of 1.5-2.0, and intermediate metabolizers with a score of 0.5-1.0.

[1]The strength of therapeutic recommendations is “moderate” for intermediate metabolizers, and “strong” for all other metabolizers.

Table is adapted from Crews K.R. et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype. Clinical pharmacology and therapeutics. 2012;91(2):321–6 (3).

Drug: Codeine

Codeine exerts its effects via the opioid receptors found within the central nervous system, the gastrointestinal system, and elsewhere in the body. Codeine is a prodrug that only weakly binds the mu opioid receptor. Its analgesic properties depend upon its conversion to morphine that binds to the mu opioid receptor with 200-fold greater affinity than codeine.

The conversion of codeine to its active metabolites takes place mainly in the liver. Usually, about 10% of codeine is O-demethylated by CYP2D6 to morphine. Morphine is further metabolized to morphine-6-glucuronide, which also has analgesic properties. Other metabolites, primarily produced by UGTB7, include codeine-6-glucuronide (~60%) and norcodeine (~5–10%), both of which share with codeine a similarly weak affinity for the mu opioid receptor (4).

Gene: *CYP2D6*

The cytochrome P450 superfamily (CYP) is a large and diverse group of enzymes that form the major system for metabolizing drugs. The CYP genes are often polymorphic and can result in reduced, absent, or increased drug metabolism. CYP2D6 is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers.

CYP2D6 is highly polymorphic—more than 90 variants are known (5). *CYP2D6*1* is the wild-type allele and is associated with normal enzyme activity. The **2* allele has near-normal enzyme activity (~80% of wild-type) (6). Other important variant alleles include (see Nomenclature section):

- *CYP2D6*4*—nonfunctioning variant (1846G>A) (7)
- *CYP2D6*5*—nonfunctioning variant (gene deletion) (8)
- *CYP2D6*6*—nonfunctioning variant (1707 del T) (9)
- *CYP2D6*10*—reduced activity variant (100C>T) (10)
- *CYP2D6*17*—reduced activity variant (includes at least 2 functional variants) (11)
- *CYP2D6*41*—reduced activity variant (2988G>A) (12, 13).

Individuals who have at least one copy of a functional allele (**1* or **2*), or two partially functioning alleles, have a phenotypically normal response to codeine (“extensive metabolizers”). About 77–92% of patients have this phenotype (3).

Individuals who have multiple copies of the *CYP2D6* gene are “ultrarapid metabolizers”. Each functional allele increases the rate of codeine metabolism, increasing the risk of an initial morphine "overdose", with more side effects and a shorter duration of pain control ([14]). The ultrarapid metabolizer phenotype has been estimated to be present in 1–2% of patients, but the prevalence varies in different populations ([15]). It is estimated to be present in up to 28% of North Africans, Ethiopians, and Arabs; up to 10% in Caucasians; 3% in African Americans, and up to 1% in Hispanics, Chinese, and Japanese ([2]).

“Intermediate metabolizers” have either two partially functioning alleles or one partially functioning and one nonfunctional allele. These individuals may not respond as well to codeine because the metabolism of codeine to morphine is reduced. Overall, 2–11% of patients have this phenotype ([15]). In Asians and in individuals of Asian descent, only about 50% of *CYPD6* alleles are functional, with the reduced function *CYP2D6*10* variant being very common (~40%). As a result, Asians are more likely to be intermediate metabolizers than Caucasians ([6]). Similarly, in Africans and African Americans, only 50% of *CYPD6* alleles are functional. However, a wider range of variants account for the remaining alleles. ([6, 10, 16, 17])

About 5–10% of patients are “poor metabolizers”, having two nonfunctioning alleles ([15]). In these individuals, codeine will provide little or no pain relief. Poor metabolizers are more commonly found in European Caucasians and their descendants. The majority allele in this population is the functional *CYP2D6*1* (70%), but the remaining alleles include the nonfunctional *CYP2D6*4* and *CYP2D6*5* variants that largely account for the poor metabolizer phenotype in these populations ([5, 9, 12]).

Genetic Testing

Genetic testing is available for many (~30) of the variant *CYP2D6* alleles. Usually a patient’s result is reported as a diplotype, such as *CYP2D6 *1/*1* ([3]). A result for copy number is also important when interpreting results for this gene.

If the test results include an interpretation of the patient’s predicted metabolizer phenotype, this should be confirmed by checking the diplotype and assigning an activity score to each allele (e.g., 0 for nonfunctional, 0.5 for reduced function, and 1 for each copy of a functional allele). The phenotype is defined by the sum of the two scores (e.g., poor metabolizers have an activity score of 0) (see Table 1) ([3]).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

Statement from the US Food and Drug Administration (FDA): When physicians prescribe codeine-containing drugs, they should choose the lowest effective dose for the shortest period of time and inform their patients about the risks and the signs of morphine overdose.

The risk of infant exposure to codeine and morphine through breast milk should be weighed against the benefits of breastfeeding for both the mother and the baby. Caution should be exercised when codeine is administered to a nursing woman. If a codeine containing product is selected, the lowest dose should be prescribed for the shortest period of time to achieve the desired clinical effect. Mothers using codeine should be informed about when to seek immediate medical care and how to identify the signs and symptoms of neonatal toxicity,

such as drowsiness or sedation, difficulty breastfeeding, breathing difficulties, and decreased tone, in their baby. Nursing mothers who are ultra-rapid metabolizers may also experience overdose symptoms such as extreme sleepiness, confusion, or shallow breathing. Prescribers should closely monitor mother-infant pairs and notify treating pediatricians about the use of codeine during breastfeeding.

Please review the complete therapeutic recommendations that are located here: ([2]).

Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC): 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) (see Table 1). 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.

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.

Please review the complete therapeutic recommendations that are located here: ([3]).

The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labelled all formulations containing the generic drug.

Nomenclature

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.4:c.506-1G>A	Not applicable - variant occurs in a non-coding region	rs3892097
*CYP2D6*5*	Not applicable - variant results in a whole gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly	NM_000106.4:c.454delT	NP_000097.2:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T Pro34Ser	NM_000106.4:c.100C>T	NP_000097.2:p.Pro34Ser	rs1065852
*CYP2D6*17*	Includes*: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	NM_000106.4:c.320C>T NM_000106.4:c.886T>C	NP_000097.2:p.Thr107Ile NP_000097.2:p.Cys296Arg	rs28371706 rs16947
*CYP2D6*41*	2988G>A	NM_000106.4:c.985+39G>	Not applicable – variant occurs in a non-coding region	rs28371725

*In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

Acknowledgments

The Pharmacogenomics Knowledgebase: http://www.pharmgkb.org

The Clinical Pharmacogenetics Implementation Consortium: http://www.pharmgkb.org/page/cpic

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Tests in GTR by Condition

Codeine response

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Tests in GTR by Gene

CYP2D6 gene