

# 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 hepatic *CYP2D6* enzyme metabolizes a quarter of all prescribed drugs, including codeine. *CYP2D6* converts codeine in to its active metabolite, morphine, which provides its analgesic effect. However, pain relief may be inadequate in individuals who carry two inactive copies of *CYP2D6* (“poor metabolizers”), because of reduced morphine levels.

In contrast, individuals who carry more than two functional copies of the *CYP2D6* gene (“ultrarapid metabolizers”) 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 drug label for codeine states that even at labeled dosage regimens, individuals who are ultra-rapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose. The label also contains a boxed warning, which states that respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a *CYP2D6* polymorphism (1).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that for a patient identified as a *CYP2D6* ultrarapid metabolizer, another analgesic should be used to avoid the risk of severe toxicity with a “normal” dose of codeine. CPIC also recommends avoiding codeine in patients identified as *CYP2D6* poor metabolizers due to the possibility of lack of effect (see Table 1) (2).

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**Table 1.** Codeine therapy recommendations based on cytochrome P4502D6 (CYP2D6) phenotype, adapted from CPIC

Phenotype	Activity score	Phenotype details	Genotype	Examples of diplotypes	Recommendations for codeine therapy <sup>1</sup>	Considerations for alternative opioids
Ultrarapid metabolizer (approximately 1–2% of patients)	>2.0	Increased enzyme activity. Increased formation of morphine following codeine administration, leading to higher risk of toxicity.	More than two copies of normal function alleles	*1/*1xN *1/*2xN	Avoid codeine use due to potential for toxicity.	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.
Extensive metabolizer (approximately 77–92% of patients)	1.0-2.0*	Normal enzyme activity. Normal morphine formation.	Two normal function alleles, or two decreased function alleles, or one normal function allele and one decreased or nonfunctional allele	*1/*1 *1/*2 *2/*2 *1/*41 *1/*4 *2/*5 *1/*10	Use label-recommended age- or weight-specific dosing.	
Intermediate metabolizer (approximately	0.5*	Intermediate enzyme activity. Reduced	One decreased function allele and one	*4/*10 *5/*41	Use label-recommended age- or weight-specific dosing.	Monitor tramadol use for response.

\* 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.

<sup>1</sup> 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 guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update. Clinical pharmacology and therapeutics. 2014;95(4):376-82 (2).

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Phenotype	Activity score	Phenotype details	Genotype	Examples of diplotypes	Recommendations for codeine therapy <sup>1</sup>	Considerations for alternative opioids
2–11% of patients)		morphine formation.	nonfunctional allele		If no response, consider alternative analgesics such as morphine or a nonopioid.	
Poor metabolizer (approximately 5–10% of patients)	0	Low or absent enzyme activity. Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief.	Two nonfunctional alleles	*4/*4 *4/*5 *5/*5 *4/*6	Avoid codeine use due to lack of efficacy.	Alternatives that are not affected by this CYP2D6 phenotype include morphine and non-opioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.

\* 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.

<sup>1</sup> The strength of therapeutic recommendations is “moderate” for intermediate metabolizers, and “strong” for all other metabolizers.

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## Drug: Codeine

Codeine is an opioid analgesic. It exerts its effects via the opioid receptors found throughout the body including the central nervous system and the gastrointestinal system. 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.

Codeine is indicated for the relief of mild to moderately severe pain, where the use of an opioid analgesic is appropriate. Codeine is a Schedule II controlled substance, and there is a risk of misuse and abuse. As with any opioid drug, the dosing regimen should be adjusted for each individual patient. When the patient no longer requires codeine, the doses should be tapered gradually to prevent withdrawal symptoms in patients who have become physically dependent (1).

For codeine to exert its opioid activity, it must first undergo o-demethylation by CYP2D6 to morphine. Only about 5-10% of codeine is metabolized in this pathway, with about 80% of an administered dose of codeine being converted to inactive metabolites and excreted. However, the percentage of codeine converted to morphine can be much higher in individuals who have 3 or more active copies of *CYP2D6* (“ultrarapid metabolizers”) (2). In contrast, individuals who lack active copies of *CYP2D6* (“poor metabolizers”) have lower levels of morphine.

Morphine is further metabolized to morphine-6-glucuronide, which also has analgesic properties. Other metabolites are thought to be mostly inactive; they include codeine-6-glucuronide (~60%) and norcodeine (~5–10%), both of which share with codeine a similarly weak affinity for the mu opioid receptor (3).

To avoid treatment complications in patients who are either ultrarapid or poor metabolizers, opioids that are not metabolized by CYP2D6 may be used (e.g., morphine, oxycodone, buprenorphine, fentanyl, methadone, hydromorphone), alongside non-opioids, depending upon the type of pain being treated (2, 4-6).

The most common adverse reactions to codeine include drowsiness, lightheadedness, dizziness, sedation, shortness of breath, nausea, vomiting, and sweating. One of the main serious adverse reactions associated with codeine is respiratory depression. The FDA-drug label for codeine now includes a boxed warning that states “Warning: Death related to ultra-rapid metabolism of codeine to morphine. Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP2D6 polymorphism” (1, 7, 8).

## Gene: *CYP2D6*

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs in the liver. The *CYP450* genes are very polymorphic and can result in decreased, absent, or increased enzyme activity.

CYP2D6 is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers. The *CYP2D6* gene is highly polymorphic, with more than 100 star (\*) alleles described (9).

*CYP2D6*\*1 is the wild-type allele and is associated with normal enzyme activity and the “normal metabolizer” phenotype. The *CYP2D6* alleles \*2, \*33, and \*35 are also considered to have near-normal activity.

About 77–92% of individuals have at least one copy of a normal function allele (\*1 or \*2), or two partially functioning alleles. These individuals are “extensive metabolizers” and are most likely to have a phenotypically normal response to codeine. However, there is a large amount of variability in codeine response within patients genotyped as extensive metabolizers, and the causes of this variation, among individuals with the same diplotype, are unknown (2).

Other *CYP2D6* alleles include variants that produce a non-functioning enzyme (e.g., \*3, \*4, \*5, and \*6) (3, 10-12) or an enzyme with decreased activity (e.g., \*10, \*17, and \*41) (13-15) (see Table 2). There are large inter-ethnic differences in the frequency of these alleles, with \*3, \*4, \*5, \*6, and \*41 being more common in Caucasians, \*17 more common in Africans, and \*10 more common in Asians (16).

About 2–11% of patients are intermediate metabolizers—they carry either two partially functioning alleles or one partially functioning and one nonfunctional allele (17). These individuals may not respond as well to codeine because the metabolism of codeine to morphine is reduced.

In Asians and in individuals of Asian descent, only about 50% of *CYP2D6* alleles are functional, and the frequency of *CYP2D6* allele duplications is as high as 45% (18). Common non-functioning variants are *CYP2D6*\*36 (the most commonly duplicated *CYP2D6* allele in the Asian population) and *CYP2D6*\*10. Both these variants contain the SNP “100C>T” (see Nomenclature table) (16, 18-20). In Africans and African Americans, again, only about 50% of *CYP2D6* alleles are functional (10, 15, 16, 21).

About 5–10% of patients are poor metabolizers—they carry two nonfunctioning alleles (17). 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 normal function *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 (11, 14, 22).

Patients who are ultrarapid metabolizers carry at least 3 copies of the *CYP2D6* gene. The ultrarapid metabolizer phenotype has been estimated to be present in 1–2% of patients, but the prevalence varies widely in different populations. 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 (1, 17).

Each normal function *CYP2D6* 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 (23). Even low codeine doses can result in toxic levels of morphine in patients with more than 2 normal function alleles (2). Several case reports have recorded

the severe or life-threatening adverse effects that have occurred in patients who were ultrarapid metabolizers and were treated with standard doses of codeine (24, 25).

## Genetic Testing

Genetic testing is available for many (~30) of the variant *CYP2D6* alleles. Usually a patient's result is reported as a diplotype, which includes one maternal and one paternal allele, e.g., *CYP2D6* \*1/\*2. When patients have more than two copies of the *CYP2D6*, the copies of the allele are denoted by an "xN", e.g., *CYP2D6*\*2x2.

If the test results include an interpretation of the patient's predicted metabolizer phenotype, this should be confirmed by checking the diplotype and calculating the *CYP2D6* activity score. Each allele is assigned an activity value: 0 for nonfunctional, 0.5 for decreased function, and 1 for each copy of a normal function allele. The total *CYP2D6* activity score is the sum of the values assigned to each allele—patients with a score of 1.0, 1.5, or 2.0 represent a range of extensive metabolizers with normal enzyme activity. Poor metabolizers have an activity score of 0, patients with a score of 0.5 are intermediate metabolizers, and patients with a score of greater than 2.0 are ultrarapid metabolizers (see Table 1) (2).

Variants in other genes, such as *COMT*, *ABCB1*, *UGT2B7* and *OPRM1*, may also influence an individual's response to codeine. However, evidence is lacking on whether genetic testing for these variants will aid optimum codeine dosing (6, 26-28).

## Therapeutic Recommendations based on Genotype

**This section contains excerpted<sup>1</sup> information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.**

**2015 Statement from the US Food and Drug Administration (FDA):** Respiratory depression and death have occurred in children who received codeine in the post-operative period following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine (i.e., multiple copies of the gene for cytochrome P450 isoenzyme 2D6 [*CYP2D6*] or high morphine concentrations). Deaths have also occurred in nursing infants who were exposed to high levels of morphine in breast milk because their mothers were ultra-rapid metabolizers of codeine.

Some individuals may be ultra-rapid metabolizers because of a specific *CYP2D6* genotype (gene duplications denoted as \*1/\*1xN or \*1/\*2xN). The prevalence of this *CYP2D6* phenotype varies widely and has been estimated at 0.5 to 1% in Chinese and Japanese, 0.5 to 1% in Hispanics, 1 to 10% in Caucasians, 3% in African Americans, and 16 to 28% in North Africans, Ethiopians, and Arabs. Data are not available for other ethnic groups. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regimens, individuals who are ultra-rapid

metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing).

**Please review the complete therapeutic recommendations that are located here: (1)**

**2014 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 1.0–2.0). Likewise, a standard starting dose of codeine is warranted in patients with an intermediate metabolizer phenotype (i.e., activity score of 0.5); these patients should be monitored closely for less-than-optimal response and should be offered an alternative analgesic if warranted. If the CYP2D6 substrate tramadol is selected as alternative therapy in intermediate metabolizers, therapy should be monitored closely due to the possibility of poor response.

If clinical genotyping identifies a patient as a CYP2D6 poor metabolizer (i.e., activity score of 0), current evidence supports the avoidance of codeine and the use of an alternative analgesic due to the possibility of lack of effect. Use of an analgesic other than the CYP2D6 substrates tramadol, hydrocodone, or oxycodone in poor metabolizers may be preferable. There is insufficient evidence in the literature to recommend a higher dose of codeine in poor metabolizers, especially considering the evidence that select adverse effects do not differ between poor and extensive metabolizers. In a patient identified as a CYP2D6 ultrarapid metabolizer (i.e., activity score of >2.0), the choice of another analgesic should be made to avoid the risk of severe toxicity with a “normal” dose of codeine.

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

**2013 Clinical practice Guideline from the “Canadian Pharmacogenomics Network for Drug Safety (CPNDS) Clinical Recommendations Group: CYP2D6 genotyping for safe and efficacious codeine therapy”:**

1. Who should be tested and when?
  - Young children about to receive codeine for pain management and women about to receive codeine for postpartum pain while breastfeeding should be tested for CYP2D6 (Grade A – strong recommendation).
  - Children and adults who continue to have pain despite high doses of codeine should be tested for CYP2D6 (Grade B – moderate recommendation).
  - Genetic testing for CYP2D6 should be considered before administering codeine for the first time in all children and adults in order to rule out non-responders and to identify individuals who may be susceptible to adverse effects from codeine (Grade C – optional recommendation).
2. What gene variants should be tested?

Given the numerous polymorphisms in CYP2D6 and the diversity of the Canadian population, a full-scale analysis of both common and rare CYP2D6 variants is advised (Grade B- moderate recommendation)

- *CYP2D6* alleles with decreased or no function: *CYP2D6* \*3- 12, 14-15, 17, 19-20, 29, 40-42, 44, 49, 50, 54- 56, 59; \*4XN, \*10XN
- *CYP2D6* alleles with normal or increased function: *CYP2D6* \*2 (normal), \*1XN (increased), \*2XN (increased), \*17XN, \*35XN (increased), \*41XN, in addition to *CYP2D6* copy number determination.

#### Recommendations: Genotype-Specific Treatment Options

- Poor metabolizers of *CYP2D6* should not receive codeine for pain relief (Grade A-strong recommendation).
- Ultrarapid metabolizers of *CYP2D6* should avoid codeine for pain relief and receive alternative analgesics that do not have potent *CYP2D6* metabolites (Grade B-moderate recommendation).
- Certain populations, especially opioid naïve breastfed neonates of mothers with functional *CYP2D6* gene duplications taking codeine and young children may be particularly susceptible to codeine-induced central nervous system depression. Breastfeeding mothers and young children who are ultrarapid metabolizers of *CYP2D6* should avoid codeine (Grade A – strong recommendation).
- In individuals with IM or EM *CYP2D6* genotypes, codeine can be used as per standard of care. Existing evidence suggests that caution is still warranted in *CYP2D6* EMs receiving codeine if they are receiving maximal therapeutic doses of codeine and have additional risk factors for toxicity.

**Please review the complete therapeutic recommendations that are located here: (29)**

*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	
<i>CYP2D6</i> *4	1846G>A	NM_000106.4:c.506-1G>A	Not applicable - variant occurs in a non-coding region	rs3892097
<i>CYP2D6</i> *5		Not applicable - variant results in a whole gene deletion		
<i>CYP2D6</i> *6	1707 del T Trp152Gly	NM_000106.4:c.454delT	NP_000097.2:p.Trp152Glyfs	rs5030655
<i>CYP2D6</i> *10	100C>T Pro34Ser	NM_000106.4:c.100C>T	NP_000097.2:p.Pro34Ser	rs1065852

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

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Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
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*36	Includes: 100C>T (Pro34Ser) 4180G>C (Ser486Thr)	NM_000106.4:c. 100C>T NM_000106.5:c. 1457G>C	NP_000097.2:p.Pro34Ser NP_001020332.2:p.Ser435Thr	rs1065852 rs1135840
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>

Nomenclature for Cytochrome P450 enzymes is available from the Human Cytochrome P450 (CYP) Allele Nomenclature Database: <http://www.cypalleles.ki.se/>

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### First edition:

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

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

## Version History

To view an earlier version of this summary (update: 18 March 2013), please click [here](#).

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## Tests in GTR by Condition

Codeine response

## Tests in GTR by Gene

CYP2D6 gene