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Codeine Therapy and *CYP2D6* Genotype

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Introduction

Codeine is used to relieve mild to moderately severe pain, and it belongs to the drug class of opioid analgesics. Codeine has also been prescribed to prevent coughing, though the antitussive administration is most often in liquid formulations and in conjunction with other medications. (1, 2)

The hepatic CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, including codeine. The CYP2D6 enzyme converts codeine into its active metabolite, morphine, which provides its analgesic effect. Consequently, pain relief may be inadequate in individuals who have 2 inactive copies of *CYP2D6* ("poor metabolizers", PMs), because of reduced morphine levels.

In contrast, individuals who have more than 2 normal-function copies of the *CYP2D6* gene ("ultrarapid metabolizers", UMs) are able to metabolize codeine to morphine more rapidly and more completely. As a result, even with therapeutic doses of codeine, these individuals may experience the symptoms of morphine overdose, which include extreme sleepiness, confusion, and shallow breathing, which in some instances can be fatal. Nursing mothers with ultrarapid CYP2D6 metabolism may also produce breast milk containing higher than expected levels of morphine that can lead to severe adverse events in their infants. (3)

The FDA-drug label for codeine states that even at labeled dosage regimens, individuals who are UMs may have life-threatening or fatal respiratory depression or experience signs of overdose (Table 1). The label also contains a boxed warning, which states that respiratory depression and death have occurred in children who received codeine following tonsillectomy, adenoidectomy, or both, and had evidence of being CYP2D6 UMs.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends that for an individual identified as a CYP2D6 UM, another analgesic should be used to avoid the risk of severe toxicity with a "normal" dose of codeine. CPIC also recommends avoiding codeine in individuals identified as CYP2D6 PMs due to the possibility of lack of effect (Table 2). (4)

The Dutch Pharmacogenetics Working Group (DPWG) have published codeine dosing recommendations based on *CYP2D6* genotype, and condition being treated (cough or pain), typical dosing, and additional risk factors, such as reduced kidney function or co-medication with CYP3A4 inhibitors. For UMs, the DPWG recommends an alternative to codeine for the treatment of pain (for example, oxycodone) (Table 3). (5)

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Table 1. The FDA Recommended Dosing for Codeine based on CYP2D6 Phenotype (2019)

CYP2D6 phenotype	Codeine dose
Ultrarapid metabolizers	Individuals who are ultrarapid metabolizers should not use codeine sulfate tablets.

Please see Therapeutic Recommendations based on Genotype for more information from the FDA.
This FDA table is adapted from (3)

Table 2. The CPIC Codeine Therapy Recommendations based on CYP2D6 Phenotype (2020)

Phenotype[a]	Activity score[b]	Implications	Genotype	Examples of diplotypes[b]	Recommendations for codeine therapy[d]
Ultrarapid metabolizer	> 2.25	Increased enzyme activity. Increased formation of morphine leading to higher risk of toxicity.	More than 2 copies of normal-function alleles	**1/*1xN*[c] **1/*2xN*	Avoid codeine use because of potential for serious toxicity. If opioid use is warranted, consider a non-tramadol opioid.
Normal metabolizer	1.25-2.25*	Normal enzyme activity. Expected morphine formation.	2 normal-function alleles, or one normal-function allele and one decreased-function allele, or combinations of duplicated alleles that result in an activity score of 1.25 to 2.25	**1/*10* **1/*41* **1/*9* **10/*41x3* **1/*1* **1/*2* **2x2/*10*	Use codeine label-recommended age- or weight-specific dosing.
Intermediate metabolizer	0.25-1*	Intermediate enzyme activity. Reduced morphine formation.	one decreased-function allele and one no-function allele, or 2 decreased-function alleles, or one normal-function alleles and one no-function	**4/*10* **4/*41* **10/*10* **10/*41* **41/*41* **1/*5*	Use codeine label-recommended age- or weight-specific dosing. If no response, and opioid use is warranted, consider a non-tramadol opioid
Poor metabolizer	0	Absent enzyme activity. Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief.	2 no-function alleles	**3/*4* **4/*4* **5/*5* **5/*6*	Avoid codeine use because of possibility of diminished analgesia. If opioid use is warranted, consider a non-tramadol option.

Table 2. continued from previous page.

Phenotype[a]	Activity score[b]	Implications	Genotype	Examples of diplotypes[b]	Recommendations for codeine therapy[d]
Indeterminant metabolizer	n/a	n/a	An individual having one or 2 uncertain-function alleles	**1/*22* **1/*25* **22/*25*	No recommendation

[a] See the CYP2D6 Frequency Table for ancestry-specific allele and phenotype frequencies from PharmGKB and CPIC.
[b] Assignment of allele function and allele activity values including citations for allele function can be found at PharmGKB (CYP2D6 Allele Definition Table and CYP2D6 Allele Functionality Table) and CPIC.
For a complete list of CYP2D6 diplotypes and resulting phenotypes, see the CYP2D6 Genotype to Phenotype Table at PharmGKB and CPIC.
[C] Where xN represents the number of CYP2D6 gene copies. For individuals with CYP2D6 duplications or multiplications, see supplemental data in (CPIC 2020) for additional information on how to translate diplotypes into phenotypes.
[d] The strength of therapeutic recommendations is "moderate" for intermediate metabolizers, and "strong" for all other metabolizers.
Table is adapted from (4)

Table 3. The DPWG Recommendations for Codeine by *CYP2D6* Genotype (2017)

CYP2D6	Recommendations for pain	Recommendations for cough
Ultrarapid	If possible, select an alternative[b] to codeine. Lower doses (<20 mg for adults, <10mg for children 12yo and older) every 6 hours (with no additional risk factors) are acceptable.	If possible, select an alternative to codeine. Noscapine* is not metabolized by CYP2D6. Lower doses (<20 mg for adults, <10mg for children 12yo and older) every 6 hours (with no additional risk factors) are acceptable.
Intermediate metabolizer[a]	1. be alert to a reduced effectiveness 2. in the case of inadequate effectiveness try a dose increase if this does not work: choose an alternative[b] 3. if no alternative is selected: advise the individual to report inadequate analgesia	No action required
Poor metabolizer[a]	1. choose an alternative[b] 2. if an alternative is not an option: advise the individual to report inadequate analgesia.	No action required

[a] It is not possible to offer adequately substantiated advice for dose adjustment based on the limited available literature for this phenotype.
[b] Do not select tramadol, as this is also metabolized by CYP2D6. Morphine is not metabolized by CYP2D6. Oxycodone is metabolized by CYP2D6 to a limited extent, but this does not result in differences in analgesia in individuals.
yo – years old
* This medication is not licensed for use within the United States, included to reflect the original source recommendations from The Netherlands.
Please see Therapeutic Recommendations based on Genotype for additional recommendations from DPWG, which take into account typical dosing, co-medication with CYP3A4 inhibitors, and risk factors such as reduced kidney function.
This table is adapted from (5)

Drug: Codeine

Codeine is an opioid analgesic. It exerts its effects via the opioid receptors found throughout the body. Target sites for the desired effects are receptors in the central nervous system, however, the gastrointestinal system is also affected due to the presence of opioid receptors, resulting in undesired, off-target effects. 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. Codeine can also be combined with acetaminophen (called Tylenol 3 or 4), which is a schedule III, controlled medication (90 milligrams or less codeine per dosage unit). Drugs and other substances that are considered controlled substances under the Controlled Substances Act (CSA) are divided into 5 schedules based on whether they have an accepted medical indication and the potential for abuse or addiction. Schedule II drugs have a high potential for abuse that may lead to severe psychological or physical dependence, and schedule III have a lower potential for abuse. Codeine is also found with some cough medications—schedule V medications that are limited to containing not more than 200 milligrams of codeine per 100 milliliters. (6) As with any opioid drug, the dosing regimen should be adjusted for each individual. When the individual no longer requires codeine, the doses should be tapered gradually to prevent withdrawal symptoms in individuals who have become physically dependent. (3)

For codeine to exert its opioid activity, it must first undergo *O*-demethylation by CYP2D6 to morphine. Only approximately 5–10% of codeine is metabolized in this pathway, with approximately 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 a combined enzyme "activity score" of >2.25 due to variant alleles of *CYP2D6* (*UMs; see Gene: CYP2D6 information below)*.(4) In contrast, individuals who lack active copies of *CYP2D6* (PMs) have lower levels of morphine.

Morphine is further metabolized to morphine-6-glucuronide, which also has analgesic properties. Morphine-3-glucuronide, a related morphine metabolite is presumed to not function as an analgesic but possesses neurotoxic effects. (4) 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. (7)

To avoid treatment complications in individuals who are either ultrarapid or PMs, opioids that are not metabolized by CYP2D6 may be used (for example, morphine, oxymorphone, buprenorphine, fentanyl, methadone, hydromorphone), alongside non-opioids, depending upon the type of pain being treated. (8, 9, 10) Tramadol is not a recommended alternative, since it is also metabolized by CYP2D6 (3, 5). Hydrocodone and oxycodone are also metabolized by CYP2D6 to more potent metabolites but the implications of CYP2D6 genotype on analgesic response and risk for toxicity is unclear (4).

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 ultrarapid 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 ultrarapid metabolizers of codeine due to a *CYP2D6* polymorphism." (3, 11, 12)

The FDA also cautions against prolonged use of codeine during pregnancy due to the risk of neonatal opioid withdrawal and fetal harm, regardless of the mother's CYP2D6 metabolizer status. (3)

Codeine sulfate tablets are "contraindicated for all children younger than 12 years of age and in post-operative pain management in pediatric individuals younger than 18 years of age following tonsillectomy and/or adenoidectomy" (3). The FDA label also recommends avoiding codeine usage by adolescents between 12 and 18 years of age with the following risk factors: "conditions associated with hypoventilation, such as post-operative status, obstructive sleep apnea, obesity, severe pulmonary disease, neuromuscular disease, and concomitant use of other medications that cause respiratory depression." (3)

In light of the opioid-associated death of a nursing infant whose mother was found to be an UM (13), the FDA does not recommend breastfeeding during treatment with codeine (3). This recommendation against breastfeeding while taking opioids includes both codeine and tramadol, as both are pro-drug substrates of

CYP2D6 (14). Additional information on the FDA's guidance regarding codeine and tramadol usage in breastfeeding women is also available from the FDA (15). However, other sources and studies—discussed below—have suggested short-term administration of codeine in the post-partum period for nursing mothers is possible with appropriate precautions and monitoring of the breastfed infant.

The American College of Obstetrics and Gynecology (ACOG) has issued a statement on the topic of pain management in the postpartum period that includes guidance for use of opioids. The ACOG recommends a stepwise approach and multimodal combination of agents in managing postpartum pain, with an emphasis on shared decision-making between the new mother and her physician regarding pain management options outside of the clinical setting. The ACOG recommends non-opioid analgesics as the first tier of medications for postpartum pain management, with low dose, mild opioids as a secondary option with acetaminophen or non-steroidal anti-inflammatory drugs. These guidelines state that oral opioids should be reserved only for breakthrough pain. Furthermore, the ACOG recommends clinicians review of the risks and benefits as well as educating the family regarding the presentation of opioid toxicity in both the woman and newborn. And the ACOG is clear to state that opiate prescriptions should be limited to the shortest reasonable course expected for acute pain. Evidence-based safety guidelines for maternal opioid use are available from the ACOG. (16)

If the clinician and new mother decide codeine is warranted, guidelines from the Lactation Database state that acute pain management for the nursing mother with established milk production can be achieved via a nonnarcotic analgesic and limiting maternal intake of low dosage oral codeine to 2–4 days. It should be noted that newborn infants seem to be particularly sensitive to the effects of narcotic analgesics and numerous professional organizations and regulatory agencies are cited as recommending other agents over codeine for pain management. (17)

A review of the literature and analysis of pharmacokinetics of codeine metabolism in nursing mothers and the rate of drug clearance in infants has indicated that longer-term (1–2 weeks) exposure via breastfeeding may be a more significant contributor to infant adverse events than maternal metabolizer status, particularly given that pregnancy-associated *CYP2D6* induction may result in higher metabolism than suggested by genotype alone. (18) Thus, even when the maternal genotype is known, the actual activity level of the CYP2D6 enzyme may be elevated and contribute to higher plasma morphine levels in the nursing mother, which may be passed into the breastmilk.

Additional factors, including further metabolism of morphine by UGT2B7, age-dependent expression levels of metabolic enzymes and clinical information not initially reported in one case of infant mortality (13) have been suggested as evidence against the likelihood that typical codeine use by a nursing mother can directly lead to infant mortality, even for UMs. (19) Codeine usage in the postnatal period with *CYP2D6* genotyping has been predicted to result in an incremental cost-effectiveness per adverse event averted (20), suggesting that when possible, determination of the mother's CYP2D6 metabolizer status is beneficial. See the section on Genetic Testing below for additional information on *CYP2D6* genotyping.

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.

The CYP2D6 enzyme is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers.

CYP2D6 Alleles

The *CYP2D6* gene is highly polymorphic, as over 100 star (*) alleles have been described and catalogued at the Pharmacogene Variation (PharmVar) Consortium, and each allele is associated with either normal, decreased, or absent enzyme function (Table 4). (21)

The combination of *CYP2D6* alleles that a person has is used to determine their diplotype (for example, *CYP2D6 *4/*4*). Based on function, each allele can be assigned an activity score from 0 to 1, which in turn is often used to assign a phenotype (for example, CYP2D6 PM). However, the activity score system is not standardized across clinical laboratories or CYP2D6 genotyping platforms. CPIC revised their activity scoring guidelines in October 2019 to promote harmonization. The CYP2D6 phenotype is defined by the sum of the 2 activity scores, which is usually in the range of 0 to 3.0: (22)

- An UM has an activity score greater than 2.25
- A normal metabolizer phenotype (NM) has an activity score of 1.25–2.25
- An intermediate metabolizer (IM) has an activity score of >0–<1.25
- A PM has an activity score of 0

Table 4. Activity Status of Selected CYP2D6 Alleles

Allele type	Activity score	*CYP2D6* alleles
Normal function	1.0	**1, *2, *27, *33*
Decreased function	0.25–0.5	**10, *17, *41, *49*
No function	0	**3, *4, *5, *6, *36*

For a comprehensive list of *CYP2D6* alleles, please See PharmVar.

The *CYP2D6*1* allele is the wild-type allele when no variants are detected and is associated with normal enzyme activity and the NM phenotype. The *CYP2D6*2*, *27, and **33* alleles are also considered to have near-normal activity.

Other CYP2D6 alleles include variants that produce a non-functioning enzyme (for example, **3*, **4*, **5*, and **6*) (7, 23, 24, 25) or an enzyme with decreased activity (for example, **10*, **17*, and **41*) (26, 27, 28) (see Table 4). There are large inter-ethnic differences in the frequency of these alleles, with **3, *4, *5, *6*, and **41* being more common in individuals with European ancestry, **17* more common in Africans, and **10* more common in Asians. (29)

Allele Frequencies Vary between Populations

Among Asians and in individuals of Asian descent, only approximately 50% of *CYPD6* alleles are normal function, and the frequency of *CYP2D6* duplications is as high as 45%, although this may have been overestimated by not accounting for tandem hybrid alleles (for example, **36+*10*). (30) Other studies of a US population suggested less than 50% of alleles detected within Asian-descent individuals are normal-function alleles in a single copy, with 30% of alleles arising from structural variants (duplications or deletions). (31) Common no-function variants are *CYP2D6*36* and *CYP2D6*4.* (31) Both these alleles contain the variant "c.100C>T" (see Nomenclature table). (29, 30, 32, 33) The *CYP2D6*36* allele is the result of a gene conversion event with the pseudogene *CYP2D7* (34). This no-function allele is most commonly found in individuals of Asian ancestry (31).

Among Africans and African Americans, only approximately 50% of *CYP2D6* alleles are normal function. (23, 28, 29, 35) African Americans also have been found to have a higher frequency of no-function structural variants or decreased-function single-copy variant alleles versus Caucasian or Hispanic Americans. (31)

Middle Eastern countries show a great diversity in phenotypic and allelic distribution for *CYP2D6* (36), though on average, these individuals show a lower frequency of PM phenotypes (0.91%) and higher ultrarapid phenotypes (11.2%) than other ethnicities (Note: Oceania and Middle Eastern ethnicities were combined in this study). (34)

Among European countries, there is diversity of allelic distribution. Gene duplications were more common in the south-eastern countries (Greece, Turkey: 6%) and less common in north-western countries (Sweden and Denmark, <1%). Meanwhile, *CYP2D6*4* and *CYP2D6*5* alleles were more common in the north and less common in the south. (37) Worldwide *CYP2D6* genotype and phenotype frequencies have been catalogued and recently published (34).

CYP2D6 Phenotype

CYP2D6 Phenotype Frequencies Vary between Populations

Normal metabolizers: Between 43–67% of individuals have 2 normal-function alleles (**1* or **2*), or one normal-function allele and one decreased-function allele, resulting in a NM phenotype based on the CPIC/PharmGKB activity scores (38). These individuals are most likely to have a phenotypically normal response to codeine. However, there is a large amount of variability in codeine response within individuals genotyped as NMs, and the causes of this variation, among individuals with the same diplotype, are unknown. (4)

Intermediate metabolizers: Between 10–44% of individuals are IMs—they have either 2 decreased-function alleles or one normal- or decreased-function and one no-function allele. (34, 38) These individuals may not respond as well to codeine because the metabolism of codeine to morphine is reduced. A study of a diverse US urban population of children found that roughly 8% of subjects were IMs, though this may be higher due to the broader range for IM activity scores. (39) Within the US, it has been observed that individuals of African or Asian descent were most likely to be classified as IM's (20–28% of population by ethnicity). (31) Similarly, PharmGKB reports that the highest frequency of IM activity scores are found in Sub-Saharan African and East Asian populations (38).

Poor metabolizers: Between 0.4–6.5% of individuals are PMs—they have 2 no-function alleles. (38, 40) In these individuals, codeine will provide little or no pain relief. Poor metabolizers are more commonly found in European Caucasians and their descendants. The no-function *CYP2D6*4* and **5* alleles largely account for the PM phenotype in these populations (24, 27, 41). It should be noted that the frequency of PMs can be much lower in certain populations including East Asian, Oceania and Middle Eastern (34). Studies of US multi-ethnic populations have estimated the prevalence of PMs to be between 1.5–5.7% (31, 39).

Ultrarapid metabolizers: Individuals who are UMs have an enzyme activity score greater than 2.5, often due increased copy number of the *CYP2D6* gene. The UM phenotype has been estimated to be present in 1–2% of individuals, 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 (3, 40). PharmGKB reports that the Oceanian population has the highest prevalence of UM phenotype (38). Ultrarapid metabolizers made up 9% of subjects in an urban multi-ethnic population with a large portion of Hispanic/Latino subjects (39). A larger study of US individuals predicted an UM phenotype in only 2.2% of individuals, regardless of ethnicity (31).

Pharmacologic Conversion of CYP2D6 Phenotype

Factors other than genotype can affect CYP2D6 enzyme activity and thus the metabolizer phenotype of any individual. Administration of multiple drugs, sometimes called polypharmacy or co-medication, can lead to a phenomenon called phenoconversion whereby an individual with one metabolizer genotype can have enzymatic activity of a different metabolizer group (higher or lower, depending on the medications). Enzymatic activity of

CYP2D6 can be inhibited or reduced by medications including duloxetine, paroxetine, fluoxetine, bupropion, amiodarone (note: this is a weak inhibitor), and quinidine (3, 42, 43, 44). This can result in normal or IMs responding to medications as if they were PMs. Thus, co-medication with multiple CYP2D6 substrates may result in reduced metabolism of these drugs. In the case of codeine, this may present as reduced analgesic effect. In contrast, discontinuing a co-medication can increase the rate of CYP2D6 metabolism to the genotype predicted activity level.

Other Genes of Note

OPRM1

The mu opioid receptor is encoded by the *OPRM1* gene. The mu opioid receptor is a G-coupled protein receptor and is a key signal transducer for the desired analgesic effect of codeine. There are more than 200 known variant alleles of *OPRM1*, and some variants have been suggested to have a role in opioid response or predisposition to opioid use disorders (45, 46). However, CPIC's expert review found inconsistent evidence linking any of these alleles to post-operative dose requirements for some opioids and the effect on morphine dose adjustment was deemed not to be clinically actionable (4).

COMT

Catechol-o-methyltransferase (COMT) is an enzyme involved in the methylation and degradation of adrenaline, noradrenaline, and dopamine. This enzyme regulates the concentration of catecholamines and thus is a key regulator of the pain perception pathways (47). The variant rs4680 (p.Val158Met) in *COMT* has been suggested to result in decreased levels of methylation activity (4, 47). However, CPIC's review finds variable evidence associating this variant with analgesic response or opioid dose requirements and thus makes no recommendations based on *COMT* genotype (4).

Gene Family: *UGT*

Codeine and morphine are metabolized to inactive compounds by UDP-glucuronosyltransferase enzymes (UGT). The enzyme UGT2B7—along with other UGT enzymes—is involved in conversion of codeine to codeine-6-glucuronide and morphine to morphine- 3- and 6-glucuronide (48). Variation in UGT2B7 has been suggested to affect codeine and morphine metabolism, but the results have not been significantly reproducible between studies (49, 50, 51, 52, 53).

Linking Gene Variation with Treatment Response

Enzymatic activity of CYP2D6 directly correlates with the systemic dose of morphine following CYP2D6 conversion of codeine. Individuals with more than 2 copies of normal functioning alleles *(*1xN/*1, *2xN/*1*, etc.) are at an elevated risk of codeine overdose symptoms. (3) These individuals are classified as UM, and are at elevated risk for toxicity. (54)

Each normal-function *CYP2D6* allele increases the rate of codeine metabolism, increasing the risk of an initial morphine "overdose", with more side effects. (55) Even low codeine doses can result in toxic levels of morphine in individuals with more than 2 normal-function alleles. (4) Several case reports have recorded the severe or life-threatening adverse effects that have occurred in individuals who were UMs and were treated with standard doses of codeine. (56, 57)

Multiple reports of toxic or fatal events have occurred in pediatric individuals who were later found to have UM genotypes (reviewed by (58)). Analysis of the Mayo Clinic RIGHT Protocol study suggested that UM individuals

were least likely to have poor pain control but had the highest rates of adverse reactions among the various metabolizer phenotypes. (59)

In contrast, individuals with alleles that encode the no-function CYP2D6 enzyme will poorly metabolize codeine and thus are unlikely to achieve the intended therapeutic analgesic effect from codeine. Aptly classified as PMs, these individuals have a higher rate of poor pain control but lower rates of adverse reactions in the RIGHT protocol study. (59)

Additional studies of the RIGHT protocol found that both PMs and UMs experienced a higher rate of adverse effects and poor pain control from opioid prescription as compared with normal or IMs. The higher adverse effects were due to the rapid codeine metabolism in UM individuals and poor pain control due to the reduced activation of codeine to morphine in the PM population. The mechanism whereby PMs experienced higher rates of adverse events such as nausea and vomiting were not discussed. Co-medication with CYP2D6 inhibitors was also noted to affect the frequency of adverse events in all phenotypes studied. (60)

The CYP2D6 IMs may also experience reduced effectiveness in pain management of codeine due to lower rates of conversion to morphine. A dose increase can be attempted for IM, but in some cases the individual may require an alternative medication that is not primarily metabolized by CYP2D6. (5)

The CYP2D6 Gene Interactions with Medications Used for Additional Indications

The CYP family of enzymes is involved in metabolism of many substances and CYP2D6 especially has been implicated in altered pharmacologic responses for many compounds. The drugs can be categorized into many different classes:

- Antipsychotics—for example, aripiprazole, risperidone, thioridazine and—to a lesser extent—clozapine is metabolized by CYP2D6. According to the FDA, aripiprazole dosage should be reduced for PMs and thioridazine is contraindicated for individuals who are known to have reduced CYP2D6 activity due to increased risk of potentially fatal side effects. Ultrarapid metabolizers may have a decreased plasma concentration of risperidone.
- Tricyclic antidepressants—for example, amitriptyline, and imipramine may require dosage adjustments, potentially guided by therapeutic drug monitoring, to achieve the desired therapeutic range in ultrarapid or PMs. Ultimately, tricyclic antidepressants may be ineffective in CYP2D6 UMs
- Serotonin and norepinephrine reuptake inhibitors—for example atomoxetine and venlafaxine may have reduced efficacy in UMs at standard doses while PMs are at risk of elevated plasma concentrations for both medications. The DPWG advises against use of venlafaxine in CYP2D6 poor and IMs.
- Cardiovascular dysfunction—for example, carvedilol, metoprolol, and propafenone are all metabolized by CYP2D6 and PMs will have higher plasma concentrations of these medications compared with NMs resulting in potentially undesired side effects or (in the case of metoprolol) extensive slowing of the heart rate.
- Anti-cancer medications—for example, tamoxifen is activated by CYP2D6 and intermediate or PMs may have reduced benefit from tamoxifen therapy.
- Various therapies for genetic disorders—for example eliglustat used in the treatment of Gaucher disease, and deutetrabenazine used in the treatment of Huntington disease. For both medications, reduced doses are recommended for CYP2D6 PMs and UMs may not achieve adequate concentrations of eliglustat. Before initiation of eliglustat therapy, CYP2D6 genotyping is required.

It is important to note that *CYP2D6* is the most common biomarker in drug responses for FDA drug labels, the list provided here is by no means exhaustive. Additional information on gene-drug interactions for *CYP2D6* are available from PharmGKB, CPIC and the FDA (search for “CYP2D6”).

Genetic Testing

Genetic testing is available for many (~30) of the variant *CYP2D6* alleles. Usually, an individual's result is reported as a diplotype, which includes one maternal and one paternal allele, for example, *CYP2D6 *1/*2*. When individuals have more than 2 copies of the *CYP2D6*, the copies of the allele are denoted by an "xN", for example, *CYP2D6*1/*2x2*. Some laboratories also use the notation of DUP to indicate an increase in copy number, but the report does not specify the number of duplications nor the allele that has been duplicated.

Genetic tests for codeine response and the *CYP2D6* gene can be found on the NIH Genetic Testing Registry. The available CYP2D6 tests include targeted single-gene tests as well as multi-gene panels and exome- or genome-wide sequencing tests.

The test results may include an interpretation of the individual's predicted metabolizer phenotype, which can be confirmed by checking the diplotype and calculating the CYP2D6 activity score, as described in the "*CYP2D6* Alleles" section above.

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. (10, 61, 62, 63)

In 2019, the US Department of Veterans Health Administration (VHA) Clinical Pharmacogenetics Subcommittee recommended that prescribers in the VHA consider *CYP2D6* genotyping before codeine use. Factors supporting this recommendation included the actionability of the genetic test result, guiding prescribers to different codeine dosing or alternate analgesic agents. (64)

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.

2019 Statement from the US Food and Drug Administration (FDA)

Life-threatening respiratory depression and death have occurred in children who received codeine. Codeine is subject to variability in metabolism based upon CYP2D6 genotype (described below), which can lead to an increased exposure to the active metabolite morphine. Based upon post-marketing reports, children younger than 12 years old appear to be more susceptible to the respiratory depressant effects of codeine, particularly if there are risk factors for respiratory depression. For example, many reported cases of death occurred in the post-operative period following tonsillectomy and/or adenoidectomy, and many of the children had evidence of being ultrarapid metabolizers of codeine. Furthermore, children with obstructive sleep apnea who are treated with codeine for post-tonsillectomy and/or adenoidectomy pain may be particularly sensitive to its respiratory depressant effect.

Some individuals may be ultrarapid metabolizers because of a specific *CYP2D6* genotype (e.g., gene duplications denoted as **1/*1xN* or **1/*2xN*). The prevalence of this CYP2D6 phenotype varies widely and has been estimated at 1 to 10% for Whites (European, North American), 3 to 4% for Blacks (African Americans), 1 to 2% for East Asians (Chinese, Japanese, Korean), and may be greater than 10% in certain racial/ethnic groups (i.e., Oceanian, Northern African, Middle Eastern, Ashkenazi Jews, Puerto Rican). 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

[1] 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.

ultrarapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose (such as extreme sleepiness, confusion, or shallow breathing). Therefore, individuals who are ultrarapid metabolizers should not use codeine sulfate tablets.

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

2020 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

For CYP2D6 normal metabolizers (i.e. CYP2D6 activity score 1.25 to 2.25), a label recommended age- or weight-specific starting dose of codeine or tramadol, as recommended in the product label, is warranted. A label recommended starting dosing is also recommended for intermediate metabolizers (i.e. activity score of 0.25 to 1); these patients should be monitored closely for less than optimal response and should be offered an alternative analgesic if warranted. For CYP2D6 poor metabolizers (i.e. activity score of 0), current evidence supports the avoidance of codeine and tramadol and the use of an alternative analgesics due to the likelihood of suboptimal or lack of effect. There is insufficient evidence in the literature to recommend a higher dose of codeine or tramadol in poor metabolizers, especially considering the evidence that some adverse events do not differ between poor and normal metabolizers (19). For CYP2D6 ultrarapid metabolizers (i.e. activity score of >2.25), codeine or tramadol should not be used, in order to avoid the risk of severe toxicity with label-recommended dosing. Non-opioid analgesics and if needed, other opioids that are not affected by CYP2D6 phenotype, are potential alternatives for use in CYP2D6 poor and ultrarapid metabolizers based on the type, severity and chronicity of the pain being treated.

Please review the complete therapeutic recommendations that are located here: (4).

2017 Summary of Recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

CYP2D6 Intermediate Metabolizers

For COUGH:

1 no action required

For PAIN:

It is not possible to offer adequately substantiated advice for dose adjustment based on the limited available literature for this phenotype.

1. be alert to a reduced effectiveness
2. in the case of inadequate effectiveness:
    1. try a dose increase
    2. if this does not work: choose an alternative
        - Do not select tramadol, as this is also metabolised by CYP2D6
        - Morphine is not metabolised by CYP2D6.
        - Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients.
    3. if no alternative is selected: advise the patient to report inadequate analgesia

Poor Metabolizers

For COUGH:

1 no action required

For PAIN:

It is not possible to offer adequately substantiated advice for dose adjustment based on the limited available literature for this phenotype.

1 choose an alternative

Do not select tramadol, as this is also metabolised by CYP2D6

- Morphine is not metabolised by CYP2D6.
- Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in analgesia in patients.
  2 if an alternative is not an option: advise the patient to report inadequate analgesia.

Ultrarapid Metabolizers

DOSES HIGHER THAN 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older AND/OR ADDITIONAL RISK FACTORS, such as co-medication with CYP3A4 inhibitors and/or reduced kidney function:

Codeine is contra-indicated

- if possible, select an alternative
  - For PAIN: do not select tramadol, as this is also metabolised by CYP2D6.

Morphine is not metabolised by CYP2D6. Oxycodone is metabolised by CYP2D6 to a limited extent, but this does not result in differences in side effects in patients.

- For COUGH: noscapine is not metabolised by CYP2D6.

DOSES LOWER THAN OR EQUAL TO 20 mg every 6 hours for adults and 10 mg every 6 hours for children aged 12 years or older AND NO ADDITIONAL RISK FACTORS, such as co-medication with CYP3A4 inhibitors and/or reduced kidney function:

- no action required

Please review the complete therapeutic recommendations that are located here: (5)

2013 Clinical practice Guideline from the "Canadian Pharmacogenomics Network for Drug Safety (CPNDS) Clinical Recommendations Group: *CYP2D6* genotyping for safe and efficacious codeine therapy" are located here: https://www.ncbi.nlm.nih.gov/pubmed/24214521 (65).

Nomenclature

Nomenclature of Selected *CYP2D6* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*2*	2851C>T (Arg296Cys)	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
*CYP2D6*3*	4181G>C (Ser486Thr)	NM_000106.6:c.886C>T	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*4*	1846G>A	NM_000106.6:c.506-1G>A	Variant occurs in a non-coding region (splice variant causes a frameshift)	rs3892097

Nomenclature of Selected continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*5*	Gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly CYP2D6T	NM_000106.6:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
*CYP2D6*17*	1023C>T[1] (Thr107Ile)	NM_000106.6:c.320C>T	NP_000097.3:p.Thr107Ile	rs28371706
	2851C>T[2] (Cys296Arg)	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*27*	3854G>A (Glu410Lys)	NM_000106.6:c.1228G>A	NP_000097.3:p.Glu410Lys	rs769157652
*CYP2D6*31*	2851C>T (Arg296Cys)	NM_000106.6:c.886C>T	NP_000097.3:p.Arg296Cys	rs16947
	4043G>A (Arg440His)	NM_000106.6:c.1319G>A	NP_000097.3:p.Arg440His	rs267608319
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*36*[3]	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4129C>G (Pro469Ala)	NM_000106.6:c.1405C>G	NP_000097.3:p.Pro469Ala	rs1135833
	4132A>G (Thr470Ala)	NM_000106.6:c.1408A>G	NP_000097.3:p.Thr470Ala	rs1135835
	4156C>T+4157A>C (His478Ser)	NM_000106.6:c.1432C>T + NM_000106.6:c.1433A>C	NP_000097.3:p.His47Ser	rs28371735 + rs766507177
	4159G>C (Gly479Arg)	NM_000106.6:c.1435G>C	NP_00097.3:p.Gly479Arg	
	4165T>G (Phe481Val)	NM_000106.6:c.1441T>G	NP_00097.3:p.Phe481Val	
	4168G>A+4169C>G (Ala482Ser)	NM_000106.6:c.1444G>A + NM_000106.6:c.1445C>G	NP_000097.3:p.Ala482Ser	rs74478221 + rs75467367
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*41*	2851C>T[2] (Cys296Arg)	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	2988G>A	NM_000106.6:c.985+39G>A	Variant occurs in a non-coding region (impacts slicing).	rs28371725
*CYP2D6*49*	100C>T (Pro34Ser)	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	1612T>A (Phe120Ile)	NM_00106.6:c.358T>A	NP_000097.3:p.Phe120Ile	rs1135822
	4181G>C (Ser486Thr)	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840

[1] In the literature, 1023C>T is also referred to as 1111C>T
[2] In the literature, 2851C>T is also referred to as 2938C>T
[3] *CYP2D6*36* is a gene conversion with *CYP2D7;* variants provided here are from the Pharmacogene Variation Consortium.
Alleles described in this table are selected based on discussion in the text above. This is not intended to be an exhaustive description of known alleles.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (66).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
Nomenclature for Cytochrome P450 enzymes is available from the Pharmacogene Variation (PharmVar) Consortium.

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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 from 8 March 2016, please click here.

To view an earlier version of this summary from 18 March 2013, please click here.

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