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Oxycodone Therapy and *CYP2D6* Genotype

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Introduction

Oxycodone (brand names OxyContin, Roxicodone, Xtampza ER, and Oxaydo), is an opioid analgesic used for moderate to severe pain caused by various conditions for which alternative analgesic treatments are inadequate. (1) Oxycodone exerts its analgesic affects by binding to the mu-opioid receptors (MOR) in the central and peripheral nervous system. While it is an effective pain reliever, this agent also has a high potential for addiction, abuse, and misuse.

Oxycodone is metabolized by members of the cytochrome P450 (CYP) enzyme superfamily. The CYP3A4, CYP3A5, and CYP2D6 enzymes convert oxycodone to either less-active (CYP3A4 and CYP3A5) or more-active (CYP2D6) metabolites. Most of the analgesic effect is mediated by oxycodone itself, rather than its metabolites. Variation at the *CYP3A4* and *CYP3A5* loci leading to altered enzyme activity is rare. A handful of altered-function alleles are known, but there is no documented evidence to support altered oxycodone response in the presence of these variant alleles. The FDA approved drug label for oxycodone cautions that co-medication with CYP3A inhibitors or inducers may lead to altered pharmacokinetics and analgesia, but does not discuss genotype-based recommendations for prescribing (1).

Genetic variation at the *CYP2D6* locus has conflicting evidence regarding altered response of individuals to oxycodone therapy. Thus, the Clinical Pharmacogenetics Implementation Consortium (CPIC) has determined that there is insufficient evidence to recommend alterations to standard clinical use based on *CYP2D6* genotype (2). Similarly, the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP) recognizes the drug-gene interaction between *CYP2D6* and oxycodone but states that the interaction does not affect analgesia achieved by the medication (3, 4). The PharmGKB online resource reports that drug labels in Switzerland (regulated by Swissmedic) state that *CYP2D6* variation can alter oxycodone response (5, 6).

Interactions among drugs from polypharmacy may be further enhanced by genetic variation, but there are no professional recommendations to alter prescribing based on drug-drug-gene interactions. Regardless of genotype, oxycodone is contraindicated in individuals with significant respiratory depression, acute or severe bronchial asthma, known or suspect gastrointestinal obstruction, or known hypersensitivity to the medication (1).

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Drug: Oxycodone

Oxycodone is a semi-synthetic derivative of thebaine, belonging to the drug class of opioid agonists. It is used to treat both chronic and acute pain of moderate to severe intensity when alternative treatments are inadequate. (1) Oxycodone has a similar half-life (2–4 hours) as morphine and approximately twice the bioavailability (7, 8). However, oxycodone is 4-fold less potent than morphine as a MOR agonist, with similar receptor activation efficiency (9). Oxycodone is approximately twice as analgesic as morphine, perhaps reflecting the increased bioavailability, but may be less effective for some pain conditions, such as diabetic neuropathy (10, 11).

However, oxycodone has a high abuse potential (11, 12). It is one of the most widely abused opioid analgesics, with increased abuse reported among all ethnic and economic groups since the 1960s (12, 13). Oxycodone is classified as a Schedule II substance by the US Drug Enforcement Agency (DEA) due the high potential for abuse leading to psychological or physical dependance (1, 13). The factors predisposing any individual to addiction are complex and as such the risk of opioid addiction should be assessed on a case-by-case basis. Clinicians are advised to ensure that the analgesic benefits outweigh the addiction, abuse, or misuse risks for each individual. A risk evaluation and mitigation strategy educational program may be offered as a part of continuing education for prescribing clinicians. (1) Clinicians should be advised that naloxone, an opioid antagonist medication is available to counter opioid overdose and individuals taking oxycodone should be at least aware of this medication. Current guidelines from the Substance Abuse and mental Health Services Administration (SAMHSA) recommend naloxone prescription to anyone on high doses of opioids or using long acting/extended release opioids.(14)

Oxycodone has multiple administration modalities, including intravenous, epidural, rectal, or oral. Oral formulations come in the form of liquid medications or tablets for immediate or extended release. Regardless of administration route, the pharmacokinetics are dose dependent, and most of the oxycodone metabolism occurs in the liver.

Oxycodone is metabolized by members of the CYP enzyme superfamily, with a small amount of oxycodone being excreted without undergoing metabolic processing. Most of the hepatic oxycodone metabolism (roughly 45–50% of the total dose) is performed by the CYP3A enzymes (CYP3A4 and CYP3A5) to form noroxycodone, a largely inactive metabolite. (11, 12, 15) Approximately 10–19% of an oxycodone dose is also metabolized by the CYP2D6 enzyme to form a potent opioid oxymorphone. Oxycodone and its metabolites can be further reduced or can undergo glucuronidation by UDP-glucuronosyltransferase (UGT) enzymes. (11)

Inhibition of the CYP2D6 enzyme by concomitant medications (such as paroxetine) reduces oxycodone analgesia (16) due to reduced oxymorphone formation. Similarly, CYP3A inhibition results in increased oxycodone and oxymorphone exposure and analgesia (17); (16). Where CYP3A4 or CYP3A5 inhibition or induction is a concern due to multiple co-medications, oxymorphone can be substituted.

Many opioids undergo CYP2D6 metabolism to varying degrees. Oxycodone is an active analgesic with minimal metabolism by CYP2D6, whereas codeine and tramadol are pro-drugs that require activation by CYP2D6 and thus are more directly affected by *CYP2D6* enzyme activity. (18, 19) Another opioid, hydrocodone, is also metabolized by CYP2D6 into an active analgesic—hydromorphone—but like oxycodone, the parent and metabolite compounds can both provide analgesic effect, though with differing potency (2, 20, 21, 22).

Oxycodone and oxymorphone both activate MOR in the central nervous system and in peripheral tissues. At pharmacologically relevant concentrations oxycodone and oxymorphone act selectively through MOR, with oxymorphone being 8-fold more potent as a MOR activator than oxycodone. Unlike oxycodone, oxymorphone has also been shown to bind to delta and kappa opioid receptors, but the demonstrated affinities greatly exceed therapeutic plasma concentrations. Following oxycodone administration, oxymorphone has been reported to only account for a small portion of total opioid exposure, while the parent, oxycodone, accounts for roughly 90%

of the total analgesic effect (23). Conversely, some experts have concluded that the small amount of oxymorphone produced following oxycodone administration may account for most of the analgesic effect (15). The relative role of the parent and oxymorphone metabolite may depend on the route of drug administration with more oxymorphone being produced following oral dosing than seen with parenteral dosing (8). In addition, oxymorphone is a higher potency MOR agonist and exhibits a longer half-life than oxycodone—it is the predominate MOR activator 6 hours after oxycodone dosing. Given the conflicting views regarding the contribution of oxymorphone to analgesia following oxycodone administration, the role of CYP2D6 activity in an individual's response to oxycodone is also debated and is discussed further below. In contrast, the CYP3A metabolite noroxycodone, exhibits a 3-fold lower reduced binding affinity than the parent and appears to be an antagonist/very weak partial agonist. (11)

Clearance of oxycodone, either unmodified or following its metabolism by cytochrome P450 enzymes and UGT enzymes, is partially dependent upon renal function, hepatic metabolism, and seems to vary with age and gender. The plasma half-life for oxycodone is 3–5 hours in healthy adults(12), it decreases by 25% in geriatric individuals (24). Plasma protein binding of oxycodone is approximately 45% and so unlikely to be a significant variable affecting free oxycodone exposure in the elderly (25). Repetitive bolus simulations suggest that geriatric individuals have a 20% higher exposure and thus some increased risk of adverse effects from oxycodone at standard dosage (1). In neonates the clearance rate increases from birth to 6 months (11) .

Oxycodone use can cause life-threatening or fatal respiratory depression. Risk of this adverse reaction is greatest at initiation of therapy, following a dose increase, or due to initiation or cessation of co-medications that alter CYP2D6 or CYP3A enzyme activities. Accidental ingestion by children can result in respiratory depression and death following a single dose of oxycodone. Respiratory depression risk is also elevated for individuals who are elderly, cachectic or debilitated due to altered pharmacokinetics and drug clearance (1).

Medications that inhibit CYP3A or CYP2D6 enzyme activities will result in an increased exposure to oxycodone. Notably, CYP3A4 inhibitors such as macrolide antibiotics, azole-antifungals and protease inhibitors may prolong opioid adverse reactions. Furthermore, discontinuing a CYP3A inducer—rifampin, carbamazepine, or phenytoin—can also increase oxycodone exposure. The FDA approved drug label specifically notes the importance of CYP3A4- associated drug interactions in the black box warning on the drug label (1).

The FDA recommends monitoring for serotonin syndrome symptoms if concomitant use is warranted with oxycodone and selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), or other drugs that affect the serotonin neurotransmitter system (1, 26). Furthermore, the FDA approved label says to discontinue oxycodone if serotonin syndrome is suspected and advises against the use of oxycodone with monoamine oxidase inhibitors (MAOIs) or for 14 days following the completion of MAOI therapy (1).

The use of oxycodone during pregnancy can result in opioid withdrawal symptoms in the neonate, which can be life threatening. There are insufficient data to determine if oxycodone use during pregnancy leads to increased rates of birth defects or miscarriages. However, animal studies suggest that the neonate may experience adverse neurobehavioral effects following in utero exposure. Additionally, data suggests that oxycodone crosses the placenta and maternal plasma levels correlate with neonate exposure (1, 11). Chronic opioid use may cause reduced fertility in both males and females that is potentially irreversible (1).

Opioids are present in breastmilk, though one study estimated that an exclusively breast-fed infant would receive, at most, 8% of the maternal weight-adjusted dose (1, 26). However, infants are particularly sensitive to opioids and are at a significant risk for respiratory depression. As such, other analgesics are preferred over oxycodone in breastfeeding mothers (26).

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 (27).

The CYP2D6 Alleles

The *CYP2D6* gene is highly polymorphic, as over 100 star (*) alleles have been described and cataloged at the Pharmacogene Variation (PharmVar) Consortium, and each allele is associated with either increased, normal, decreased, or absent enzyme function (Table 1). (28)

The combination of *CYP2D6* alleles that a person has is used to determine their diplotype (for example, *CYP2D6 *4/*4*). Based on their impact on enzyme function, each allele can be assigned an activity score from 0 to 1, which in turn is then used to assign a phenotype (for example, CYP2D6 PM). However, the activity score system is not standardized across all clinical laboratories or *CYP2D6* genotyping platforms. The CPIC revised their activity scoring guidelines in October 2019 to promote harmonization. The CYP2D6 phenotype is predicted from the diplotype activity score defined by the sum of the allele score values, which usually ranges from 0 to 3.0: (29)

- An ultrarapid metabolizer (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 poor metabolizer (PM) has an activity score of 0

Table 1. Activity Status of Selected *CYP2D6* Alleles

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

For a comprehensive list of *CYP2D6* alleles, please See PharmVar. Activity scores from (29).

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*) (30, 31, 32, 33) or an enzyme with decreased activity (for example, **10*, **17*, and **41*) (34, 35, 36) (see Table 1). 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. (37)

Larger structural variants at the *CYP2D6* locus have also been described, including gene duplications, deletions, tandem alleles, and gene conversions. As one might expect, deletions result in a no-function allele (for example, the **5* allele is a deletion). Duplications have been reported for alleles with normal function and decreased function, as well. In the case of allele duplications, the activity scores for the full complement of *CYP2D6* alleles are summed to determine the predicted metabolizer phenotype. Additional details on structural variants are available from PharmVar (38).

The frequency of the *CYP2D6* star alleles with altered function varies across global populations, resulting in different frequencies of the resulting metabolizer phenotype(s). Given CYP2D6's role in metabolism of many drugs, the literature on allele and phenotype frequency is expansive. Most populations have a high frequency for normal-function star alleles and thus a high proportion of the population are NMs. However, reduced-function alleles like *CYP2D6*10* are highly prevalent in east and southeast Asian populations, leading to a higher proportion of IM phenotype individuals in this ancestral group. Many nations in sub-Saharan Africa have higher frequencies of decreased-function alleles like *CYP2D6*17* and **29*, which can correlate with lower metabolizer scores in these individuals. More details regarding published allele and phenotype frequencies are available in the CYP2D6 supplemental chapter.

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-medications, can lead to a phenomenon called phenoconversion whereby an individual with one metabolizer genotype can have the enzymatic activity of a different metabolizer group (higher or lower, depending on the medications). The enzymatic activity of CYP2D6 can be inhibited or reduced by medications including duloxetine, paroxetine, fluoxetine, bupropion, and quinidine (21, 39, 40, 41). This can result in NMs or IMs responding to medications as if they were PMs. Thus, co-medication with multiple CYP2D6 strong or moderate inhibitors may result in reduced metabolism of drug substrates. In contrast, discontinuing a co-medication can increase the rate of CYP2D6 metabolism.

Other Genes of Note

The *CYP3A4* and *CYP3A5* Genes

Other cytochrome P450 enzymes are involved in the metabolism of oxycodone. The CYP3A enzymes, encoded by *CYP3A4* and *CYP3A5*, perform most of the oxycodone metabolism. Similar to CYP26, the CYP3A enzymes are also susceptible to phenoconversion due to medications that inhibit or activate these enzymes, as described above. (1)

Variation at the *CYP3A4* locus is relatively uncommon and CPIC has not assigned a functional status to most variants (28). Although around 40 variant *CYP3A4* alleles have been reported, most have not been shown to alter CYP3A4 activity (42, 43). To date, only 3 loss-of-function *CYP3A4* alleles have been identified (*CYP3A4*6, CYP3A4*20* and *CYP3A4*26*) (Table 2) (44, 45).

The *CYP3A4*22* allele has decreased function and explains 12% of the variation in CYP3A4 activity (46). This variant is present in 3.2–10.6% of the Dutch population and 5.2–8.3% of the population in America (47). The Allele Frequency Aggregator project reports this reduced-function allele to be present in approximately 5% of the global population, with the lowest prevalence in Asian and African populations (48). The 1000 Genomes Project phase 3 data release estimates global prevalence to be slightly lower (~1%); a minor allele frequency of 5% is reported for the European average (49).

The *CYP3A4*20* allele has a premature stop codon that results in a loss-of-function of *CYP3A4*. It appears to be the most common *CYP3A4*-defective allele but is still relatively rare, with approximately 0.2% of European Americans and 0.05% African Americans who are heterozygous. However, in Spain, the *CYP3A4*20* allele is present in 1.2% of the population, and up to 3.8% in specific Spanish regions (44).

Table 2. Activity Status of Selected *CYP3A4* Alleles

Allele type[#]	*CYP3A4* alleles
Normal function	**1*

Table 2. continued from previous page.

Allele type[#]	*CYP3A4* alleles
Decreased function	**22*
No function	**6*, **20*, **26*

For a comprehensive list of *CYP3A4* alleles, please see PharmVar.
[#]As of the date of publication, there is no "CPIC Clinical Function" assessment provided for the *CYP3A4* alleles within PharmVar. The activity status provided here is based on the literature and historic assessment. In the event of a discrepancy between the functional classifications provided herein and PharmVar's data, the authors defer to PharmVar and CPIC.

The *CYP3A5* locus has less than 10 known genetic variants. The *CYP3A5*3*, *CYP3A5*6*, and *CYP3A5*7* alleles are important no-function alleles and the **1* allele is the normal-function allele (Table 3) (28). The combination of alleles present predicts either normal (homozygous **1*), intermediate (at least one copy of **1* or compound heterozygous for no-function alleles), or PM phenotypes (homozygous for a single no-function allele) (50, 51). The PM phenotypes have been seen more commonly in individuals identified as "White" than African American or Black (52, 53). The *CYP3A5*3* allele has been observed at a high frequency in Egyptian and Italian populations (54, 55).

Table 3. Activity Status of Selected *CYP3A5* Alleles

Allele type	*CYP3A5* alleles
Normal function	**1*
No function	**3*, **6*, **7*

For a comprehensive list of *CYP3A5* alleles, please see PharmVar.

The *OPRM1* Gene

The MOR is encoded by the *OPRM1* gene. The MOR is a G-coupled protein receptor and is a key signal transducer for the desired analgesic effect of opioids such as tramadol and 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 (56, 57). 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 (2).

The *COMT* Gene

The catechol-o-methyltransferase (COMT) enzyme is 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 (58). The variant rs4680 (p.Val158Met) in *COMT* has been suggested to result in decreased levels of methylation activity (2, 58). However, CPIC's review found variable evidence associating this variant with analgesia response or opioid dose requirements and thus makes no recommendations based on *COMT* genotype (2).

Linking Gene Variation with Treatment Response

Altered CYP2D6 enzyme activity has been associated with altered levels and ratios of oxycodone, noroxycodone, and oxymorphone levels in the blood; lower CYP2D6 activity correlated with a decrease in this ratio in plasma and urine (11, 59, 60, 61, 62). However, there are conflicting reports regarding the associated impact on analgesia or adverse outcomes.

Several studies report improved analgesia, or higher rates of adverse reactions, or both in individuals with higher levels of CYP2D6 activity. One study in 33 healthy volunteers reported a modest but significant decrease in

analgesic effect of oxycodone in CYP2D6 PM genotyped individuals in 3 out of 5 tests. Genotyping in this study was limited to analysis of variants for *CYP2D6*3, *4, *6* and **9* with no detection of duplication nor deletion; individuals were classified as CYP2D6 PMs if they had 2 no-function alleles based on this limited genotyping. (63) A small study of 10 healthy volunteers reported a correlation between CYP2D6 activity and oxycodone analgesia, with CYP2D6 UM participants also reporting an increased incidence of negative side effects and more intense adverse reactions to oxycodone compared with other metabolizer phenotypes. This group also found inhibition of CYP2D6 by co-medication with quinidine reduced the peak analgesic effect along with the oxymorphone exposure. This study genotyped *CYP2D6* variation by microarray and thus reported testing for a total of 32 alleles, including the *CYP2D6*5* deletion and duplication of a subset of alleles (64, 65). A study of 121 post-operative individuals found a direct correlation between CYP2D6 predicted enzyme activity and oxymorphone/oxycodone ratio as well as higher oxycodone consumption in CYP2D6 PMs for 48 hours post-operative self-controlled analgesia, though the pain scores were similar across metabolizer groups. This study interrogated 8 defined *CYP2D6* alleles, including the *5 deletion and gene duplication (66). Similarly, Deodhar and colleagues support the phenotypic assessment of CYP2D6 activity when oxycodone is prescribed for pain management, which could include pharmacogenomics testing to enable identification of CYP2D6 PMs or evaluation of polypharmacy leading to phenoconversion or both. (15) Another recent review suggests that within European populations, individuals who are CYP2D6 UMs have an increased risk of adverse events and additionally noted the potential impact of phenoconversion due to CYP2D6 inhibitors, which may reduce analgesic effect (67).

In contrast, multiple studies suggest the differences in oxymorphone/oxycodone ratios due to CYP2D6 activity do not impact pain management or other symptoms. A larger study of 270 individuals who had recently undergone surgical procedures were genotyped for CYP2D6 and intravenous oxycodone use for 24 hours post-surgery was monitored. This study found no significant differences in the frequency of oxycodone non-responders between CYP2D6 PM and other metabolizer phenotypes, nor differences in average oxycodone consumption between the groups, indicating that CYP2D6 metabolism did not affect oxycodone analgesia even though oxymorphone/oxycodone ratios were lower in the CYP2D6 PMs group. It should be noted that genotyping in this study was limited to detection of the **3, *4, *6* and **9* alleles, **5* was specifically excluded in the analysis and the **1* allele was assigned in the absence of any detected variants (68). A similar study in 450 individuals who were being treated for cancer pain observed changes in oxymorphone/oxycodone ratios but no difference in pain intensity, nausea, tiredness nor cognitive function, however the scope of CYP2D6 genotyping in this study was limited and the **2* duplication, **3, *4, *5, *6, *7* and **8* alleles were the only alleles specifically examined (59).

Because of the conflicting and limited evidence for either CYP2D6 metabolizer phenotypes, COMT function, or OPRM1 function being involved with altered oxycodone response, both CPIC and DPWG have no recommendations regarding dosing or selection when oxycodone is considered (2, 3).

As reported by PharmGKB, the Swiss drug labels for oxycodone state that *CYP2D6* polymorphism can alter the efficacy of the medication or lead to undesired effects; "slow" metabolizers (PMs) may experience weaker analgesia and "ultra-fast" metabolizers (UMs) may have higher analgesia and increased risk of adverse effects (69).

A large study of urine drug test samples found an association between another member of the CYP450 family: CYP2C19. The CYP2C19 UMs had a higher oxymorphone/oxycodone ratio than PMs, like CYP2D6, suggesting that CYP2C19 may play a minor role in oxycodone metabolism. However, these observations warrant further research to determine if CYP2C19 genetic variations are associated with oxycodone response (60).

Genetic variation in the *CYP3A4* locus is exceedingly rare and has not been associated with altered oxycodone analgesia. However, many reports have stated that induction of CYP3A4 and CYP3A5 by co-medications such as

rifampin and carbamazepine are associated with decreased analgesia, though at least one report found no effect by co-medication (11, 70).

Drug-drug interactions have been reported to influence treatment responses, most likely due to enzyme inhibition or induction. Adverse reactions were more common in elderly individuals taking oxycodone concomitantly with CYP2D6 or CYP3A4 inhibitor medications (71). Rifampin has been reported to reduce analgesia from multiple opioid medications, including oxycodone, though the data is limited (72).

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* allele, the copies 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. Depending on the testing methodology and platform used, a laboratory may or may not be able to specify the number of duplicated CYP2D6 alleles nor the allele that has been duplicated.

Studies in oncology and cardiovascular surgical intervention have estimated that 25–56% of these populations may be prescribed oxycodone or other opioids to manage pain during their treatment; multiple authors recommend pharmacogenomic testing in these individuals to optimize management of pain or other symptoms (20, 73, 74).

Genetic tests for oxycodone response, the *CYP2D6* gene, the *CYP3A4* gene, and the *CYP3A5* gene can be found on the NIH Genetic Testing Registry (GTR). The available tests include targeted single-gene tests as well as multi-gene panels 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. Variant *CYP2D6* alleles to be included in clinical genotyping assays have been recommended by the Association for Molecular Pathology (75).

Variants in other genes, such as *COMT* and *OPRM1*, may also influence an individual's response to oxycodone, though there are no established guidelines for dose alterations or drug selection based on genetic variation at any of the loci described in this summary.

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.

2021 Statement from the US Food and Drug Administration (FDA):

Cytochrome P450 3A4 Interaction [drug-drug interactions]

The concomitant use of oxycodone hydrochloride tablets with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome

[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 labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations, shown in square brackets, where necessary.*

P450 3A4 inducer may result in an increase in oxycodone plasma concentration. Monitor patients receiving oxycodone hydrochloride tablets and any CYP3A4 inhibitor or inducer.

[…]

Drug interactions: Inhibitors of CYP3A4 and CYP2D6, Clinical Impact [drug-drug interactions]

The concomitant use of oxycodone hydrochloride and CYP3A4 inhibitors can increase the plasma concentration of oxycodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of oxycodone hydrochloride and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of oxycodone hydrochloride is achieved… After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the oxycodone plasma concentration will decrease, resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to oxycodone.

[…]

Drug Interactions: CYP3A Inducers, Clinical Impact [drug-drug interactions]

The concomitant use of oxycodone hydrochloride and CYP3A4 inducers can decrease the plasma concentration of oxycodone, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to oxycodone. After stopping a CYP3A4 inducer, as the effects of the inducer decline, the oxycodone plasma concentration will increase, which could increase or prolong both the therapeutic effects and adverse reactions, and may cause serious respiratory depression.

[…]

Pharmacokinetics: Metabolism

A high portion of oxycodone is N-dealkylated to noroxycodone during first-pass metabolism, and is catalyzed by CYP3A4. Oxymorphone is formed by the O-demethylation of oxycodone. The metabolism of oxycodone to oxymorphone is catalyzed by CYP2D6.

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

2021 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

There is insufficient evidence and confidence to provide a recommendation to guide clinical practice at this time for oxycodone or methadone based on *CYP2D6* genotype or *COMT* genotype or *OPRM1* genotype (Tables S5 and S6, no recommendation, CPIC level C).

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

2018 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

CYP2D6 IM: oxycodone[e]

[and] CYP2D6 PM: oxycodone[e]

NO action is required for this gene-drug interaction.

The reduced conversion of oxycodone to the more active metabolite oxymorphone does not result in reduced analgesia for patients.

CYP2D6 UM: oxycodone[e]

NO action is required for this gene-drug interaction.

The increased conversion of oxycodone to the more active metabolite oxymorphone does not result in an increase in side effects in patients.

Please review the complete therapeutic recommendations that are located here: (3, 4)

Nomenclature for Selected Alleles

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	NM_000106.6:c.457G>C	NP_000097.3:p.Arg296Cys	rs16947
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*3*	2550delA	NM_000106.6:c.775del	NP_000097.3:p.Arg259fs	rs35742686
*CYP2D6*4*	1846G>A	NM_000106.6:c.506-1G>A	Variant occurs in a non-coding region (splice variant causes a frameshift)	rs3892097
*CYP2D6*5*	Gene deletion			
*CYP2D6*6*	1707 del T	NM_000106.6:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*17*	1022C>T	NM_000106.6:c.320C>T	NP_000097.3:p.Thr107Ile	rs28371706
	2851C>T	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*27*	3854G>A	NM_000106.6:c.1228G>A	NP_000097.3:p.Glu410Lys	rs769157652
*CYP2D6*31*	2851C>T	NM_000106.6:c.886C>T	NP_000097.3:p.Arg296Cys	rs16947
	4043G>A	NM_000106.6:c.1319G>A	NP_000097.3:p.Arg440His	rs267608319
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*36*[1]	100C>T	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	4129C>G	NM_000106.6:c.1405C>G	NP_000097.3:p.Pro469Ala	rs1135833
	4132A>G	NM_000106.6:c.1408A>G	NP_000097.3:p.Thr470Ala	rs1135835
	4156C>T+4157A>C	NM_000106.6:c.1432C>T + NM_000106.6:c.1433A>C	NP_000097.3:p.His47Ser	rs28371735 + rs766507177
	4159G>C	NM_000106.6:c.1435G>C	NP_00097.3:p.Gly479Arg	
	4165T>G	NM_000106.6:c.1441T>G	NP_00097.3:p.Phe481Val	
	4168G>A+4169C>G	NM_000106.6:c.1444G>A + NM_000106.6:c.1445C>G	NP_000097.3:p.Ala482Ser	rs74478221 + rs75467367
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840

Nomenclature of Selected continued from previous page.

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*41*	2851C>T	NM_000106.6:c.886T>C	NP_000097.3:p.Cys296Arg	rs16947
	2989G>A	NM_000106.6:c.985+39G>A	Variant occurs in a non-coding region (impacts slicing).	rs28371725
	4181G>C	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840
*CYP2D6*49*	100C>T	NM_000106.6:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
	1612T>A	NM_00106.6:c.358T>A	NP_000097.3:p.Phe120Ile	rs1135822
	4181G>	NM_000106.6:c.1457G>C	NP_000097.3:p.Ser486Thr	rs1135840

[1] *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.

Nomenclature of Selected *CYP3A4* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP3A4*6*	17661_17662insA 277Frameshift	NM_017460.5:c.830_831insA	NP_059488.2:p.Asp277Glufs	rs4646438
*CYP3A4*20*	1461_1462insA 488Frameshift	NM_017460.5:c.1461dup	NP_059488.2:p.Pro488Thrfs	rs67666821
*CYP3A4*22*	15389C>T	NM_017460.6:c.522-191C>T	Not applicable—variant occurs in a non-coding region	rs35599367
*CYP3A4*26*	17642C>T R268Stop	NM_017460.6:c.802C>T	NP_059488.2:p.Arg268Ter	rs138105638

*CYP3A4*1.001* is the wild-type allele and is determined to be present with no variants are detected.

Nomenclature of Selected *CYP3A5* Alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP3A5*3*	6981A>G	NM_000777.5:c.219-237A>G	Not applicable—variant occurs in a non-coding region	rs776746
*CYP3A5*6*	14685G>A	NM_000777.5:c.624G>A	NP_000768.1:p.Lys208= (Alters mRNA splicing)	rs10264272
*CYP3A5*7*	27126_27127insT	NM_000777.5:c.1035dup	NP_000768.1:p.Thr346fs	rs41303343

*CYP3A5*1* is the wild-type allele and is determined to be present with no variants are detected.
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (76).
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; the authors defer to that authority with regards to any discrepancies in allele definitions.

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